ORIGINAL ARTICLE

Comparison of Two and Three Stage Esophagectomies for Esophageal Carcinoma: Early Results in A High Output Center

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ABSTRACT

Objective: Despite the advancements inmanagement and surgical expertise, esophageal cancer continues to be the sixth most common cause of cancer related deaths. The aim of study was to compare various variables of Two-stage and Three-stage esophagectomies leading to the morbidity and mortality.
Methodology: A retrospective cross-sectional study was conducted in Thoracic Surgery Department, JPMC, Karachi from 2019-2021. All resectable and operatable tumors were included. Data was retrieved from a pre-formed data sheet and was analyzed using SPSS-22.
Result: A total of 114 patients were included in this study, with 66(57.9%) males. Mean age of presentation was 45.25±15.32 years. Squamous cell carcinoma was encountered in 75 patients (65.8%). The most common location of tumor was lower thoracic esophagus (LTE) seen in 66 patients (57.9%) Ivor Lewis esophagectomy (2 stage) was performed in 69(60.5%) patients, whereas McKeown (three stage) was conducted in 45(39.5%). Tumor free margins were seen in 111(97.4%). Longer duration (5hrs) of surgery was 62.7% found in McKeown esophagectomy. Total 30-day mortality was 7.9% (9/114), with respiratory failure as the most common cause. Overall mortality was 7% (8/114), predominant in two stage esophagectomy. However, major complications such as anastomotic leak 5.26% (6/114) and early stenosis 29.8% (34/114) were noted in Three stage surgery.
Conclusion: Despite smaller duration of surgery, technical feasibility and low morbidity, two staged esophagectomy bears comparable mortality as compared to the three staged esophagectomy. However, both procedures are relatively safe and effective provided accurate indications, patient selection and technical expertise.

Keywords: Anastomotic leak, esophageal carcinoma, ivor lewis esophagectomy, McKeown esophagectomy, squamous cell, stricture

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INTRODUCTION

Esophageal carcinoma (EC), previously the eight most common cancer, has escalated to become the seventh most frequently encountered tumor worldwide. Squamous cell carcinoma of esophagus (SCCE) and adenocarcinoma of esophagus (ACE) are the prominent subtypes[1-5]. Rare malignant variant includes leiomyosarcoma which can be encountered in 0.1-0.5% of patients[6,7]. Majority of EC are reported to affect people during the 5th to 7th decade of their lives[3,7]. Males have two to four folds chances of developing EC with the ratio further worsening with histological subtypes[3].

SCCE remains the most common subtype that predominates Asian and developing countries[1,5]. ACE, on the other hand, is seen more in USA and European countries. The histological subtypes are seen to affect particular segments of the esophagus[1,3,5]. SCCE has propensity to develop in the proximal and middle thoracic esophagus , whereas ACE is found in the distal esophagus[1,3,5]. Risk factors play a vital role in the development of EC. Smoking , alcohol, hot beverages, betel nuts, diet deficient in vitamins and poor social status are known factors for SCCE[1,2,5]. On the contrary, gastroesophageal reflux disease (GERD), obesity and

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smoking are established risk factors for ACE[1,3,5]. Principal complaint remains progressive dysphagia followed by weight loss and regurgitation[3]. Other symptoms include chest pain that may be dull or burning in nature, odynophagia and chronic cough[3].

Literature states that pathological staging corresponds to the clinical staging in more than one fourth of the cases, which undeniably validates the role of pre-operative staging[2]. Endoscopic ultrasound (EUS), Computed tomography (CT) and Positron emission tomography (PET) are the widely used radiological investigations after endoscopic biopsy has been performed[2,3,5]. EUS holds importance in identifying the presence of regional nodes (N) along with tumor size and extent also referred as 'T'. It aids in differentiating T1-3 and permits needle aspiration of nodes. CT scan despite being able to identify esophageal wall thickness = 3mm is useful to identify stage T3 and T4 only. However, it is of prime importance for the nodal and metastic (M) staging[2,3,5]. Addition of PET scan to the CT, assists in the diagnosis of N and M but it fails to differentiate among the four T stages[2,8]. Few authors advocate that PET-CT avoids the need for unwanted and other relevant investigations if metastasis is evident[2].

