

Surgical management of esophageal cancer: Experience of the National Cancer Institute, Egypt

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Abstract: Objective: This study demonstrated the experience of the National Cancer Institute, Cairo University with esophageal cancer over a period of 7 years. **Methods:** This retrospective chart review included all patients diagnosed as esophageal cancer and had surgery at the National Cancer Institute (NCI) in the period from 2009-2015. **Results:** During the study period, 275 patients were diagnosed as esophageal cancer fulfilling the inclusion criteria. Squamous cell carcinoma (SCC) accounted for 61% of cases. Males were more commonly affected than females (1.5:1). Near half of the cases presented with locally advanced disease, while 16.7% of patients had metastatic deposits on presentation. Direct surgical exploration was done for 96 patients (34.9%), as 66 patients (24%) were referred to receive neoadjuvant therapy; 17 of them showed regressive course and referred for surgical resection. After surgical exploration, 84 patients had surgical resection. Transthoracic approach was done 10 about 60% of cases. Postoperative morbidities were recorded in 55 patients (65.5%) and in-hospital mortality in 17 patients (20.2%). Common surgical complications recorded were anastomotic leakage and massive intraoperative blood loss. Twenty five patients (29.8%) developed postoperative pneumonia; 10 of them died in-hospital. The cumulative overall survival was 56.7%. Postoperative morbidity, lymph node involvement, and inadequate lymphadenectomy were the independent factors affecting survival. **Conclusion:** Surgical resection of esophageal cancer was possible in only 30% of cases. Postoperative complications and mortalities are rather high. Overall survival is low and unacceptable. Improvement of management modalities and early diagnosis are the required for better outcome in this high-volume hospital.

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1. Introduction:

Worldwide, esophageal cancer (EC) is the eighth most common incident cancer and the sixth most common cause of cancer deaths. More than 80% of cases and deaths are reported in developing countries.[1] It is a serious malignancy with highly aggressive nature and poor survival outcome.[2] In Egypt, EC constituted 1.2% of all cancer cases among males and 0.8% of all cancer cases among females.[3]

Esophageal cancer encompasses two pathologically distinct diseases; squamous cell carcinoma (SCC) and adenocarcinoma (ADC). The two diseases have different risk factors and incidence rates.[4] Squamous cell carcinoma accounts for 70% of cases of EC globally.[5] Patients with EC cancer usually present late in a relatively locally advanced or even metastatic stage due to the muscular and expansive nature of the esophagus. Therefore, endoscopy is the mainstay of evaluation of these cases.[6] Computed tomography (CT) is another imaging modality that can be used for detection and staging of EC.[7]

Management of EC depends on characteristics of the patient and tumor. Surgical resection,

chemotherapy, chemoradiotherapy, or combinations of these modalities can be used for treatment EC.[5] Surgery can be performed for Tis, T1 and some T2 stages.[8] It is debatable if neoadjuvant chemoradiotherapy may be offered for T2 EC cancer.[9] There are several alternative approaches for esophagectomy. The main two techniques are the transhiatal esophagectomy (THE) and transthoracic esophagectomy.[10]

This retrospective review demonstrated the experience of the National Cancer Institute, Cairo University; a major tertiary hospital in Egypt, with esophageal cancer over a period of 7 years.

2. Patients and Methods:

This study showed a retrospective chart review of all patients who were diagnosed as esophageal cancer and had surgery at the National Cancer Institute (NCI) in the period from 2009-2015.

On the basis of computed tomography (CT), it was decided whether the case is early-stage (resectable) disease or locally advanced (T3-4). The CT findings of the latter cases showed doubtful plane of tumor with the adjacent organ, definite evidence of

adjacent organ invasion, bulky mediastinal nodes, or excisable coeliac nodes. Locally advanced cases underwent various treatment modalities: chemotherapy (CTH), radiation therapy (RTH), or neoadjuvant chemoradiation before surgery. The decision was dependent on the treating oncologist. Three weeks after completion of neoadjuvant treatment, patients were reassessed with chest CT and if responsive, they were surgically operated upon.

Patients with obvious T4 lesion and no response to preoperative treatment, patients with tracheo-esophageal fistula, and those with stage IVb disease were excluded. Surgical approach also varied, but a 5-cm tumor-free margin was always attempted to achieve. Both the transhiatal (THE) and transthoracic (TTE) approaches were used. In the last 2 years, we always performed two-incision right TTE (Ivor-Lewis) or three-incision right TTE (McKeon) esophagectomy. Nodal dissection varied from simple sampling to standard two-field (2-FD) or, in more recent years, three-field (3-FD) lymphadenectomy. Patients with microscopic residual tumor (R1), or macroscopic residual (R2) received postoperative chemoradiation. Some patients after curative R0 resection also received chemotherapy. The median follow up period was 12 months (range: 5-84 months).

