



Esophageal Carcinoma in El-Gharbia Governorate, Egypt: Clinico-Epidemiologic Study and Treatment Outcome

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Abstract: Background: Esophageal carcinoma (EC) is rare and little is known about them in Egypt. Gharbia population-based cancer registry (GPBCR) is the first population-based cancer registry in Egypt located in the Tanta Cancer Center (TCC). It has been successfully functioning since January 1999, covering 4.1 million population. We aimed to determine EC characteristics in Egyptian patients. Materials and methods: Retrospective analysis of 70 cases with ECs, who were identified in GPBCR between January 2000 and December 2002; of whom 35 were treated at TCC. Patients' medical records were reviewed regarding clinic-epidemiologic, treatment, and follow-up data. Results: Median age was 60 years (range, 18-83 years) with male predominance (63%). Dysphagia was the most common presentation (75%). The lower third was the commonest site (55%) followed by the middle third (25%). Squamous cell carcinoma (SCC) was the commonest histology (66%) followed by adenocarcinoma (AC; 24%). Majority of ACs (70%) were located in the lower esophagus while SCC had no site of preference ($p=0.04$). Less than one third of patients were candidates for radical treatment while the majority of patients received palliative and supportive treatment. Surgery, radiotherapy and chemotherapy were employed in 43%, 20%, and 34% of patients respectively. The median progression-free survival and overall survival were 6 and 7 months, respectively. Site, histology, stage and treatment modality had no significant impact on survival. Conclusions: Esophageal carcinoma in Gharbia Governorate, Egypt is characterized by predominance of male gender, lower third location and squamous histology. Overall and progression free survivals are dismal.

Keywords: Egypt, Gharbia Population-Based Cancer Registry, Esophageal Cancer

1. Introduction

Esophageal cancer (EC) is a highly lethal malignancy and has a very poor survival: 16% of the cases in the US and 10% in Europe survive at least five years [1]. An estimated 455,800 new cases and 400,200 deaths occurred in 2012 worldwide [2]. There are two major histologies of EC; squamous cell carcinoma (SCC) and adenocarcinoma (AC). Although most clinical studies have not differentiated between the two histologies, an increasing amount of evidence supports the view that they differ in terms of pathogenesis, epidemiology, tumor biology, and prognosis [3].

SCC and AC account for over 95% of ECs. For most of the twentieth century, SCC has predominated. In the 1960s, SCC accounted for more than 90% of all ECs in the US, and AC were considered so uncommon that some authorities questioned their existence. For the past two decades, however, the incidence of esophageal AC has increased dramatically in Western countries, such that the two tumors now occur with almost equal frequency [4, 5]. These changes suggest underlying etiologic differences. SCC is usually the result of tobacco and/or alcohol abuse while AC is associated with gastroesophageal reflux disease (GERD) [6-8]. The incidence of SCC varies considerably among geographic regions. The highest rates are found in Asia (particularly in

China and Singapore), Africa, and Iran (the so-called “EC belt”). Incidence rates vary internationally by more than 21-fold [2,9,10]. Geographic variation has also been reported within individual countries [11].

Regardless of histology, approximately 50% to 60% of patients with ECs present with incurable locally advanced or metastatic disease. Distant metastases to the liver, bone, and lung are seen in nearly 30% of patients [12]. However, most have tumors that invade through esophageal wall (T3) or are node-positive and long-term survival is uniformly poor. Only approximately 15% of these patients can be cured using multimodality therapy. The optimal treatment for these patients is controversial. However, in many institutions, initial chemo-radiotherapy or perioperative chemotherapy is preferred over upfront surgery for patients with T2 tumor stage or higher or regional nodal disease. Prolonged progression-free survival is possible in only a few of such patients while palliation is the goal of treatment for the majority.

Little information was available about EC in Egypt and the aim of our work was to study the clinico-pathological characteristics of EC in an Egyptian district, Gharbia, which contains the first population-based cancer registry in Egypt, and to report the outcome of this disease with the use of different treatment modalities.

