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ORIGINAL ARTICLE

Perioperative Mortality in Cancer Esophagus—a Case Control Study at a High-Volume Regional Cancer Center in South India

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Abstract

Surgery for esophageal cancers carries high rates of morbidity and mortality despite improvements in perioperative care especially with increasingly safe anesthesia and postoperative ICU care. A case control study was conducted on 713 patients operated for esophageal cancer over a period of 8 years (2009–2016). Multiple preoperative, intraoperative, and postoperative clinical and laboratory parameters were compared between patients who succumbed to the surgery, i.e., 30-day mortality, and those who did not. Of the preoperative parameters, age > 58.5 years ($p = 0.01$), history of dysphagia with significant weight loss ($p = 0.028$), diabetes ($p = 0.002$), ischemic cardiac disease ($p = 0.0001$), low FEV1 < 69.5% ($p = 0.036$), preoperative length of hospital stay > 6.94 days ($p = 0.001$), involvement of gastroesophageal junction ($p = 0.04$), and ASA score > 2 ($p = 0.002$) were significantly associated with perioperative mortality. Intraoperatively, blood loss ($p = 0.003$), intraoperative ($p = 0.015$) and postoperative ($p = 0.0001$) blood transfusion, splenectomy ($p = 0.0001$), and excessive intraoperative intravenous fluids ($p = 0.003$) were associated with mortality. Decreased postoperative day 1 serum albumin level < 2.38 mg/dl ($p = 0.0001$), increased ICU stay > 7.32 days (SD+/- = 6.28, $p = 0.03$), number of positive lymph nodes > 2.97 (SD+/- = 4.19, $p = 0.013$), conduit necrosis ($p = 0.0001$), recurrent laryngeal nerve palsy ($p = 0.013$), pulmonary venous thromboembolism ($p = 0.0001$), multiple organ dysfunction syndrome ($p = 0.0001$), LRTI ($p = 0.0001$), arrhythmia ($p = 0.005$), sepsis ($p = 0.0001$), and ARDS ($p = 0.0001$) were the postoperative complications that were significantly associated with mortality. Comprehensive patient care involving preoperative optimization, improved surgical skills, rigorous intraoperative fluid management, and dedicated intensive care units will continue to play a major role in further minimizing mortality and morbidity associated with esophageal cancer surgeries.

Keywords Surgery · Esophageal cancer · Perioperative morbidity · 30-day mortality

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Introduction

The year 1877 marked a new era in esophageal surgery when Vincenz Czerny performed the first successful resection of cervical esophagus for carcinoma, followed by Franz Torek (1913) who was the first to successfully carry out subtotal thoracic esophagectomy [1]. It was been more than a century now and yet this surgery continues to intimidate the most experienced surgeons worldwide despite strides of improvement in delineating detailed anatomy, perioperative care, anesthesia, and meticulous surgical techniques.

Mortality rates following different types of esophagectomy have reduced significantly from as high as 72% in 1940 (when the world literature for esophageal surgeries was first reviewed by Oschner and DeBakey) to less than 10% in most of the tertiary cancer referral centers of today [2]. The incidence of complications has been reported to a range from 17% to 74% according to the expertise of the concerned centers [3]. Few of them are life-threatening such as pulmonary complications, thrombo-embolism, and conduit necrosis while many may be benign, e.g., transient arrhythmia and neck anastomotic leak. Nevertheless, they significantly prolong hospital stay and contribute immensely to the morbidity associated with this surgery.

Most of the data available from the Indian subcontinent is limited to specific clinical/biochemical factors associated with perioperative morbidity and mortality. However the data regarding entire spectrum of perioperative clinical/biochemical factors associated exclusively with 30-day mortality in Indian subcontinent is essentially non-existent. The objectives of our retrospective case control study were to evaluate in detail the preoperative, intraoperative, and postoperative clinical factors associated with mortality after esophageal resection for cancer at our high-volume institute and set a baseline rate of our complications that will serve as a benchmark for future prospective studies in Indian subcontinent.