Data of the patients were collected from their medical records at the Epidemiology and Biostatistics and Pathology Departments. These data included patients' demographics, presenting complaint, preoperative diagnosis (endoscopy and pathology reports), and preoperative staging with CT scan. Treatment details were collected including neoadjuvant therapy, operative details, and adjuvant treatment. Postoperative management details were recorded including ICU and hospital stay, complications, and in-hospital mortality. Pathological reports were recorded with determination of pathological subtype, grade, site, resection margin, extent of lymphadenectomy, and TNM and overall stage. Overall survival was calculated from the date of diagnosis to date of death or last follow up visit.

Statistical Analysis

Statistical analysis was done using IBM® SPSS® Statistics version 23 (IBM® Corp., Armonk, NY, USA). Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done using independent sample t-test or Mann-Whitney test. Comparison between 3 groups was done using ANOVA test, then post-Hoc "Scheffe test" was used for pair-wise comparison. Comparison between 3 groups was done using Kruskal-Wallis test (non-parametric ANOVA). Survival analysis was done using Kaplan-Meier method and comparison between two survival curves was done using log-rank test.

Multivariate analysis was done using Cox-regression method for the significant factors affecting survival on univariate analysis. A p-value < 0.05 was considered significant.

3. Results:

During the study period, 275 patients with esophageal cancer were diagnosed and treated in the NCI fulfilling the inclusion criteria. Squamous cell carcinoma (SCC) accounted for 61% of cases while adenocarcinoma (ADC) was diagnosed in the remaining 39% (ratio: 1.57:1). The majority of patients were above the age of 50 years with no significant difference between SCC and ADC ($p = 0.503$). Males were more commonly affected (61.1%) compared to females with a ratio of 1.5:1. This sex disparity was much more obvious in ADC (2.5:1) than in SCC (1.3:1) ($p=0.014$). Adenocarcinoma was significantly more common in rural areas ($p = 0.015$).

The lower third of esophagus harbored almost half of the lesions. Squamous cell carcinoma was detected over the entire length of the esophagus, while ADC occurred mainly in lower third and GEJ, and only 8.3% occur in middle third with no lesion in upper third ($p<0.001$). Near half of the cases presented with locally advanced disease, while 16.7% of patients had metastatic deposits on presentation. Fewer cases of SCC were metastatic at presentation compared to ADC (12.8% vs. 23.9%, respectively), but the difference was not statistically significant ($p = 0.070$) (Table 1). Lesions in the upper third were locally advanced in 81.8% of cases, and rarely metastatic (single patient). Metastasis was more common in the other sites ($p < 0.001$) (Table 2).

The most common presentation was dysphagia (84%) followed by vomiting (8%). Other symptoms included hematemesis and epigastric pain in lower third and GEJ lesions, and weight loss in middle third lesions, and hoarseness of voice in upper third lesions. The mean duration of complaint in the upper, middle, lower third and GEJ lesions were 4.5, 4.3, 4.8, 7.8 months, respectively.

On endoscopy, the majority of lesions appeared as fungating-polypoidal masses with no significant difference between ADC and SCC cases ($p=0.252$). There was no significant difference between SCC and ADC lesions regarding appearance on CT ($p=0.307$). No regional lymphadenopathy was observed in 56.8% of ADC cases and 68.4% of SCC cases ($p=0.162$) (Table 3).

Management

About 71% of the patients were in a good general condition, while 29% were referred to palliative therapy regardless of their intended plan of management. The medical condition or the tumor burden of these patients interfered with the intended

plan of management (surgery). A higher proportion of ADC patients were fit for definitive treatment compared to SCC patients ($p=0.031$). Patients with metastatic disease were unfit for treatment in 40% of

cases ($p = 0.020$). Patients with middle third lesions were unfit for treatment in 41.1% of cases compared to 9.1% of those with lesions of the GEJ ($p=0.016$).