2. Materials and Methods

This is a retrospective study on patients with EC identified through the Gharbia population-based cancer registry (GPBCR) which is a regional cancer registry covering the Gharbia Governorate and was established in 1998. It is located in the Tanta Cancer Center (TCC) of the Ministry of Health and Population and was initially funded by the National Cancer Institute of the US [13]. Tanta, the capital city of the Gharbia Governorate, is situated in the middle of the Nile Delta, about 100 kilometers north of Egypt’s capital city, Cairo. Data on age, sex, sub-site, histological subtype, grade, stage and treating center were obtained from the registry.

Unfortunately, clinical data particularly pertaining to presentations, treatments and follow up, other than mentioned above were not contained in GPBCR. Thus, we tried to further track as much cases as possible through reviewing cases that presented to TCC. We could identify 35 cases whose information on complaints, treatment modalities, relapse, dates (of diagnosis, surgery and relapse), and survival were obtained.

The Institutional Review Board (IRB) of the Egyptian National Cancer Institute (NCI) approved the study. Inclusion criteria were adult patients (age of 18 years or more) with EC and a confirmed malignant histology between January 2000 and December 2002. Exclusion criteria were non-confirmed histologic subtype (i.e. diagnosed based on death certificate, radiology or unspecified malignant type). Between January 2000 and December 2002, 77 cases with ECs contained in GPBCR were identified. Seven cases were excluded as their diagnoses were based on death certificate with no histologic confirmation or subtyping.

Statistical analysis: All analyses were done using SPSS® software program version 15 (SPSS Inc., Chicago, IL, USA). Nominal and categorical data were compared for different histologies using the Chi squared test or Fisher’s Exact test. Survival was calculated using the Kaplan-Meier method and groups were compared using the log-rank test. A probability (p) ≤ 0.05 (two sided) was considered statistically significant.

3. Results

ECs represented 11% of all GIT cancers. Median age was 60 years (range, 18-83 years) with male predominance (1.7:1). The lower third was the commonest site. When stage was known, loco-regional disease was the commonest presentation (69%). SCC was the commonest histologic subtype (66%) followed by AC. Other subtypes (7/70) included undifferentiated, anaplastic or unspecified carcinoma (2 cases each) and unspecified malignant neoplasm in one case. Grade 2 and 3 tumors were the commonest (78%). Table 1 shows the patient characteristics. TCC cases were generally similar to non-TCC cases.

Table 1. Characteristics of 70 patients with esophageal carcinoma histologically confirmed in Gharbia-population based cancer registry (GPBCR).

Characteristic	All cases		TCC cases		Non-TCC cases		p value
	n (70)	%	n (35)	%	n (35)	%	
Age in years (mean \pm SD)	57 \pm 13		55 \pm 14		59 \pm 11		0.13
Sex							
Male	44	63	23	66	21	60	0.62
Female	26	37	12	34	14	40	
Known site	60	86	35	100	25	71	0.27
Upper third	8	13	2	6	6	24	
Middle third	15	25	10	28	5	20	
Lower third	33	55	22	63	11	44	
Overlapping	10	17	1	3	3	12	
Known SEER Stage	45	64	29	83	16	46	
Localized	24	53	11	38	13	81	
Regional	7	16	6	21	1	6	0.07
Distant	14	31	12	41	2	13	
Histology subtype							
Squamous cell carcinoma	46	66	24	69	22	63	
Adenocarcinoma	17	24	6	17	11	31	

Characteristic	All cases		TCC cases		Non-TCC cases		p value
	n (70)	%	n (35)	%	n (35)	%	
Other (e.g. NOS)	7	10	5	14	2	6	0.46
Known Grade	61		32		29		
1	7	12	2	6	5	17	
2	27	44	11	34	16	55	
3	21	34	14	44	7	24	
4	6	10	5	16	1	4	0.24

NOS: not otherwise specified; SEER: Surveillance Epidemiology and End Results; TCC: Tanta Cancer Canter, Gharbia, Egypt

No significant difference in age, sex, and stage distribution between patients having SCC and AC. The only significant difference was in tumor location; 70% of AC were located in the lower esophagus while SCC had no site of preference ($p=0.04$). Table 2 shows comparison between patients having SCC and AC.