Management options for patients with EC include endoscopic mucosal resection (EMR), esophagectomy with or without neoadjuvant therapy, chemoradiotherapy (CRT) or the other palliative management[1,3,4] based upon the stage of the disease. The limited diseases can be approached by EMR or esophagectomy alone whereas locally advanced diseases benefit from neoadjuvant therapy prior to the resection[1,3,4]. Esophagectomy with lymphadenectomy remains the most important modality, following neoadjuvant therapy resulting in the improvement of overall survival (OS). Pre-operative CRT or chemotherapy (cT) alone indeed have benefits including decreased positive nodes, better pathological response rate and downstaging of tumors permitting surgical maneuvers without any significant effect on the post-operative complications[1,4].

Well known procedures include Ivor Lewis Esophagectomy (ILE), McKeown Esophagectomy (ME) and transhiatal esophagectomy. Procedures can be performed via open or minimally invasive approaches with preference to the transthoracic route due to its ability to allow better lymph node dissection. Both types of surgeries have similar margin and lymph node clearance[9].

Despite the global advances in the management and surgical expertise, EC unfortunately continues to be the sixth most common cause of cancer related death[1-4]. Studies report a five-year survival rate(SR) of up to 20% with an alarming lower survival rate of less than 10% in Pakistan, China and Iran[1,3,5]. Not much work defines the early outcome in local literature strengthening the perspective of this study to review variables, neoadjuvant therapies, complications and early outcome in terms of the two most commonly performed surgeries.

METHODOLOGY

IRB/ERC Approval:

A retrospective cross-sectional study was conducted in the Department of Thoracic surgery, Jinnah Postgraduate Medical Centre Karachi from year 2019-2021 after ethical approval was obtained holding letter No. F.2-81/2022-GENL/162/JPMC.

All patients presenting with esophageal carcinoma that underwent esophagectomy were included in this study. Two types of surgeries were performed, termed as Two staged and three stage esophagectomy. Two stage esophagectomy also called ILE includes two components. First stage includes a midline laparotomy for mobilizing stomach, with preservation of right gastroepiploic artery, kockers maneuver, hiatal enlargement, ligation of short gastric vessels, gastric artery, pyloroplasty and feeding jejenostomy[10]. Second stage comprises of right posterolateral thoracotomy with mediastinal pleura dissection, esophagus mobilization, ligation of azygous vein, delivery of stomach in chest followed with conduit creation using GIA® linear staplers and removal of tumor segment. End to side esophagogastric anastomosis was performed above the level of azygous vein with the circular GIA® staplers[10].

Three staged esophagectomy also called ME had similar abdominal component with simultaneous esophagus mobilization in the neck via left oblique incision along the anterior border of sternocleidomastoid. The esophagus was slinged and wound was temporarily closed. The thoracic component was performed similar to ILE with the difference that conduit was created in the chest with closure of stomach and anchor suture were applied on the proximal esophagus to aid in pulling of the conduit into the neck[11]. Third stage was completed with end to side esophagogastric anastomosis via hand sewn technique. Regional node dissection was performed in both the procedures[10,11]. Drains included Nasogastric (NG) tube, chest tube and abdominal drains which were removed as per indication.

Data was retrieved from a pre-formed data sheet which included variables such as age, gender, BMI, risk factors, site of tumor, histological type, segment length, clinical staging, type of surgery, duration, volume of blood loss, complications, mortality, pathological

staging, neoadjuvant therapy, adjuvant chemotherapy or adjuvant chemoradiotherapy etc.