Table 1: Epidemiology of esophageal cancer cases presented to the NCI between 2009 and 2015

	Total n=275	SCC n=187	ADC n=88	p value
Age				
< 50 years	65 (23.6%)	48 (25.7%)	17 (19.3%)	0.503
50-70 years	170 (61.8%)	112 (59.9%)	58 (65.9%)	
> 70 years	40 (14.5%)	27 (14.4%)	13 (14.8%)	
Sex				
Male	168 (61.1%)	105 (56.1%)	63 (71.6%)	0.014
Female	107 (38.9%)	82 (43.9%)	25 (28.4%)	
Social Level				
Urban	133 (48.4%)	81 (43.3%)	52 (59.1%)	0.015
Rural	142 (51.6%)	106 (56.7%)	35 (39.8%)	
Site				
Upper third	44 (16.0%)	44 (23.5%)	0 (0.0%)	
Middle third	73 (26.5%)	66 (35.3%)	6 (6.8%)	< 0.001
Lower third	136 (49.5%)	74 (39.6%)	61 (69.3%)	
Gastroesophageal junction	22 (8.0%)	2 (1.1%)	20 (22.7%)	
Stage				
Early	88 (32.0%)	62 (33.2%)	26 (29.5%)	0.070
Locally Advanced	142 (51.6%)	101 (54.0%)	41 (46.6%)	
Metastatic	45 (16.4%)	24 (12.8%)	21 (23.9%)	

SCC: Squamous cell carcinoma, ADC: Adenocarcinoma

Table 2: Relation between disease site and stage of esophageal cancer cases presenting to the NCI between 2009 and 2015

	Early	Locally Advanced	Metastatic
Upper third	7 (15.9%)	36 (81.8%)	1 (2.3%)
Middle third	29 (39.7%)	31 (42.5%)	13 (17.8%)
Lower third	48 (35.3%)	62 (45.6%)	26 (19.1%)
Gastroesophageal junction	4 (18.2%)	13 (59.1%)	5 (22.7%)

Table 3: Diagnostic and staging modalities of esophageal cancer patients presenting to the NCI between 2009 and 2015

	Total n=275	SCC n=187	ADC n=88	p value
Endoscopy				
Fungating	134 (48.7%)	84 (44.9%)	50 (56.8%)	
Nodular	48 (17.5%)	36 (19.3%)	12 (13.6%)	0.252
Ulceration	66 (24.0%)	46 (24.6%)	20 (22.7%)	
Stricture	27 (9.8%)	21 (11.2%)	6 (6.8%)	
CT Scan				
CMT	147 (53.5%)	104 (55.6%)	43 (48.9%)	
STM	86 (31.3%)	52 (27.8%)	34 (38.6%)	0.307
Stricture	6 (2.2%)	4 (2.1%)	2 (2.3%)	
Free	36 (13.1%)	27 (14.4%)	9 (10.2%)	
T Stage				
Clear surrounding planes	150 (54.5%)	101 (54.0%)	49 (55.7%)	
Invading surroundings	125 (45.5%)	86 (46.0%)	39 (44.3%)	0.795
N Stage				
Single	14 (5.1%)	9 (4.8%)	5 (5.7%)	
Multiple	83 (30.2%)	50 (26.7%)	33 (37.5%)	0.162
No regional lymphadenopathy	178 (64.7%)	128 (68.4%)	50 (56.8%)	
M Stage				
No Metastases	230 (83.6%)	163 (87.2%)	67 (76.1%)	
Metastases	45 (16.4%)	24 (12.8%)	21 (23.9%)	
Pulmonary	15 (5.5%)	8 (4.3%)	7 (8.0%)	
Hepatic	23 (8.4%)	13 (7.0%)	10 (11.4%)	0.102
Both	7 (2.5%)	3 (1.6%)	4 (4.5%)	

SCC: Squamous cell carcinoma, ADC: Adenocarcinoma, CMT: Circumferential mural thickening, STM: soft tissue mass

Table 3: Fitness for definitive treatment of Esophageal Cancer patients presenting to the NCI between 2009 and 2015

	Fit for treatment n=195	Unfit for treatment n=80	p value
Pathology			
Adenocarcinoma	70 (79.5%)	18 (20.5%)	0.031
Squamous cell carcinoma	125 (66.8%)	62 (33.2%)	
Stage			
Early	57 (64.8%)	31 (35.2%)	0.020
Advanced	111 (78.2%)	31 (35.2%)	
Metastatic	27 (60.0%)	18 (40.0%)	
Site			
Upper third	34 (77.3%)	10 (22.7%)	0.016
Middle third	43 (58.9%)	30 (41.1%)	
Lower third	98 (72.1%)	38 (27.9%)	
Gastroesophageal junction	20 (90.9%)	2 (9.1%)	

Table 4: Management modalities of esophageal cancer patients presenting to the NCI between 2009 and 2015