Table 2. Comparison between squamous cell carcinoma and adenocarcinoma in patients with esophageal cancer included in Gharbia-population based cancer registry (GPBCR).

Characteristic	SCC cases		AC cases		p value
	n	%	n	%	
Number	46	66	17	24	
Age in years (mean \pm SD)	55.7 \pm 12.8		57.8 \pm 11.4		0.55
Sex					0.24
Male	26	56.5	13	76.5	
Female	20	43.5	4	23.5	
Known site					0.04
Upper third	7	15.2	0	0	
Middle third	12	26.1	1	5.9	
Lower third	17	37	12	70.6	
Overlapping	10	21.7	4	23.5	
Known SEER Stage					0.61
Localized	18	56.3	5	50	
Regional	6	18.8	1	10	
Distant	8	25	4	40	

SCC: Squamous cell carcinoma; AC: Adenocarcinoma; SEER: Surveillance Epidemiology and End Results

Clinical data other than mentioned above were not contained in GPBCR. We could identify 35 cases that presented to TCC whose information is discussed below in more details.

Most patients had symptoms related to their disease with dysphagia being the commonest (75%) followed by odynophagia (7%), vomiting (5%) or symptoms related to metastases (e.g. dyspnea in 19%). Distant metastases were encountered in 12/35 (34%) patients; lungs (7/12), liver (2/12) and others including bone and distant lymph nodes and pleural effusion (one patient each).

Ten patients (29%) were candidates for radical treatment while the majority of patients received palliative and supportive treatment. Fifteen patients (43%) underwent surgery; 5 with a curative intent (esophagectomy) and 10 as a palliative measure (feeding gastrostomy). Three out of the five patients that had surgery with a curative intent eventually relapsed. Eleven patients received radiotherapy; 7 as radical and 4 as palliative. It was post-operative in 2 out of the 5 patients who underwent radical surgery and in 3 of the radical patients it was concomitant with weekly cisplatin. One-third (12/35) of patients received chemotherapy, that was given with a palliative intent in 9/12 patients and the regimen used was 5FU/Cisplatin (median number of cycles was 4; range 1-6). Weekly cisplatin was given concomitant with radical radiotherapy in 3/12 patients.

After a median follow up of 5 months (range, 1-36 months), only four patients were alive; all with evidence of disease while 31 patients were dead. Deaths were disease related in all but two cases. The median overall survival (OS) was 7 months (95% CI, 4.4-9.6 months; figure 1A). The one- and two-year OS rates were 30% and 17%, respectively. The median progression free survival (PFS) was 6 months (95% CI, 3.3-8.7 months; figure 1B). The one- and two-year PFS rates were 30% and 13%, respectively.