For Data analysis, SPSS version 22 was used. For descriptive data such as age, BMI, volume loss, duration of surgery etc. mean and standard deviation were calculated. For categorical variables such as gender, histological type, type of esophagectomy, neoadjuvant therapy and other frequencies and percentages were calculated. Independent sample T test was use for comparison of means. Chi square was applied for categorical variables and p value=0.05 was considered statistically significant.

RESULTS

A total of 114 patients were included in this study which included 66(57.9%) males and 48(42.1%) females. The mean age of presentation was 45.25±15.32 years (median 45.5) with BMI and weight of 22.15±2.92 Kg/m2, 51.93±8.52kg respectively. Around 23(20.1%) patients were less than 30 years of age. Common risk factors included smoking in 45 (39.1%), GERD in 32(27.8%), poor dietary habits in 25(21.7%) and alcohol consumption in 9(7.8%). Three variants of esophageal tumor were seen with squamous cell being the most common encountered in 75(65.8%). The most common location of tumor was lower thoracic esophagus (LTE) seen in 66(57.9%) patients and stomach/cardia was involved in 41(36%). Table 1 represents type of tumor and location.

In 75 patients with SCCE, most common location was middle thoracic esophagus (MTE) seen in 45(60%;p<0.001). However, in38 adenocarcinoma patients LTE was involved in 37(97.3%;p<0.001),with tumor invading cardia in 29(76.13%;p<0.001) patients. In 38 cases of adenocarcinoma, 28(73%;p<0.001) were males, whereas in SCC males and females were equally affected (n=37:49.3% and 38;50.6% respectively). Out of 32 patients having GERD, 27(84.35%;p<0.001) developed ACE, smoking was seen in both, however it was predominant in squamous cell carcinoma (37/45,p=0.003). Patients with poor dietary habits developed SCCE(21/25,p=0.03).

Pre-operatively, on basis of CT scan, the mean tumor length was 5.45±1.46 cm and to AJCC clinical staging II was most common stage seen in 53(46.5%) patients. Table 2 represent stratification according to AJCC clinical staging.

Neoadjuvant therapy was given in 101(91.8%) patients. Stage III and IVA required neoadjuvant therapy (47/51;p=0.02 and 10/10;p=0.29 respectively). In 63 patients out 75(84%; p=0.08) of SCCE, neoadjuvant was given. All patients of ACE , received neoadjuvant as part of perioperative chemotherapy.

ILE (2 stage) was performed in 69(60.5%) patients, whereas ME (three stage) was conducted in 45(39.5%). Tumor free margins were seen in 111(97.4%). Clear margins proximally were 3.5±1.19cm and distally 5.07±1.22 cm. The mean volume of blood loss was 780.2±264.53 ml and duration of surgery was 4.81±0.83 hours. Nasogastric tube was removed on 6.76±1.33 days.

Total number of nodes removed were 20.77±3.90(8-30) with mean positive 3.94±3.16(0-18). Most common pathological staging post operatively were pT2N1M0, pT3N2M0 (n= 23; 20.2% each) followed by pT2N2M0 (n=20;17.5%) and pT3N1M0(n16;14%). Other incidental findings included splenectomy 5(4.4%) and carcinoid tumor in 2(1.75%).

Mortality within 30 days was seen in 9(7.9%) due to respiratory failure(RF) in 6(5.3%) and acute myocardial infarction(AMI) secondary to arrhythmias in 3(2.6%). Both AMI and RF were common in ILE (n=2/3; 4/6 respectively). The mean and median age among mortality group was 66.5±4.56 and 65.5 years respectively. Complications included stenosis in 39(34.2%) out of which 32(82.05%; p<0.001) required dilation. Hoarseness in 11(9.64%) and anastomotic leak (AL) encountered in 7(6.1%) patients, which was managed conservatively. Five (71.4%; p=0.03) of AL later on developed stenosis.

