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Major Perioperative Morbidity Does Not Affect Long-Term Survival in Patients Undergoing Esophagectomy for Cancer of the Esophagus or Gastroesophageal Junction

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Abstract
Introduction The incidence of cancer of the esophagus/GE junction is dramatically increasing but continues to have a dismal prognosis. Esophagectomy provides the best opportunity for long-term cure but is hampered by increased rates of perioperative morbidity. We reviewed our large institutional experience to evaluate the impact of postoperative complications on the long-term survival of patients undergoing resection for curative intent.
Methods We identified 237 patients who underwent esophagogastrectomy, with curative intent, for cancer between 1994 and 2008. Complications were graded using the previously published Clavien scale. Survival was calculated using Kaplan–Meier methodology and survival curves were compared using log-rank tests. Multivariate analysis was performed with continuous and categorical variables as predictors of survival, and examined with logistic regression and odds ratio confidence intervals.
Results There were 12 (5 %) perioperative deaths. The average age of all patients was 62 years, and the majority (82 %) was male. Complication grade did not significantly affect long-term survival, although patients with grade IV (serious) complications did have a decreased survival ($p = 0.15$). Predictors of survival showed that the minimally invasive type esophagectomy ($p = 0.0004$) and pathologic stage ($p = 0.0007$) were determining factors. There was a significant difference in overall survival among patients who experienced pneumonia ($p = 0.00016$) and respiratory complications ($p = 0.0004$), but this was not significant on multivariate analysis.
Conclusions In this single-institution series, we found that major perioperative morbidity did not have a negative impact on long-term survival which is different than previous series. The impact of tumor characteristics at time of resection on long-term survival is of most importance.

Introduction

Esophageal cancer is a devastating disease with a grim prognosis. The National Cancer Institute's Surveillance Epidemiology and End Results (SEER) reports 5-year survival rates for localized esophageal cancer to be 37.4 %, regional to be 18.8 %, and distant to be 3.2 % [1]. Surgery remains the treatment of choice for prolonged survival and the chance for a definitive cure. However, esophagectomy is a complicated procedure that often is associated with increased risks of postoperative morbidity and mortality.

Known factors that improve postoperative prognosis are early stage at resection, R0 resection, and complete response to neoadjuvant chemoradiotherapy. However, there is still debate on the impact of postoperative complications and associated morbidity on long-term survival. In 2004, a retrospective analysis of 510 patients who underwent esophagogastrectomy for esophagus or gastroesophageal (GE) junction carcinoma at Memorial Sloan–Kettering Cancer Center [2] reported that patients with no technical complications had better overall survival than patients with technical complications. A 2009 retrospective analysis of 150 patients who underwent transthoracic esophagectomy for curative intent at Leuven University Hospitals reported a strong correlation between severity of complications and time to tumor recurrence [3]. A 2008

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retrospective analysis by Lagarde et al. [4] of 191 patients who died from tumor recurrence concluded that postoperative complications are independently associated with a shorter time interval to death due to recurrence.

On the other hand, in 2006, a retrospective analysis of 522 patients who underwent resection of thoracic esophagus and GE carcinoma at Veneto Region's Center for Esophageal Diseases reported that long-term prognosis is dependent exclusively on the tumor characteristics and is not affected by surgical complications [5]. Similarly, a 2006 retrospective analysis of 434 patients who underwent resection of squamous cell carcinoma of the esophagus at University of Hong Kong Medical Centre reported no affect on long-term survival in patients with surgical complications [6].

There also are conflicting reports on the effect of respiratory complications on long-term prognosis, the most common of which is pneumonia. Examining 38 patients who developed pneumonia amongst 118 total patients, a 2004 study reported that pneumonia not only affected perioperative mortality but also long-term survival [7]. This is in contrast to a study from 2011, which did not find any significant difference in disease-free survival as a result of respiratory complications of atelectasis, pneumonia, or acute respiratory distress syndrome [8].