Methods

Between January 2009 and December 2016, 713 patients underwent esophageal resection at Kidwai Cancer Institute, Bangalore, India. Only patients with histologically proven esophageal cancer, both squamous and adenocarcinoma of esophagus along with Siewerts type I and II gastroesophageal junction (GEJ) tumors were included in the study. Patients with cervical esophageal cancer were not part of this analysis as they followed different/non-surgical treatment protocols. Patients with benign histology, salvage esophagectomy, and age less than 18 years were excluded from the study. Institution ethics committee approval was taken for collection of retrospective data. Informed consent was obtained from all individuals included in the study in the preoperative period to use their clinical data for research purpose without breach of identity.

Preoperative Evaluation

Complete history-taking and thorough clinical assessment was done for every patient. Those presenting with positive supraclavicular lymph nodes, otherwise non-metastatic were referred for definitive chemoradiotherapy. All patients had basic hematological and biochemical tests, electrocardiograph, pulmonary function tests, and chest radiographs done. Endoscopy and biopsy was done for all cases whereas bronchoscopy was added for those having lesions in middle third of the esophagus. Other imaging modalities added were CT scan of thorax and abdomen along with bone scintigraphy to rule out skeletal metastasis as part of institution's metastatic work-up protocol. PET scan and endoscopic ultrasound were rarely performed due to non-availability. While undergoing preoperative evaluation, patients were counseled to discontinue smoking and quit alcohol. Chest physiotherapy, incentive spirometry, and nebulization were instituted until the day of surgery. High-calorie and high-protein diets form a routine part of our preoperative patient preparation for all major surgeries.

Intraoperative and Postoperative Care

Four types of esophagectomies are performed at our center—conventional open transhiatal esophagectomy (THE), McKeown's tri-incisional esophagectomy, and Hybrid McKeown's esophagectomy (thoracoscopy, laparotomy, and neck incision; or thoracoscopy, laparoscopy and neck incision). Robotic surgery was started in November 2016; however, those patients are not included in this study. All patients receive epidural anesthesia and those with high risk also receive a central line and arterial line for intraoperative fluid and blood pressure monitoring respectively. In all patients, anastomosis is performed in the neck and intrathoracic anastomosis is rarely performed. Bilateral intercostal drainage (ICD) tubes are placed along with corrugated rubber drain near neck anastomosis. Feeding jejunostomy (FJ) is done routinely for early enteral feeding. Patients are either extubated on table or in the ICU. Chest physiotherapy and pulmonary toileting is continued postoperatively. We try to maintain postoperative hemoglobin and serum albumin levels above 10 mg/dl and 3 mg/dl respectively. ICD tubes are removed when output is less than 50 ml per day. Patients are kept on maintenance intravenous fluids 1.5 to 2 l/day until postoperative day (POD) 5 or 6 when oral fluid is allowed and if no leak is detected neck drain is removed. We do not routinely perform contrast studies for detection of leak as it is not cost-effective in our setup. FJ Feeds are given to supplement calorie intake until patient resumes full diet per orally. Parenteral nutrition is

instituted in situations when patient cannot resume adequate oral diet by POD 5, i.e., in cases of major anastomotic leaks or prolonged ventilatory support.

Data Analysis

Patients were divided into those who died within 30 days of surgery (30-day mortality) and those who did not (controls). Clinical, biochemical, and pathological parameters of cases and controls were divided into preoperative, intraoperative, and postoperative parameters (Table 1). Data was entered in Microsoft Excel 2010 and was analyzed using SPSS version 2010. The qualitative data was represented in the form of frequency and percentage and quantitative data with mean and standard deviation. The association between two qualitative data was calculated using chi-squared test and comparison of mean between quantitative data was calculated using unpaired *t* test. Multivariate analysis was done by applying logistic regression analysis. *P* value less than 0.05 was considered as statistically significant.