Adjuvant therapy was given in 75(65.7%) where chemotherapy alone was given in 38(50.6%) and chemoradiotherapy (CRT) in 37(49.3%) patients. Node positive patients required both chemotherapy and CRT (p=0.01,p=0.007 respectively). Table 3 compares the various factors and outcomes of two stage vs three stage esophagectomies.

Table 1: Histological type and location of tumor

A	**Histological type**	**Number(%)**
1	Squamous cell carcinoma	75(65.8%)
2	Adenocarcinoma	38(33.3%)
3	Leiomyosarcoma	1(0.9%)
B	**Location of tumor**	**Location of tumor**
1	Lower thoracic esophagus	66(57.9%)
2	Middle thoracic esophagus	47(41.2%)
3	Upper thoracic esophagus	1(0.9%)

Table 2: Stratification according to AJCC clinical staging

AJCC clinical staging	**Number(%)**
II	53(46.5%)
III	51(44.7%)
IVA	10(8.8%)

Table 3: Compares the various factors and outcomes of two stage vs three stage esophagectomies

	Variable	Two stage		Three stage		p-value
		Number	%	Number	%	
A	**Histological type**					
1	Adenocarcinoma	29/38	76.3	9/38	23.6	<0.001*
2	Squamous cell carcinoma	40/75	53.3	35/75	46.6	<0.001*
3	Leiomyosarcoma	-	-	1/1	100	<0.001*
B	**Duration of surgery**					
1	< 5 hours	50/63	79.3	13/63	20.6	<0.001*
2	= 5 hours	19/51	37.2	32/51	62.7	<0.001*
C	**Stage**					
1	Clinical stage	II=31/53	58.4	III= 26/51	50.9	0.05*
2	Advanced stage	17/35	48.5	18/35	51.4	0.08
3	pT2N1M0	20/26	76.9	6/26	23.07	0.05*
4	pT3N1M0	4/16	25	12/16	75	0.002*
5	Positive margins	3/3	100	0	-	0.15
D	**Morbidity and Mortality**					
1	Expired in 30 days	8/9	88.8	1/9	11.1	0.07
2	Hoarseness	2/11	18.18	9/11	81.8	0.03*
3	Leak	1/7	14.2	6/7	85.71	0.01*
4	Stenosis	5/39	12.8	34/39	87.17	0.001*

NG= Nasogastric tube, p=pathological, *=significant p values

DISCUSSION

Esophageal carcinoma continues to remain among the ten most common cancers affecting human beings[1,4,5,11]. Around 17'000 to 570,000 cases per year are being reported across different regions of the world[1,2]. Incidence rate in Iran, China and Africa is 50 to 100 cases per 100,000 each year, whereas a lower rate of 5 to 10 cases is encountered in Western nations[12]. A recent ten-year retrospective study in Karachi, Pakistan reported 1009 new cases diagnosed with EC[3]. We report here 114 cases that underwent surgery during the course of our study.

In our study, more than half were males which are consistent with the literature[5,12,13]. Furthermore, studies suggest that males are at two-fold risk for SCCE compared to females. However, our study had an equal ratio. The risk for males in ACE ranges up to 1.7 to 8 times[2,5,12-14]. We report 2/3rd of the ACE patients as males. EC commonly tends to affect people at fifty years or above. We encountered mean age group of 45.25±15.32 years[3,7]. Dawsey et al, reported 1-6% of patients being less than 30 years of age which was alarmingly high at 20.1% in our study[12]. Hence, it is not only the disease of the elderly but it can affect young as well.

We saw SCCE as the most common subtype with majority located in MTE (n=45,p<0.001) followed by LTE(28;37.3%). Previous studies stated middle followed by proximal esophagus as sites for SCCE whereas a recent study in USA correlated to our study[13]. Smoking and poor dietary habits promote malignant squamous cell formation and we saw a similar pattern (p=0.003 and p=0.03 respectively). ACE continues to be found in LTE similar to our study (p<0.001). GERD, an established risk factors for ACE, was significant in our cases as well (p<0.001)[1,3,5,14,15]. Studies previously have supported MTE as a commonest location for EC, contrary to our study that reports LTE in 57.9%[13]. A recent study conducted in USA reported LTE as most common location with ACE being predominant histological type[14]. In our study 56% (n=37) of LTE were ACE whereas remaining were SCCE.