To further examine this important question, we reviewed our large single-institution experience to determine the impact of perioperative complications on long-term survival in patients with cancers of the esophagus and GE junction who have undergone esophagectomy.

Patients and methods

Using an institutional review board-approved institutional esophagectomy database, we identified patients who underwent esophagectomy for invasive adenocarcinoma or squamous cell carcinoma of the esophagus, GE junction, or stomach cardia at Thomas Jefferson University Hospital (TJUH) between January 1994 and December 2008. There were 237 patients who had undergone surgery with curative intent. In many cases, we performed a retrospective review of the medical records of patients to retrieve specific data, such as neoadjuvant treatments, surgical data, histologic, and pathologic data of the resected specimen, postoperative surgical and medical complications, adjuvant therapy, recurrence, and survival.

Operative procedure

The type of esophageal resection was assigned according to the operative note and was performed at the discretion of the operating surgeon. The type of esophagectomy performed included: Ivor-Lewis (laparotomy and right thoracotomy), transhiatal (laparotomy and neck incision), 3-hole (laparotomy, thoracotomy, and neck incision), and minimally invasive esophagectomy (MIE), which includes laparoscopy and video-assisted thoracoscopy (VATS), laparoscopic transhiatal, and thoracoscopic 3-hole.

Pathology

All patients had squamous cell carcinoma or adenocarcinoma of the esophagus, GE junction, or gastric cardia. Patients were staged according to the 6th edition of the AJCC staging system [9]. Resections were defined as complete removal of tumor with microscopic examination of margins showing no tumor cells (R0), microscopic examination of margins showing tumor cells (R1), and macroscopic examination of margins showing tumor cells (R2). Patients who underwent R2 resection (noncurative intent) were eliminated from survival analysis. A pathologic complete response (pCR) was defined as a patient who did not have any viable tumor in the specimen at the time of surgical resection.

Complications

We graded postoperative technical and medical complications related to the operation using a modification of the Clavien classification [10]. Complications were classified into six grades (Table 1). In brief, grade 0 patients did not experience any complications. Grade 1 was assigned to patients who experienced complications that did not result in a change of the postoperative course. Complications that required pharmacological treatment, blood transfusion, or total parenteral nutrition were assigned to grade 2. Any complication that required invasive or radiological intervention was assigned to grade 3. Patients who experienced life-threatening complications requiring ICU stay were given a grade 4 complication: 4a for single-organ dysfunction and 4b for multiorgan dysfunction. Perioperative mortality was assigned to grade 5. Perioperative complications and morbidity were recorded during the initial hospital stay—from day of surgery to discharge. Complications resulting in patients being readmitted within 30 days of surgery also were considered. Perioperative mortality was considered to include any patient who died within 90 days of surgery or during the postoperative stay for their esophagectomy.

Survival and statistical analysis

Survival data were obtained from the medical records and the Social Security Death Index. Survival (months) was calculated from the date of surgery. Patients were followed for survival for at least 1 year postoperation.

Table 1 Clavien complication scale

Grade	Definition
0	No complications
1	Deviation from normal postoperative course without need for medical or surgical intervention
2	Complications requiring pharmacological treatment, transfusion, or total parenteral nutrition
3	Complications requiring invasive or radiological intervention
	3a—Does not require general anesthesia
	3b—Requires general anesthesia
4	Life-threatening complications requiring intensive care unit management
	4a—Single-organ dysfunction
	4b—Multi-organ dysfunction
5	Death

Survival analysis was calculated by using Kaplan–Meier methodology and curves were compared by using log-rank tests. Continuous variables (length of stay) were compared by using Student's t test, with $p < 0.05$ considered to be significant. Categorical variables were compared using Chi-square. A multivariate analysis was performed with continuous and categorical variables as predictors of survival and was examined with logistic regression and odds ratio confidence intervals. The following complications were included in the multivariate analysis: pneumonia, respiratory failure, anastomotic leakage, and wound infection.