Results

Seven hundred thirteen patients were included in the study. The demographic data is presented in Table 2. Thirty-four (4.7%) patients died within 30 days of surgery. Mean age for cases was 58.53 years and that of control group was 53.96 years ($p = 0.010$). There was increased mortality for patients hailing from rural areas however it was not significant. For unknown reasons, patients of high-income group had exceptionally high rate of mortality. Statistically significant mortality occurred in patients with diabetes, hypertension, ischemic cardiac diseases, and those with ASA score more than two (Table 2).

Of the total number of patients, 450 (63.11%) had middle 1/3 of the esophagus involvement. Although the mortality group had a higher rate of middle 1/3 esophageal cancer involvement (67.64%), it was not statistically significant. Increased mortality was not associated with final staging parameters or administration of neoadjuvant therapy. Involvement of gastroesophageal junction and iatrogenic

Table 1 Clinical, biochemical, and pathological parameters assessed

Clinical, biochemical, and pathological parameters		
Preoperative	Intraoperative	Postoperative
Age	Type of surgery	Time of extubation
Gender	Total blood loss	Blood transfusion
Urban/rural	Blood transfusion	Days of ICU stay
Addiction	Intravenous fluids	Day 1 hemoglobin
Economic status	Splenectomy	Day 1 albumin
Symptoms (dysphagia, weight loss)	Total operative time	FJ feeds
Performance status		Parenteral nutrition
Hemoglobin		Day of start of oral liquids
Serum albumin		Anastomotic leak
Neutrophils		Conduit necrosis
Length of hospital stay		Recurrent laryngeal nerve palsy
Blood transfusion		Pulmonary complications
Endoscopic level of lesion		Arrythmia
Comorbidities		Sepsis
ASA score		Wound infection
BMI		Chylothorax
GEJ involvement		Final stage
Histopathological grade		T stage
Neoadjuvant therapy		N stage
		Total nodes extracted
		Number of nodes positive
		Ratio of positive nodes to extracted nodes
		CRM status
		LVSI/PNI

ASA, American Society of Anesthesiologists physical status score; BMI, body mass index; CRM, circumferential radial margin; FJ, feeding jejunostomy; GEJ, gastroesophageal junction; ICU, intensive care unit; LVSI, lymphovascular invasion; PNI, perineural invasion

Table 2 Assessment of patient demographics and comorbidities

Patient demographics and comorbidities		Group		Chi-squared	*p* value
		Case	Control		
Gender	Male	18	364	0.006	0.939
	Female	16	315		
Origin	Urban	15	203	3.085	0.079
	Rural	19	476		
Addiction	Present	19	287	2.45	0.118
	Absent	15	392		
Economic status	High	26	343	8.736	0.003
	Low	8	336		
Diabetes	Yes	10	77	9.87	0.002
	None	24	602		
Hypertension	Yes	10	112	3.809	0.051
	None	24	567		
Cardiac disease	Yes	13	84	18.428	0.0001
	None	21	595		
ASA score	*1,2*	14	455	9.6	0.002
	3,4	20	224		

injury to spleen leading to splenectomy were strongly associated with mortality. THE was the most commonly performed procedure (61.57%), and none of the surgical procedures were independently associated with increased mortality (Table 3).