	Neoadjuvant n=66	Surgery n=96	Definitive Chemo/Radiotherapy n=38	Palliative n=75
Pathology				
ADC	22 (25.0%)	36 (40.9%)	3 (3.4%)	27 (30.7%)
SCC	44 (23.5%)	60 (32.1%)	35 (18.7%)	48 (25.7%)
Stage				
Early	6 (6.9%)	55 (63.2%)	13 (14.9%)	13 (14.9%)
Advanced	55 (37.8%)	41 (28.9%)	25 (17.6%)	21 (14.8%)
Metastatic	5 (10.9%)	0 (0.0%)	0 (0.0%)	41 (89.1%)
Site				
Upper third	8 (18.2%)	9 (20.5%)	24 (54.5%)	3 (6.8%)
Middle third	21 (28.8%)	18 (24.7%)	10 (13.7%)	24 (32.9%)
Lower third	29 (21.3%)	59 (43.4%)	4 (2.9%)	44 (32.4%)
GEJ	8 (36.4%)	10 (45.5%)	0 (0.0%)	4 (18.2%)

SCC: Squamous cell carcinoma, ADC: Adenocarcinoma, GEJ: Gastroesophageal Junction

Surgical exploration without any prior therapy was done for 96 patients (34.9%), while 66 patients (24%) were referred to receive neoadjuvant therapy. Definitive chemo/radiotherapy was given to 38 patients (13.8%) either because of poor performance status, site and stage of tumor, or desire of the patients. Some patients declined surgery to avoid functional disturbance after such operation. Of those who received neoadjuvant therapy, 17/66 patients (25.7%) showed regressive course and referred for surgical resection. Best supportive care and palliative therapy was given to 75 patients (27.2%). After surgical exploration, 29/113 patients (25.7%) turned out to be inoperable. Therefore, surgical resection was done for 84 patients.

Surgical Procedures

All upper third lesions were treated with total pharyngolaryngectomy (TPL) with gastric pull-up and tracheostomy (Table 5). Transthoracic approach was more lengthy in duration than the other approaches ($p = 0.032$). Adequate proximal margin was achieved in significantly higher proportion of trans-hiatal approaches ($p = 0.002$). Adequate distal margin was achieved in significantly higher proportion of TPL approaches ($p = 0.031$). Adequate Lymphadenectomy

was significantly more in TPL approach but the difference was not statistically significant ($p = 0.082$).

Outcome of treatment

Postoperative morbidities were recorded in 55 patients (65.5%). These complications were respiratory ($n=29$, 34.6%), cardiovascular ($n=18$, 21.4%), surgical ($n=26$, 30.9%), and other complications ($n=13$, 15.4%). In-hospital mortality occurred in 17 patients (20.2%). Morbidities occurred more frequently in older patients but the difference was not statistically significant ($p=0.093$), also mortality did not differ by age ($p=0.131$). Also, there was no significant association of morbidities and mortalities with pre-, intra- and postoperative risk factors (Tables 6-8).

Postoperative anemia ($Hb < 10$ gm/dL) was significantly associated with higher postoperative morbidities ($p = 0.037$) and in-hospital mortality ($p < 0.001$). Low postoperative albumin level (≤ 2.5 mg/dl) was associated with higher in-hospital mortality ($p < 0.001$). The in-hospital mortality was significantly higher in patients who did not start feeding more than 4 postoperative days ($p < 0.001$) (Table 8).

Table 5: The intraoperative factors in different surgical approaches done for 84 patients with esophageal cancer presenting to the NCI between 2009 and 2015

	Trans-thoracic n=51	Trans-hiatal n=12	TPL n=9	Abdominal n=12	p value
Site					
Upper (n=9)	0 (0.0%)	0 (0.0%)	9 (100.0%)	0 (0.0%)	*
Middle (n=19)	16 (84.2%)	3 (15.8%)	0 (0.0%)	0 (0.0%)	
Lower (n=42)	30 (71.4%)	7 (16.7%)	0 (0.0%)	5 (11.9%)	
GEJ (n=14)	5 (35.7%)	2 (14.3%)	0 (0.0%)	7 (50.0%)	
Duration					
< 4 hrs	8 (15.7%)	6 (50.0%)	3 (33.3%)	6 (50.0%)	
4-6 hrs	33 (64.7%)	6 (50.0%)	4 (44.4%)	6 (50.0%)	0.032
> 6 hrs	10 (19.6%)	0 (0.0%)	2 (22.2%)	0 (0.0%)	
Blood Loss					
< 500 ml	14 (27.5%)	6 (50.0%)	2 (22.2%)	2 (16.7%)	*
500-1000 ml	27 (52.9%)	5 (41.7%)	4 (44.4%)	7 (58.3%)	
> 1000 ml	10 (19.6%)	1 (8.3%)	3 (33.3%)	3 (25.0%)	
Adequate Proximal Margin	14 (27.5%)	7 (58.3%)	0 (0.0%)	0 (0.0%)	0.002
Adequate Distal Margin	27 (52.9%)	3 (25.0%)	6 (66.7%)	10 (83.3%)	0.031
Adequate Lymphadenectomy	17 (33.3%)	4 (33.3%)	7 (77.8%)	6 (50.0%)	0.082