Results

Patient characteristics

We identified all patients who underwent an operation with curative intent for invasive squamous cell carcinoma or adenocarcinoma ($n = 237$). The average age of patients was 62 (range, 32–86) years. The majority of patients were men (82.3 vs. 17.7 %, M/F 4.6:1). There were 140 (59.1 %) patients that were nonsmokers, whereas 97 (40.9 %) had an active smoking history. The majority of patients received neoadjuvant chemoradiation treatment ($n = 155$, 65.4 %), predominantly 5-fluorouracil and cisplatinum with 45 Gy external beam radiation. Of the 155 patients who received neoadjuvant treatment, 33 (21.3 %) patients had a pCR. Of the 237 procedures (Table 2), the most common were transhiatal ($n = 110$, 46.4 %) and Ivor-Lewis ($n = 58$, 24.5 %). There also were 26 (11.0 %) were minimally invasive esophagectomy procedures. Adenocarcinoma was present in 201 tumors (84.8 %). The median length of postoperative stay (LOS) was 12 (range, 1–116) days.

Table 2 Patient characteristics

Characteristics	*N*	%
Total	237	
Mean age (years)	62 (range 32–86)	
Gender, male	195	82.3
Smoker	97	40.9
Induction chemoradiation	155	65.4
Procedure		
Transhiatal	110	46.4
Ivor-Lewis	58	24.5
3-hole	42	17.7
MIE	26	11
Histology		
Adenocarcinoma	201	84.8
Squamous cell carcinoma	36	15.2
Tumor location		
Proximal 1/3	5	2.1
Middle 1/3	17	7.2
Distal 1/3	80	33.8
GE junction	106	44.7
Stomach cardia	29	12.2
Pathologic stage		
0	39	16.5
I	51	21.5
II	84	35.4
III	52	21.9
IV	11	4.7
R0	212	89.5

MIE minimally invasive esophagectomy, *GE* gastroesophageal

Negative margin resection was achieved in 212 patients (89.5 %) and R1 resection in 16 patients (6.8 %). The majority of tumors (Table 2) were located at the GE junction ($n = 106$, 44.7 %) and distal esophagus ($n = 80$, 33.8 %). The most frequent pathologic stage was stage II ($n = 84$, 35.4 %).

Postoperative complications

There were 100 (42.2 %) patients who had an unremarkable postoperative course (complication grade 0; Table 3).

Table 3 Complication grade breakdown

Grade	*n*	%
0	100	42.2
I	12	5.1
II	53	22.4
III	25	10.5
IV	35	14.7
V	12	5.1

Twelve patients (5.1 %) had perioperative mortalities (grade 5). The majority, 57.8 % ($n = 137$), of patients had postoperative complications (grades 1–4). Among patients with complications, 9.6 % ($n = 12$) were grade 1, 42.4 % ($n = 53$) were grade 2, 20 % ($n = 25$) were grade 3, and 28 % ($n = 35$) were grade 4. The median survival among the 225 patients (excluding 12 patients with perioperative mortalities) was 20.8 months.

Patients were divided into three classes: those with no complications (group 1—grade 0, $n = 99$, 42 %), those with minor complications (group 2—grade 1–2, $n = 65$, 27.5 %), and those with major complications and mortality (group 3—grades 3–5, $n = 72$, 30.5 %). Patient characteristics (age, gender, smoking history, histology, tumor location, pathologic stage, induction therapy, operative procedures) between the two groups were not found to be