Preoperative pulmonary function evaluation showed that patients with poor FEV1 had high risk of mortality whereas none of the preoperative biochemical parameters, i.e., hemoglobin, neutrophil count, or serum albumin levels, were associated with mortality. Increased preoperative length of stay was associated with greater mortality; however, even though total operative time was more for mortality group (mean 203.82 min vs 186.08 min for control group), it did not reach statistical significance ($p = 0.071$). Neither preoperative hemoglobin nor preoperative blood transfusion was associated with mortality. However, intraoperative blood loss (mean = 652.94 ml for mortality group) and intraoperative and postoperative blood and excess intravenous fluid transfusion with low postoperative day (POD) 1 serum albumin levels (less

Table 3 Treatment given and pathological parameters assessed (THE–transhiatal esophagectomy)

Treatment given and pathological parameters		Group		Chi-squared	*p* value
		Case	Control		
Level of lesion	Middle 1/3	23	427	0.315	0.575
	Lower 1/3	11	252		
Type of surgery	McKeown	10	133	2.007	0.367
	THE	19	420		
	Hybrid McKeown	5	126		
GEJ involved	Yes	10	322	4.221	0.04
	No	24	357		
Splenectomy	Yes	5	7	36.592	0.0001
	No	29	672		
Stage	I	4	112	0.534	0.766
	II	11	210		
	III	19	357		
T Stage	0,1,2	10	224	0.188	0.665
	3.4	24	455		
N stage	0,1	24	511	0.377	0.539
	2,3	10	168		
Neoadjuvant treatment	Yes	1	77	2.344	0.126
	No	33	602		

than 2.38 mg/dl, SD = 0.551, $p = 0.0001$) were independently associated with higher mortality.

The mortality group had higher number of positive nodes than the control group (2.97 versus 1.82, $p = 0.13$). Nevertheless, the mean number of lymph nodes extracted remained similar in both groups (12.03 versus 12.59). Although the ratio of positive lymph nodes to the total nodes extracted was higher in mortality group (23.56 versus 16.66), it did not reach statistical significance.

Ventilatory requirements were not only higher (though not significant) in the mortality group but they also had significantly prolonged ICU stay (both primary ICU and step down ICU) (7.32 days versus 6.29 days, $p = 0.036$) compared to the control group. There was small but statistically significant difference in the timing of resumption of oral liquids between the two groups (5.56 versus 6.38 days, $p = 0.007$) (Table 4). Postoperative lower respiratory tract infection was the most common complication (38.84%) followed by anastomotic leak (11.92%), wound infection (8.8%), and arrhythmia (7.8%) in that order. We had only one case of conduit necrosis that was managed conservatively due to localized necrosis. Unfortunately, the patient succumbed to pulmonary thrombo-embolism despite being on prophylactic anticoagulation. Rate of RLN palsy was exceptionally low

Table 4 Clinical, biochemical, and pathological assessment

Clinical/biochemical/pathological characteristics		N	Mean	Standard deviation	*p* value
Age	Case	34	58.53	8.035	.010
	Control	679	53.96	10.126	
FEVI %	Case	34	69.56	16.059	.036
	Control	679	77.25	20.988	
Preoperative hemoglobin	Case	34	12.79	2.115	.999
	Control	679	12.79	2.480	
Preoperative neutrophils	Case	34	6.53	2.501	.195
	Control	679	6.06	2.026	
Preoperative serum albumin	Case	34	3.94	.422	.348
	Control	679	4.01	.419	
Preoperative length of hospital stay (days)	Case	34	16.94	9.059	.001
	Control	679	13.07	6.271	
Operative time (minutes)	Case	34	203.82	67.913	.071
	Control	679	186.08	55.086	
Intraoperative blood loss (ml)	Case	34	652.94	257.300	.003
	Control	679	552.58	186.582	
Preoperative blood transfusion	Case	34	.29	1.088	.930
	Control	679	.28	1.013	
Intraoperative blood transfusion	Case	34	.88	1.200	.015
	Control	679	.57	.703	
Postoperative blood transfusion	Case	34	.82	1.193	0.0001
	Control	679	.30	.612	
Postoperative day 1 hemoglobin	Case	34	11.32	2.319	.332
	Control	679	11.63	1.762	
Intraoperative fluids	Case	31	6.06	2.421	.003
	Control	546	5.26	1.410	
Postoperative day 1 albumin	Case	34	2.38	.551	0.0001
	Control	679	2.84	.512	
Total lymph nodes	Case	34	12.03	3.927	.685
	Control	679	12.59	7.981	
Positive lymph nodes	Case	34	2.97	4.196	.013
	Control	679	1.82	2.522	
Ratio of positive to total lymph nodes	Case	34	23.56	30.151	.088
	Control	679	16.66	22.585	
Day of extubation	Case	34	2.18	3.919	.067
	Control	679	1.49	1.981	
Number of ICU stay days	Case	34	7.32	6.285	.036
	Control	679	6.29	2.522	
Oral diet start day	Case	34	5.56	3.145	.007
	Control	679	6.38	1.622	