* no p value because of small number of cases in subgroups

TPL: total pharyngolaryngectomy, GEJ: Gastroesophageal Junction

Table 6: Preoperative risk factors for postoperative morbidity and mortality of Esophageal Cancer patients presenting to the NCI between 2009 and 2015

	Postoperative Morbidity n=55		In-hospital Mortality n=17	
	No. (%)	p value	No. (%)	p value
Age				
< 50 yrs (n=26)	13 (50.0)		2 (7.7)	
50-60 yrs (n=42)	29 (69.0)	0.093	10 (23.8)	0.131
> 60 yrs (n=16)	13 (81.3)		5 (31.3)	
Site				
Upper third (n=9)	7 (77.8)		1 (11.1)	
Middle third (n=19)	14 (73.7)	0.444	5 (26.3)	0.814
Lower third (n=42)	27 (64.3)		8 (19.0)	
GEJ (n=14)	7 (50.0)		3 (21.4)	
Stage				
Early (n=42)	28 (66.7)	0.818	10 (28.6)	0.551
Advanced (n=42)	27 (64.3)		7 (14.3)	
Number of Comorbidities				
None (n=30)	16 (53.3)		6 (20.0)	
Single (n=36)	26 (72.2)	0.218	6 (16.7)	0.631
Two or more (n=18)	13 (72.2)		5 (27.8)	
Neoadjuvant				
Received (n=17)	11 (64.7)	0.940	3 (17.6)	1.000
Not Received (n=67)	44 (65.7)		14 (20.9)	
Respiratory diseases (n=27)	21 (77.8)	0.103	3 (11.1)	0.152
Cardiovascular diseases (n=17)	12 (70.6)	0.620	7 (41.2)	0.242

GEJ: Gastroesophageal Junction

Table 7: Intraoperative risk factors for postoperative morbidity and mortality of esophageal cancer patients presenting to the NCI between 2009 and 2015

	Postoperative Morbidity n=55		In-hospital Mortality n=17	
	No. (%)	p value	No. (%)	p value
Procedure				
Trans-thoracic (n=51)	35 (68.6)		8 (15.7)	
Trans-hiatal (n=12)	5 (41.7)	0.279	1 (8.3)	0.108
TPL (n=9)	7 (77.8)		3 (33.3)	
Abdominal (n=12)	8 (66.7)		5 (41.7)	
Duration				
< 4 hrs (n=23)	14 (60.9)		5 (21.7)	
4-6 hrs (n=49)	32 (65.3)	0.705	10 (20.4)	0.938
> 6 hrs (n=12)	9 (75.0)		2 (16.7)	
Blood loss				
< 500 ml (n=24)	15 (62.5)		2 (8.3)	
500-1000 ml (n=43)	27 (62.8)	0.565	10 (23.3)	0.198
> 1000 ml (n=17)	13 (76.5)		5 (29.4)	
Anastomosis Site				
Neck (n=40)	22 (55.0)	0.054	7 (17.5)	0.551
Chest (n=44)	33 (75.0)		10 (22.7)	

TPL: total pharyngolaryngectomy

Table 8: Postoperative risk factors for postoperative morbidity and mortality of esophageal cancer patients presenting to the NCI between 2009 and 2015

	Postoperative Morbidity n=55		In-hospital Mortality n=17	
	No. (%)	p value	No. (%)	p value
Hemoglobin				
< 10 gm/dL (n=30)	24 (80.0)	0.037	13 (43.3)	< 0.001
≥ 10 gm/dL (n=54)	31 (57.4)		4 (7.4)	
Albumin				
≤ 2.5 mg/dL (n=30)	21 (70.0)	0.516	12 (40.0)	< 0.001
> 2.5 mg/dL (n=54)	34 (63.0)		5 (9.3)	
Diet Start				
1-3 days (n=11)	7 (63.6)	0.051	1 (9.1)	< 0.001
≥ 4 days (n=64)	39 (60.9)		7 (10.9)	
None (n=9)	9 (100.0)		9 (100.0)	
Feeding				
Oral (n=41)	26 (63.4)	0.865	6 (14.6)	0.859
Ryle (n=23)	14 (60.9)		2 (8.7)	
Feeding Jejunostomy (n=11)	6 (54.5)		0 (0.0)	

Hospital stay

All patients enter ICU after operation, with only 10 patients (12%) staying for one or two days (a routine practice after such major operation); and they did not need readmission. Another 55 patients (65.5%) needed 3-5 days in ICU due to associated comorbidities or occurrence of intraoperative or postoperative complications. The remaining 19 patients (22.6%) needed six days or more for close monitoring and management of postoperative complications; that either were successfully managed or ended in mortality. Twenty-four patients (28.6%) were discharged within 12 days, 26 (30.9%) required prolonged stay (13-18 days) in hospital for adequate postoperative recovery. The remaining 34 patients (40.5%) stayed longer than 19 days for proper management of complications.