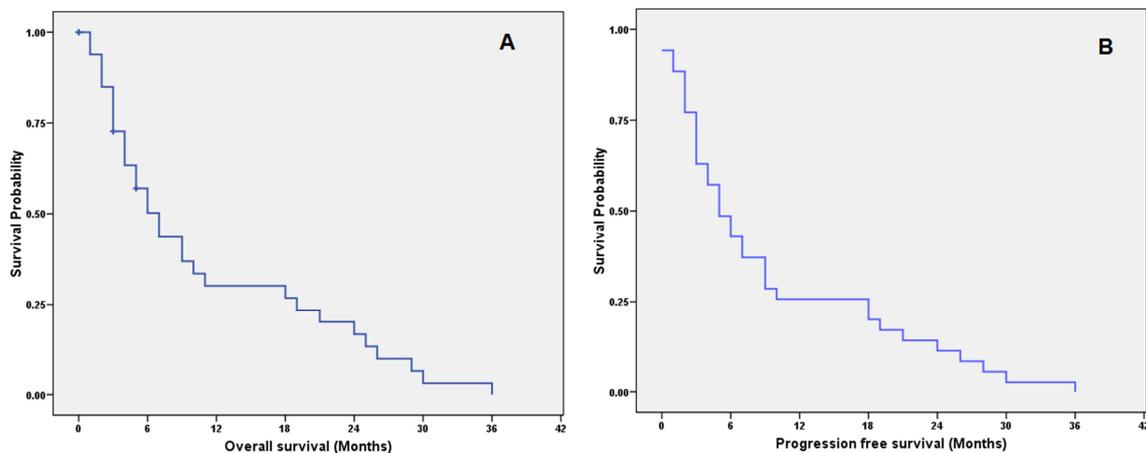


Figure 1. A: overall survival and B: progression free survival in 35 patients with esophageal carcinoma.

Comparing histologic subtypes showed that SCC had a median OS of 6 months (95% CI, 2.4-9.5 months) and AC had a median survival of 7 months (95% CI, 2.7-11.3 months; $p= 0.55$; figure 2A). For PFS, SCC had a median

PFS of 6 months (95% CI, 2.4-9.6 months) and AC had a median PFS of 5 months (95% CI, 0-11 months; $p= 0.31$; figure 2B). However, the differences were not statistically significant.

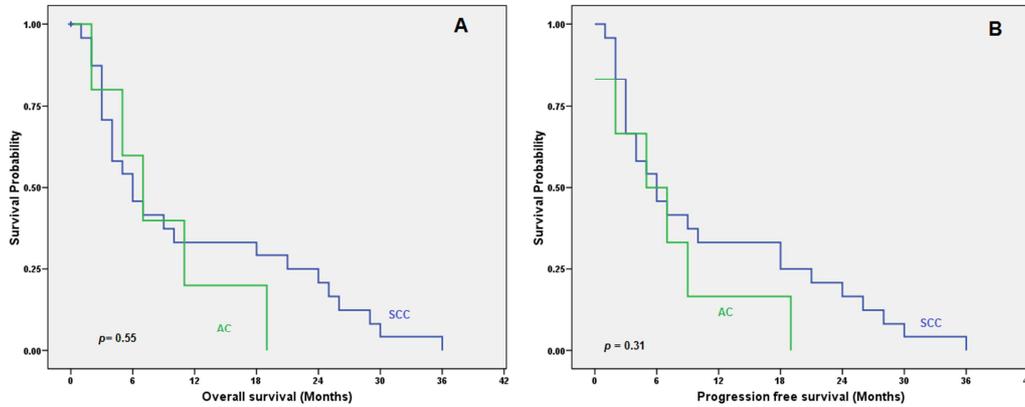


Figure 2. A: overall survival and B: progression free survival in 30 patients with esophageal carcinoma according to histologic subtype.

Comparing primary sub-sites showed that lower third carcinomas had a median OS of 7 months (95% CI, 4.3-9.7 months) and non-lower third carcinomas had a median of 6 months (95% CI, 1.2-10.8 months; $p= 0.83$; figure 3A). The

median PFS For lower third carcinomas was 5 months (95% CI, 1.5-8.5 months) and that of non-lower third was also 5 months (95% CI, 2.2-7.8 months; $p= 0.60$; figure 3B). The differences were not statistically significant.