FEV1, forced expiratory volume in 1st second,; ICU, intensive care unit

($n = 9$, 1.2%, 1 permanent and 8 temporary). Except for chylothorax (3%), wound infection and anastomotic leak of the other described complications significantly contributed to mortality (Table 5).

After applying multiple regression analysis for every death-splenectomy and GEJ involvement, the odds ratio increased by 29.372 and 0.313 respectively. The Cox and Snell R^2 and Nagelkerke R^2 explains between 3.3% and 10.2% of the variance of all the above variables for death.

Discussion

A great man of science, Claude Bernard once said "We must study cases of death with great care and try to discover in them the cause of mortal accidents so as to master the cause and avoid the accidents." Aligning with this principle, we have analyzed multiple variables including preoperative, intraoperative, and postoperative parameters. The prime purpose of the study was to clearly define our areas of concern in the group of patients who succumbed after esophageal resection.

Old age has been traditionally attributed to higher rates of complication following major surgeries. Our study population was slightly younger compared to other studies with mean age 56.2 years. Older patients in our cohort (mean = 58.53 years) had significantly higher rate of mortality [2].

We noted higher rate of mortality in patients of higher economic status. Other factors causing mortality in higher economic status group would be increased rates of GE junction tumors, obesity, and comorbidities like diabetes and hypertension.

Diabetes, cardiovascular disease, sub-optimal pulmonary reserve (FEV1 < 69.5%), and ASA more than 2 significantly contributed to mortality. Similar results were obtained in the study by Abunasra et al. in which multivariate analysis identified age, FEV1, and diabetes as independent predictors of death [4]. However in contrast to above, the population-based study by Backemar M.D. et al. showed no increased risk for mortality in patients with more than 2 comorbidities [5].

Multivariate analysis adjusted for other confounding factors showed that involvement of GEJ by tumor (both by squamous cell carcinoma of lower esophagus extending into GEJ and Siewert's type I and II) was associated with increased mortality in contrast to Abunasra et al. in which upper third esophageal tumors had increased mortality. However, the authors realized that only 2.5% (as against 46.5% in our study) of the study population contributed to this finding and was not representative of the entire study population [4]. None of the pathologic staging parameters except positive nodes (> 2.9)

Table 5 Assessment of postoperative complications following esophagectomy

Complications		Group		Chi-squared value	*p* value
		Case	Control		
Chylothorax	Yes	1 (4.5%)	21 (95.5%)	0.002	0.96
	No	33 (4.8%)	658 (95.2%)		
Conduit necrosis	Yes	1 (100.0%)	0 (0%)	19.999	0.0001
	No	33 (4.6%)	679 (95.4%)		
RLN palsy	Yes	2 (22.2%	7 (77.8%)	6.115	*0.013*
	No	32 (4.5%)	672 (95.5%)		
Pulmonary TE	Yes	5 (41.7%)	7 (58.3%)	36.592	0.0001
	No	29 (4.1%0	672 (95.950		
MODS	Yes	2 (100.0%)	0 (0.0%)	40.054	0.0001
	No	32 (4.5%)	679 (95.5%)		
Postop LRTI	Yes	25 (9.0%)	252 (91.0%)	18.074	0.0001
	No	9 (2.1%)	427 (97.9%)		
Wound infection	Yes	0 (0.0%)	63 (100.0%)	3.64	0.063
	No	34 (5.2%)	616,994.8%)		
Postop arrhythmias	Yes	7 (12.5%)	49 (87.5%)	7.999	0.005
	No	27 (4.1%)	630 (95.9%)		
Postop sepsis	Yes	9 (39.1%)	14 (60.9%)	61.795	0.0001
	No	25 (3.6%)	665 (96.4%)		
Postop ARDS	Yes	3 (30.0%)	7 (70.0%)	14.218	0.0001
	No	31 94.45)	672 (95.6%)		
Anastomotic leak	Yes	1(1.2%)	84(98.8%)	2.742	0.098
	No	33 (5.3%)	595(94.7)		