Surgical Complications

Surgical complications recorded were anastomotic leakage (n=12; 14.3%), intraoperative blood loss requiring massive blood transfusion or circulatory support in (n=6; 7.1%), bronchopleural

fistula (n=4; 4.8%), and single case of chylous fistula, reactionary hemorrhage, pancreatic tear, and empyema. There was no significant effect of the surgical approach (p=0.234), procedure duration (p = 0.911), site of placing anastomosis (p = 0.422), and type of anastomosis closure (p = 0.447) on the frequency of anastomotic leakage. Leakage stopped and anastomosis healed with conservative management in five patients. Surgical exploration was done in four cases; repair was successful in only one of them. Postoperative leakage was associated with prolonged hospital stay, i.e. 19 days or more for the majority of patients. Six patients (50%) died during the postoperative period.

Twenty five patients (29.8%) developed postoperative pneumonia. There was no significant effect of any of the preoperative risk factors on the development of postoperative pneumonia (Table 10). Table 11 shows that the only factors associated with higher risk of developing pneumonia were placing anastomosis in the neck (p = 0.015) and associated surgical complications (p < 0.001).

Table 9: Intraoperative Risk Factors for postoperative leakage in esophageal cancer patients presenting to the NCI between 2009 and 2015

	Number	Percentage	p value
Procedure			
Trans-thoracic (n=51)	5	9.8	0.234
Trans-hiatal (n=12)	2	16.7	
Total pharyngolaryngectomy (n=9)	3	33.3	
Abdominal (n=12)	2	16.7	
Duration			
< 4 hrs (n=23)	3	13.0	0.911
4-6 hrs (n=49)	8	16.3	
> 6 hrs (n=12)	1	8.3	
Site of anastomosis			
Neck (n=40)	7	17.5	0.422
Chest (n=44)	5	11.4	
Type of anastomosis			
Stapler (n=16)	1	6.3	0.447
Hand sewn (n=68)	11	16.2	

Table 10: Preoperative Risk Factor for Pneumonia in esophageal cancer patients presenting to the NCI between 2009 and 2015

	Number	Percentage	p value
Age			
< 50 yrs (n=26)	8	30.8	
50-60 yrs (n=42)	11	26.2	0.695
> 60 yrs (n=16)	6	37.5	
Stage			
Early (n=42)	14	33.3	0.474
Advanced (n=42)	11	26.2	
Site of lesion			
Upper third (n=9)	5	55.6	0.093
Middle third (n=19)	8	42.1	
Lower third (n=42)	10	23.8	
Gastroesophageal Junction (n=14)	2	14.3	
Respiratory Complications			
Present (n=27)	9	33.3	0.622
Absent (n=57)	16	28.1	
Number of comorbidities			
None (n=30)	8	26.7	
Single (n=36)	14	38.9	0.218
Two or more (n=18)	3	16.7	

Nine patients (36%) with postoperative pneumonia stayed in ICU for 3-5 days, with 64% stayed for six days or more, readmitted to ICU or died postoperatively. Ten patients (40%) died postoperatively and only 3 patients (12%) were discharged within 12 days.

The median overall survival of the studied group (n=67) was 12 months (range: 10-14). The cumulative

overall survival was 56.7%. Advanced stage, lymph node involvement, development of postoperative morbidity, and inadequate lymphadenectomy were associated with worse overall survival (Table 12).

Multivariate analysis revealed that development of postoperative morbidity, lymph node involvement, and inadequate lymphadenectomy were the independent factors affecting survival (Table 13)

Table 11: Intra- and postoperative Risk Factors for Pneumonia in esophageal cancer patients presenting to the NCI between 2009 and 2015

	Number	Percentage	p value
Procedure			
Trans-thoracic (n=51)	14	27.5	
Trans-hiatal (n=12)	3	25.0	
Total pharyngolaryngectomy (n=9)	5	55.6	0.406
Abdominal (n=12)	3	25.0	
Duration of surgery			
< 4 hrs (n=23)	7	30.4	0.946
4-6 hrs (n=49)	14	28.6	
> 6 hrs (n=12)	4	33.3	
Site of anastomosis			
Neck (n=40)	17	42.5	0.015
Chest (n=44)	8	18.2	
Blood Loss			
< 500 ml (n=24)	7	29.2	0.851
500-1000 ml (n=43)	12	27.9	
> 1000 ml (n=17)	6	35.3	
Surgical Complications			
Present (n=26)	15	57.7	< 0.001
Absent (n=58)	10	17.2	