Table 4 Complication grades

	None (grade 0)	Minor (grades 1–2)	Major/mortality (grades 3–5)	*p* value
Number	99	65	72	
Mean age (years)	60.1	62.2	63.1	0.16
Gender				0.18
Male	76 (76.8)	56 (86.2)	62 (86.1)	
Female	23 (23.2)	9 (13.8)	10 (13.9)	
Smoker				0.55
No	58 (58.6)	42 (64.6)	40 (55.6)	
Yes	41 (41.1)	23 (35.4)	32 (44.4)	
Histology				0.91
Adenocarcinoma	83 (83.8)	57 (87.7)	61 (84.7)	
Squamous cell carcinoma	16 (16.2)	9 (12.3)	11 (15.3)	
Tumor location				0.55
Proximal 1/3	2 (2)	1 (1.6)	2 (2.8)	
Middle 1/3	9 (9.1)	5 (7.7)	3 (4.2)	
Distal 1/3	34 (34.3)	19 (29.2)	27 (37.5)	
GE junction	38 (38.4)	35 (53.8)	32 (44.4)	
Stomach cardia	16 (16.2)	5 (7.7)	8 (11.1)	
Pathologic stage				0.73
0	15 (15.2)	12 (18.5)	11 (15.3)	
I	20 (20.2)	13 (20)	18 (25)	
II	33 (33.3)	27 (41.5)	24 (33.3)	
III	27 (27.3)	11 (16.9)	14 (19.4)	
IV	4 (4.0)	2 (3.1)	5 (6.9)	
Induction therapy				
CRT	67 (67.7)	41 (63.1)	46 (63.9)	0.8
pCR	15 (15.2)	9 (13.8)	9 (12.5)	0.88
Procedure				0.16
Transhiatal	43 (43.4)	39 (60.0)	28 (38.9)	
Ivor-Lewis	28 (28.3)	12 (18.5)	17 (23.6)	
3-hole	15 (15.2)	9 (13.8)	18 (25)	
MIE	13 (13.1)	5 (7.7)	8 (11.1)	
LOS (day)				
Mean	12.0	13.1	29	<0.0001
Median	10	12	20.5	
Resection				0.43
R0	86 (86.9)	60 (92.3)	66 (91.7)	
R1	7 (7.1)	4 (6.2)	5 (6.9)	
Unknown	6 (6)	1 (1.5)	1 (1.4)	
Mean survival (mo)	28.0	29.8	21.1	0.08

pCR pathologic complete response, *CRT* chemoradiation therapy, *MIE* minimally invasive esophagectomy, *LOS* length of stay, *GE* gastroesophageal

Table 5 Complication breakdown

Complication	*n*	Grade
Respiratory failure (requiring intubation)	35 (14.8)	4
Supraventricular arrhythmia	34 (14.3)	2
Anastomotic leakage	32 (13.5)	2
Pleural effusion (requiring thoracentesis or chest tube)	30 (12.7)	3a
Wound infection	27 (11.4)	1
Pneumonia	26 (11.0)	2
Reoperation	25 (10.5)	3b
Bacteremia	21 (8.9)	2
Deep venous thrombosis	12 (5.1)	2
Ventilatory support >48 h	18 (7.6)	2
Adult respiratory distress syndrome	14 (5.9)	2
Perioperative mortality	12 (5.1)	5

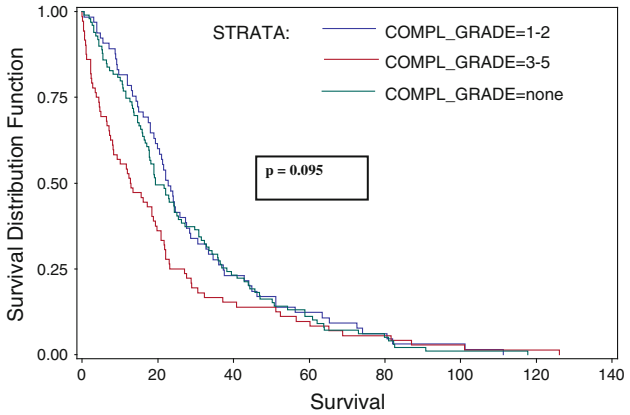

Fig. 1 Kaplan–Meier survival curve demonstrating overall survival of patients with esophageal cancer undergoing esophagectomy broken down by types of complications: *green* line indicates patients who experienced no postoperative complications (Clavien grade 0); *blue* line indicates patients who experienced minor postoperative complications (Clavien grades 1 and 2); and *red* line indicates patients who experienced major postoperative complications or mortality (Clavien grades 3, 4, and 5) (Color figure online)

significantly different (Table 4). There was no significant difference in completeness of resection between the two groups. However, the median LOS ($p < 0.0001$) was significantly different between patients in group 1 (12 days), group 2 (13.1 days), and group 3 (29 days).