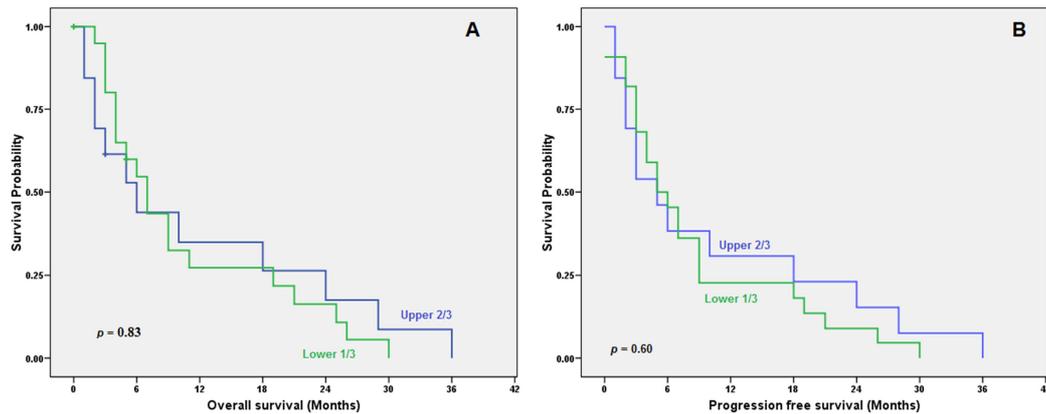


Figure 3. A: overall survival and B: progression free survival in 35 patients with esophageal carcinoma according to primary site.

Different SEER stages were not statistically different in OS or PFS (figure 4). Similarly, the OS and PFS were very poor regardless of the therapy used with no significant differences (figure 5).

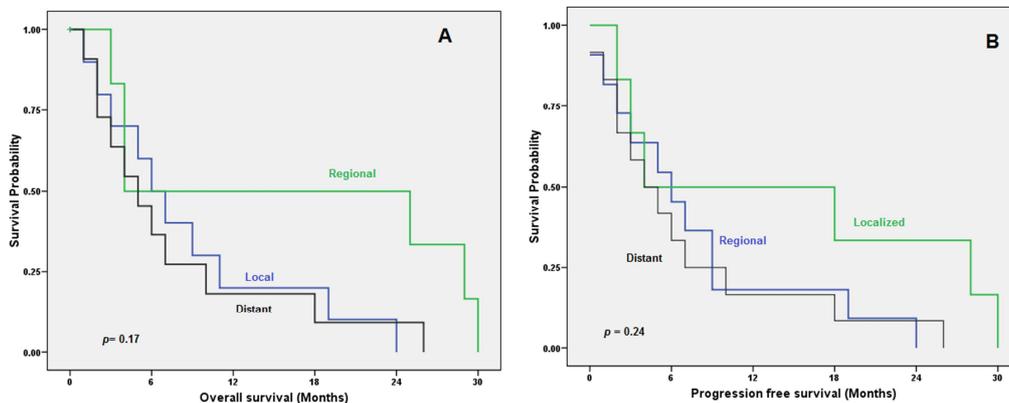


Figure 4. A: overall survival and B: progression free survival in 35 patients with esophageal carcinoma according to SEER stage.

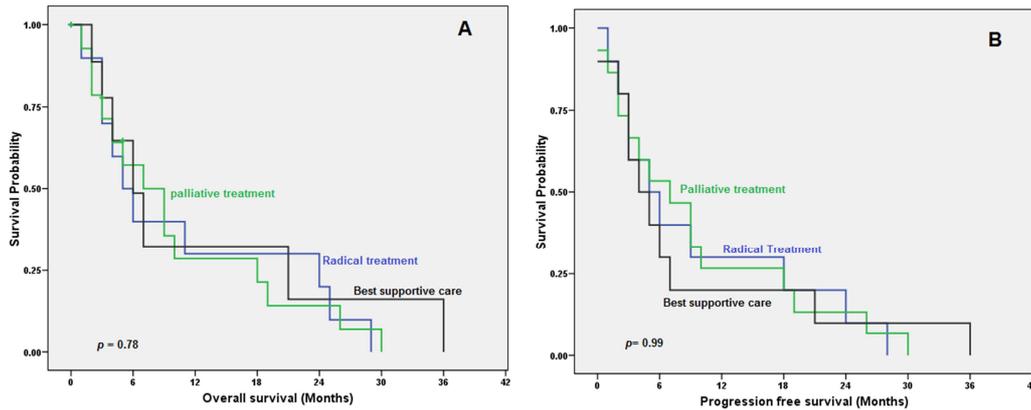


Figure 5. A: overall survival and B: progression free survival in 35 patients with esophageal carcinoma according to treatments used.