Table 12: Overall survival of the studied group in relation to the prognostic factors (n=67)

	n	Events	Cumulative Survival (%) at 12 months	Median Survival (95% CI) (months)	p value
Whole Group	67	60	56.7	12 (10-14)	
Morbidity					
Present	38	37	71.1	10.0 (7.0-13.0)	0.013
Absent	29	23	62.1	18.0 (7.4-28.5)	
Site					
Upper	6	4	50	9.0 (1.0-17.0)	0.482
Middle	15	14	40	11.0 (6.0-16.0)	
Lower	34	31	58.8	13.0 (7.3-18.7)	
GEJ	12	11	66.7	12.0 (1.8-22.2)	

	n	Events	Cumulative Survival (%) at 12 months	Median Survival (95% CI) (months)	p value
Pathology					
ADC	32	30	56.3	12.0 (7.8-16.2)	0.442
SCC	35	30	57.1	12.0 (6.2-17.8)	
Grade					
II	53	48	56.6	12.0 (7.9-16.1)	0.749
III	14	12	57.1	13.0 (2.1-23.9)	
Lymphadenectomy					
Adequate	22	17	54.5	17.0 (2.1-31.9)	0.015
Inadequate	45	43	46.7	12.0 (10.1-13.9)	
T Stage					
T2	25	20	56.0	15.0 (3.6-26.4)	0.031
T3 and T4	42	40	54.8	12.0 (9.3-14.7)	
N Stage					
N0	22	16	72.7	23.0 (16.6-29.4)	0.001
N1+	25	25	40.0	9.0 (7.4-10.6)	
Stage53					
Stage I- II	25	19	68.0	19.0 (10.4-27.6)	< 0.001
Stage III	28	28	42.9	9.0 (6.4-11.6)	
Treatment plan					
Surgery	16	15	37.5	9.0 (7.1-10.9)	0.711
Neo+Surgery	14	13	57.1	17.0 (11.5-22.5)	
Surgery+Adj	37	32	59.5	13.0 (11.0-15.0)	
Procedure					
Transthoracic	43	38	53.5	12 (8.2-15.8)	0.384
Transhiatal	11	11	63.6	12 (7.7-16.3)	
TPL	6	4	50.0	9 (1.0-17.0)	
Abdominal	7	7	71.4	15 (9.9-20.1)	

Table 13: Multivariate model of factors affecting overall survival of the studied group (n=67)

	B	p value	HR (95%CI)
Postoperative morbidity	0.767	0.026	2.15 (1.10-4.23)
Inadequate lymphadenectomy	1.165	0.002	3.20 (1.54-6.66)
N stage (N1+ vs. N0)	1.301	< 0.001	3.67 (1.77-7.61)

4. Discussion:

Over the 6-year period of the study, 275 patients with EC were diagnosed and treated in NCI, Cairo University. In the current series SCC accounted for 61% of esophageal cancers; with the highest affection in the sixth and seventh decades of life. Male to female ratio was 1.57:1. Worldwide, SCC is the most prevalent histological type of EC, but in certain developed countries including Australia, United States and some European nations, ADC of the esophagus dominates.[1] It has been reported that the incidence of SCC increases with age, reaching a peak in the seventh decade. The major risk factors include alcohol consumption and tobacco use.[2] This may explain the higher affection of males in the current study as tobacco smoking is more prevalent among males. It was reported that active smoking is associated with a 5 to 9-fold increased risk of SCC.[3]

In the current study, ADC was mainly identified in the lower third of the esophagus and the gastroesophageal junction (GEJ), while SCC was found along the whole length of the esophagus. This finding is consistent with previous studies demonstrating that adenocarcinoma occurs in the distal esophagus in approximately 75% of cases.[4] It was frequently linked to gastroesophageal reflux disease (GERD).[5] In fact, GERD is a very prevalent disease affecting about 9%-33% in the Middle East

region.[5] A retrospective study conducted in a secondary referral hospital in Egypt reported that among patients presenting with gastro-esophageal reflux symptoms, 24% have reflux esophagitis, but 92% of them had only grade 1 lesions.[6]

Nearly 70% of the patients of the current series presented with locally advanced or metastatic disease. Lesions in the upper third were locally advanced in 81.8% of cases, and rarely metastatic (single patient). This is a major problem in cases of EC; late presentation is almost the rule. This problem is commonly encountered in previous series especially in low-income countries[7,8]. In a Malaysian study, 90% of the patients presented in stage III or IV.[9]