The most common complications (Table 5) were respiratory failure requiring intubation ($n = 35$, 14.8 %), supraventricular arrhythmia ($n = 34$, 14.3 %), anastomotic leakage ($n = 32$, 13.5 %), pleural effusion requiring thoracocentesis or a chest tube ($n = 30$, 12.7 %), wound infection ($n = 27$, 11.4 %), and pneumonia ($n = 26$, 11 %).

Overall survival (Fig. 1) was compared for patients with no (grade 0), minor complications (grades 1 and 2), and major complications and mortality (grades 3, 4, and 5). There was not a significant difference in overall survival by complication grade ($p = 0.095$), even though patients with major complications did fare slightly worse (especially in the first 5 years). In the bivariate analysis, the survival was worst for patients with grade 4 complications; however, this was not statistically significant ($p = 0.15$).

Table 6 Specific complications

Number	Pneumonia		Respiratory failure/ ARDS/ ventilatory support		Wound infection		Anastomotic leak	
	n	%	*n*	%	*n*	%	*n*	%
Number	26	11	42	17.8	27	11.4	32	14.3
Mean LOS (days)	35.2		37.0		22.6		24.7	
p value	0.0018		<0.0001		0.14		0.015	
Mean survival (months)	15.0		15.8		21.5		27.2	
p value	0.00016		0.0004		0.17		0.88	

LOS length of stay, *ARDS* adult respiratory distress syndrome

When examining specific complications (Table 6), we found a significant increase in length of stay for patients who had postoperative pneumonia, respiratory failure, or anastomotic leakage. There was a significant difference in overall survival ($p = 0.0002$) among patients who developed pneumonia ($n = 26$, 15.0 months) and patients who did not ($n = 210$, 27.8 months), as well as among patients who developed respiratory failure ($n = 42$, 15.8 months) and patients who did not ($n = 194$, 28.7 months). The impact of pneumonia ($p = 0.24$) and respiratory failure ($p = 0.15$) was lost on multivariate analysis as a predictor of survival. Multivariable analysis (Table 7) on the predictors of survival showed that type of esophagectomy ($p = 0.0004$) and pathologic stage ($p = 0.0007$) were determining factors. Patients who underwent an Ivor-Lewis esophagectomy had a higher risk for death ($p = 0.0079$), whereas patients who had a MIE had a lower risk for death ($p = 0.005$). As the pathologic stage increases, so does risk of death, particularly among patients with stage II ($p = 0.0078$) and III ($p = 0.0002$) esophageal cancers.

Discussion

Esophageal resection is a complicated procedure associated with increased morbidities and mortality. However, there is still a debate of the impact of postoperative complications and its impact on prognosis and survival. We observed that patients whose postoperative periods were unremarkable or had minor complications (grades 0, 1–2) had shorter

lengths of stay, but no significant difference in survival compared with patients with major morbidities (grades 3–5). This study shows that one of the most important and independent predictor of survival is pathologic stage; stage II and III tumors were associated with a significantly higher risk of death. These results agree with those reported by Ferri and colleagues, as well as Ancona and colleagues at Veneto Region's Center for Esophageal Diseases, who concluded that surgical complications play no role on long-term prognosis, which is entirely dependent on pathology and tumor characteristics [3].