Leiomyosarcoma a rare smooth muscle tumor of esophagus affects patient after fourth decade of their life. It develops in MTE and LTE with a slow growth rate. Wide resection with lymph node resection remains the main modality[6,7]. Adjuvant radiotherapy may locally control the disease. Only 165 cases have been reported till date and we came across a single case with similar findings as mentioned[6].

Transthoracic resection of esophagus with lymph node clearance remains the procedure of choice[9,16-18]. Lymph node dissection holds a pivotal importance in the overall survival[18]. Two field nodal resection is adequate for nodal clearance. In our study a mean of 20.77±3.90 nodes were removed which is comparable to the literature[19].

Transthoracic approaches include ME and ILE. ME is associated with higher morbidity but low mortality as compared to ILE. Morbidities include AL, hoarseness, stenosis, longer duration of surgery, blood loss[9,20]. In our study hoarseness, AL and stenosis were predominantly seen in ME (p=0.03;0.01;<0.001 respectively). In ME group 13.3% (n=6/45) suffered AL similar to literature[20]. For ILE, leak rates range from 4-15%, we found a lower rate of 1.4%(n=1/69). As per our study, 85% of the overall AL belonged to ME[21]. Hoarseness is attributed to RLN injury due to the cervical esophagus mobilization. We saw 81.8% of the total hoarseness in ME vs ILE.

The duration of surgery seen in ME is prolonged,[9,19,22] owing to an additional step of the neck dissection. Operative mortality within 30 days' ranges from 0 to 4.5%[16,19,23], which was found to be 7.9%(n=9/114) in our study. Pulmonary complication and AMI remained the prominent factors in our study. Pulmonary complications leading to death developed in 5.26 % in our study and were more prevalent in ILE than ME. Andrew M et al, stated pulmonary complications of 12%, 18% in ME and ILE respectively[19,20]. We saw 2/3rd of the pulmonary complications leading to mortality in ILE. A meta-analysis by Theochari et al, showed 1.9% of patients developing AMI after esophagectomy[24]. We found 2.6%(n=3/114) patients suffering a fatal myocardial infarction mainly in ILE.

Neoadjuvant approach should be considered as a standard treatment of patients with locally advanced and operable EC. Preoperative CRT significantly increases the pathologic complete response (pCR) rate, ranging from 18% to 43% which is an independent favorable prognostic factor for survival and for locoregional and systemic recurrences[4]. In our study, of the total 101 patients who received neoadjuvant therapy, highest number of the recipients belonged to the stage III i.e. 46.5%. As reported by a Watanabe M, neoadjuvant chemotherapy is currently a standard treatment for Stage II/III SCC in Japan[25]. Similarly, 86.6% of our patients having SCC were given the neoadjuvant treatment before surgery.

CONCLUSION

It was a retrospective high output center study conducted to compare the attributable factors affecting two and three staged esophagectomies in terms of morbidity and mortality. All patients included, were managed as a multimodality approach based upon the type and stage of the disease. The standard practice consisted of clinical staging followed by suitable neoadjuvant therapy and further surgical resection. The variables contributing to the outcomes in terms of respective complications and later death within thirty days were studied. Three staged esophagectomy thus found to be safer for better clearance margins and negligible deaths. On the other hand, two stage esophagectomy without possessing significant risks of stenosis, hoarseness and anastomotic leak, was associated with early mortality mainly due to cardiac and respiratory failure. However, much work still needs to be done locally to enhance timely surgical referrals and incorporate effective screening methods providing optimum chances of survival to the patients.

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