The late presentation of disease adds to the difficulty of treatment of EC. It leads to only supportive or palliative care. In the current series, best supportive care and palliative therapy was offered for 75 patients (27.2%). The treatment modality depends largely on fitness for definitive treatment in general and surgery in particular. In the current series, nearly 71% of patients were fit for aggressive management. Thus, direct surgical exploration without any prior therapy was possible in 96 patients (34.9%), while 66 patients (24%) received neoadjuvant therapy, then 17 patients had surgical exploration. Higher fitness and physiological reserve are required to help the patient tolerate the burdens of surgery. Determinants of

fitness are interrelated and include lung and cardiac function, body composition, inflammatory mediators, and exercise performance. Older age has been shown to have a negative impact on these fitness variables.[10]

In the current series, fitness for definitive treatment was significantly associated with ADC pathological type ($p=0.031$), early stage ($p = 0.020$) and lesions involving the GEJ compared to middle third lesions ($p=0.016$). Transthoracic approach was in nearly 60% of cases; while total pharyngolaryngectomy (TPL) was used in only 9 patients (10.7%), who have upper third lesions. Distal tumors ($n=12$) were treated through the abdominal approach.

After surgical exploration, 29/113 patients (25.7%) turned out to be inoperable. This may reflect the poor assessment of the stage by CT scan and the lack of proper assessment by the alternative simple techniques as endoscopic ultrasonography (EUS). This would save unnecessary surgery and delay to the start of neo adjuvant therapy in a large proportion of patients. Moreover, due to lack of proper assessment of the response of tumor to neoadjuvant therapy by CT scan instead of positron emission tomography (PET/CT), only 25% of patients showed regressive course and a chance for resectability. Therefore, we presented the data of 84 patients who underwent surgical resection.

For proper staging, it was recommended that all patients should first undergo CT to exclude distant metastasis.[11] If metastasis is not detected, endoscopic EUS, or PET-CT can be considered. It was shown that EUS is more sensitive and specific than CT for identification of T-stage of esophageal cancer and for sampling of suspicious lymph nodes.[12,13] PET-CT can detect occult metastases in about 15% of patients.[14,15]

Trans-thoracic approach was the most commonly used in the current series, as half of the lesions were situated in the middle third of the esophagus. Transthoracic approach was more lengthy ($p = 0.032$). Adequate proximal margin was achieved in significantly higher proportion of trans-hiatal approaches ($p = 0.002$). Adequate distal margin was achieved in significantly higher proportion of TPL approaches ($p = 0.031$). Adequate Lymphadenectomy was significantly more in TPL approach but the difference was not statistically significant ($p = 0.082$). Generally, in-hospital mortality and surgical complications were comparable relative to the type of surgical approach.

In the current series, in-hospital mortality rate after esophagectomy was about 20% and morbidity rate was 65%. These figures are considerably high than what is reported in comparable high-volume centers. Other centers reported mortality rates of 10%

[16] to 14% [17]. There was no clear association between in-hospital mortality rate and the risk factors including age, site of lesion, stage and presence of associated morbidities. Previous studies found that age increased 30-day mortality rate from 10.7% for patients 65-69 years old to more than 20% for those older than 80 years.[18] In the current cases, patients above 60 years were only 19% of those who had esophagectomy.

Postoperative pulmonary complications were recorded in about 35% of cases in the current series. Previous studies reported rates of postoperative pulmonary complications 16%.[19] Pulmonary complications have been designated as the most common cause of post-esophagectomy deaths.[20]. Pulmonary complications leads to between 45.5% and 55% of all deaths postesophagectomy.[21,22] Postoperative pneumonia in the current series was responsible for 10 out of the 17 in-hospital deaths; i.e. 59%.

One-year cumulative overall survival in the current series was 56.7% among the 84 patients who had surgical resection. Development of postoperative morbidity, lymph node involvement, and inadequate lymphadenectomy were independently associated with worse overall survival. Surgical resection is the mainstay of treatment in esophageal cancer so long as the patient is in a good medical condition. It is supposed to improve long-term survival.[23] However, survival in these cases is always disappointing with less than 25% of patients surviving at 5 years after esophagectomy.[24]

In conclusion, definitive surgical management was possible in only 30% of patients presenting with esophageal cancer to the NCI during a 7-year period ended in 2015. All cases with operated upon using open techniques, mainly through the transthoracic approach. No cases of minimally invasive surgery were recorded. Treatment outcome in terms of postoperative morbidities and mortality and one-year overall survival were unsatisfactory if we consider the high experience of surgeons and high-volume nature of the NCI. Locally advanced stage at presentation may be a reason for disappointing results. Therefore, early detection and increasing awareness of the patients of the early symptoms of the disease may help diagnosis in stages more amenable to definitive treatment. Multidisciplinary approach can improve the outcome of treatment.

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