Table 7 Multivariable predictors of death after esophagectomy

Predictor	Risk ratio	95 % CI	*p* value
Age (years)			0.18
31–54	1.00	[a]	
55–60	0.51	0.20–1.30	
61–69	0.39	0.15–1.01	
70–86	0.86	0.33–2.33	
Gender (female)	1.19	0.50–2.85	0.69
Tumor location			0.93
GE junction	1.00	[a]	
Proximal and middle 1/3	0.85	0.20–3.62	
Distal 1/3	1.17	0.53–2.61	
Cardia	1.34	0.35–5.12	
Type of esophagectomy			0.0004
Transhiatal	1.00	[a]	
3-hole	0.55	0.22–1.41	
Ivor-Lewis	3.56	1.40–9.08	
MIE	0.17	0.05–0.59	
Pathologic stage			0.0007
0	1.00	[a]	
1	1.49	0.50–4.42	
2	3.71	1.41–9.74	
3	11.98	3.25–44.19	
4	6.38	0.94–43.29	
Histology (adenocarcinoma)	1.40	0.47–4.23	0.55
Complication grade			0.84
0	1.00	[a]	
I	1.26	0.25–6.40	
II	0.57	0.23–1.41	
III	1.05	0.34–3.18	
IV	0.73	0.14–3.77	
V	>999.99	<0.001–>999.99	
Specific complication			
Pneumonia	2.19	0.59–8.11	0.24
Respiratory failure/ARDS/ventilatory support	3.31	0.64–17.1	0.15
Wound infection	1.16	0.33–4.11	0.82
Anastomotic leak	1.09	0.33–3.57	0.89

MIE minimally invasive esophagectomy, *ARDS* adult respiratory distress syndrome, *GE* gastroesophageal

[a] Reference group

Major perioperative morbidities may not have a significant effect on long-term survival due to the high-volume of esophagectomies performed at our institution (Fig. 2). TJUH is a high-volume institution and National Cancer Institute designated cancer center with a multidisciplinary approach, employing standardized clinical pathways to treat patients undergoing major surgeries. Finlayson and colleagues [11] reported an 8.5 % higher difference in mortality rate, particularly among older patients, in low-volume centers compared with high-volume centers. When comparing the trend in referrals to high-volume institutions resulting in a concentration of major procedures in a smaller number of hospitals from 1999–2008, Finks and colleagues [12] found a significant 11 % decrease in operative mortality among esophagectomy patients. The experience of not only the surgical team, but also the nursing and ICU staff, may benefit in detecting and treating postoperative complications efficiently and effectively, reducing its severity. Ghaferi and colleagues [13] at the University of Michigan attributed the "failure to rescue" (defined as fatalities among patients with complications) in high-risk surgeries, such as esophagectomy as a principal factor, demonstrating that although low-volume centers have a slightly higher overall complication rate, they also have a significantly higher failure to rescue rate of 30.3 % compared with 13.1 % in high-volume centers. Advancements in addressing postoperative complications with procedures, such as endoscopic stenting for anastomotic leak, which are more readily available at specialized institutions, also may contribute to a decrease in operative mortality [14, 15]. What we observed in this single-institution review may not be applicable to most hospitals.

Furthermore, the use of the modified Clavien classification to grade postoperative complications in a major surgery, such as esophagectomy, may not be reliable. For example, complications, such as transient confusion, are graded similar to wound infections as grade 1. However, it has been reported that postoperative infections do have a negative impact on long-term survival in major gastrointestinal cancer resections [16, 17]. In a study conducted by Lerut and colleagues on the impact of postoperative complications after transthoracic esophagectomy using the modified Clavien classification, similar results were reported that there was no difference in survival curves between grades 2, 3, and 4 complications [5]. Using a generalized grading system may dilute the real impact of specific complications in patients who undergo esophagectomy. It may be necessary to devise a separate and unique postoperative classification system for this type of major surgery.