ARDS, acute respiratory distress syndrome; LRTI, lower respiratory tract infection; MODS, multiple organ dysfunction syndrome; RLN, recurrent laryngeal nerve; TE, thromboembolism

and perineural invasion were associated with increased mortality.

Increased blood loss during surgery was a major factor for need for more crystalloid and blood transfusions (intra and postoperatively) both of which predicted increased postoperative mortality. 52.7% of our total study population and 55.7% of those who succumbed to surgery had stage III disease where tumor resections were more aggressive and required splenectomy (1.6%). This further aggravated morbidity and mortality rates. Simon Law et al. and other authors too documented similar findings and deduced that reduction in mortality rate correlated well with decreased blood loss and judicious perioperative fluid management [2, 6–8].

Ryan et al. emphasized postoperative day 1 serum albumin < 2 g/dl as a better predictor of adverse surgical outcomes than many other preoperative risk factors. We found POD 1 serum albumin levels < 2.38 g/dl significantly associated with perioperative mortality probably due to increased intraoperative blood loss. Even though levels more than 2.8 g/dl did serve as a protective factor for perioperative mortality, its role in decreasing morbidity due to other complications would require further subgroup analysis from our database [9].

Pulmonary and other resultant (sepsis, ARDS, MODS) complications have been recognized as the main culprit for perioperative mortality and morbidity in many contemporary studies [10]. Incidence of LRTI was 38.8% in our study which eventually significantly contributed to mortality in 73.5% of perioperative deaths. Arrhythmia and sepsis were other factors that proved to be strongly related to perioperative mortality. The incidence of RLN palsy (1.2%) was impressively low in our study owing to extensive experience in neck dissection at our center where we prefer neck anastomosis as a safer alternative.

The strength of our study is that at present it is the only study in Indian subcontinent comprehensively evaluating perioperative clinical and biochemical factors related to 30-day mortality in esophageal cancer in a large group of patients in the same time frame. This can serve as benchmark for future prospective studies in this subcontinent.

The pitfalls of our study were that it is a retrospective study with less number of patients in the neoadjuvant treatment group, exclusion of length of tumor in the analysis and absence of enhanced recovery after surgery (ERAS) program for esophageal surgeries at our institute. We do not perform 3 field lymphadenectomy at our institution and hence could not perform comparative analysis with the standard 2 field lymphadenectomy done at our center. However, we eagerly await the results of a similar trial being conducted at another contemporary cancer center catering to a similar population (NCT00193817). We also intend to standardize our data collection from year 2018 as per the definitions set by "The Esophageal Complications Consensus Group" [3].

Conclusions

Perioperative mortality after esophagectomy is a crucial part of quality assessment for hospitals. Given the fact that ours is a high-volume institute catering to a large population of south, east, and northeast India especially West Bengal, Bihar, Uttar Pradesh, and Assam, we need to define our own problems and develop solutions for the same. In a resource-limited country like ours, we need to reassess the current guidelines for perioperative management of esophageal cancer to suitably adapt to our setting. This retrospective study has laid the foundation to recognize our pitfalls and areas of concern while providing an impetus for more organized management of esophageal cancer.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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