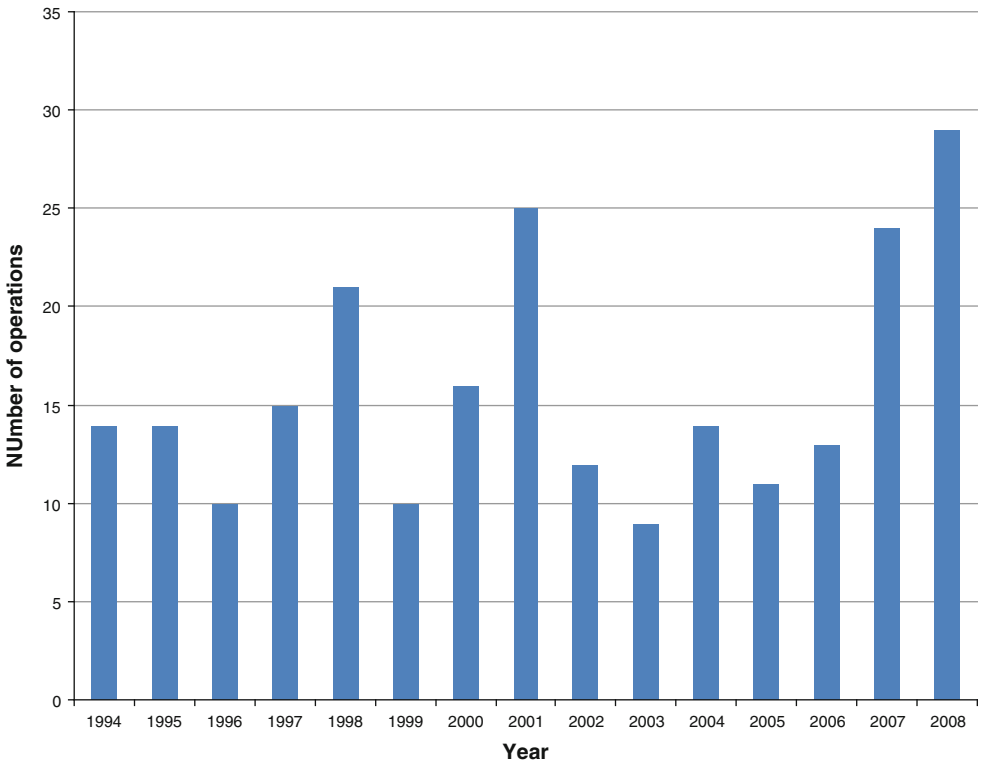

Fig. 2 Histogram demonstrating the number of esophageal resections for curative intent performed at Thomas Jefferson University Hospitals from 1994–2008

Analysis of the impact of specific complications found that wound infection, anastomotic leak, and severe respiratory morbidities (adult respiratory distress syndrome, respiratory failure, ventilatory support >48 h) did not significantly affect survival, although there was a significant difference in overall survival among patients who experienced pneumonia compared with patients who did not. These results agree with D'Annoville et al. [8], who found that technical complications were associated with worse immediate hospital outcomes, but did not affect long-term survival. In addition, major postoperative morbidities were found to significantly increase patient LOS. A recent study in Bangalore, India, with a study population ($n = 236$) similar to ours, reported that anastomotic leak, delayed wound healing, and postoperative weight loss increased the risk of relapse [18]. This may have to do with a release in cytokines (interleukin (IL)-6, IL-8, IL-1, tumor necrosis factor α) in response to stress, with the resulting inflammation associated with infection causing a hormonal milieu more conducive to the regrowth of cancer cells, known as "inflammatory oncotaxis" [19, 20]. Further research on whether or not the significant increase in patient LOS as a result of major postoperative complications has an effect on relapse-free survival is needed.

In conclusion, esophagectomy is a major invasive procedure that can be performed safely at high-volume centers. Although the procedure is associated with potential postoperative morbidities, postoperative complication rates are reasonable when performed and cared for by an experienced medical team. The impact of major postoperative complications on long-term survival may not be as consequential as previously reported; instead, tumor characteristics at the time of resection may be the most important.

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