4. Discussion

Esophageal cancer is the eighth most common cancer worldwide, with 3.2% of the total new cases estimated in 2012, and the sixth most common cause of death from cancer with 4.9% of the total deaths. Around 80% of the cases worldwide occur in less developed regions [14]. The Arabic world has generally very low incidences of EC. In Egypt, it represents 1.7% of all cancers [15] with lower incidence reported in Gharbia province (0.9% of all cancers). The age-standardized incidence rates worldwide were 11.5 in males and 4.7 in females, while it was 1.4 in Egyptians. The low rates of EC might be explained by the relatively low levels of alcohol consumption in Arab countries with a Muslim majority. In contrast to alcohol, there is a high prevalence of smoking, which would tend to increase the rates. The low EC rates suggest under-diagnosis in all the countries in the region [13].

There is no national cancer registry in Egypt, this makes comparison with other countries difficult, and we cannot compare districts within Egypt. There are many hospital-based cancer registries in a tertiary care centers which delivers oncology services to population in many governorates in Egypt. GPBCR is the first population based cancer registry in Egypt. It has been successfully functioning, since January 1999, covering a population of 4.1 million (8 districts and 318 villages). The registry records all incident cancer cases among residents of Gharbiah diagnosed within and outside the Gharbiah Governorate. Although notification of cancer is not obligatory by law, a Ministerial decree that was issued to request collaboration with the registry has enhanced data collection efforts.

Estimates of the incidence of these tumors from registries may be limited by problems related to how the tumors were classified. This was illustrated for gastric cardia AC in a study in which its incidence was estimated from a cancer registry in Sweden, and the results were compared to a gold-standard population in which classification was based upon detailed review of patient records [16]. It was estimated that the true gastric cardia incidence could be up to 45% higher or 15% lower than estimates provided by analysis of the cancer

registry. However, a large database study in the United States concluded that rising incidence of AC represented a real increase in disease burden and not a reclassification of SCC or adjacent gastric carcinoma or an over diagnosis of esophageal AC [17].

Most early (superficial) EC are not specifically symptomatic and are usually detected during screening for or surveillance of Barrett's esophagus. Among patients with locally advanced EC, obstruction of the esophagus by the tumor causes progressive solid food dysphagia often accompanied by weight loss. This usually occurs once the esophageal lumen diameter is less than 13 mm, which indicates advanced disease. Most of our patients had dysphagia being the commonest (75%) symptoms related to their disease that would denote late presentation of our patients.

In our cases, SCC was the commonest histologic subtype (66%) followed by AC (24%). This rate is not so high as reported in the highest-risk area (the "EC belt"), where 90% of cases are SCC [18, 19]. Temporal trends in incidence vary for the two major histologic types of EC. Incidence rates for AC have been increasing in several Western countries, in part due to increases in known risk factors such as overweight and obesity. In contrast, rates for SCC have been steadily decreasing in these same countries because of long-term reductions in tobacco use and alcohol consumption. However, SCC has been increasing in certain Asian countries such as Taiwan, probably because of increases in tobacco and alcohol consumption [20]. Worldwide, the incidence of AC is rising dramatically, while the incidence of SCC is decreasing [21].

Due to its retrospective nature, incomplete patients' follow-up data is obvious in our study as only 50% of patients had complete information. Survival was disappointing similar to what reported in many studies treating patients at that time. According to data from the US Surveillance, Epidemiology and End Results (SEER) Program, the five-year survival for all patients with EC improved only modestly over the last 30 years, from 5% in the years 1975 to 1977, to 19% during the period 2001-2007 [22]. These figures are indicative of advanced stage of disease (local-regional or metastatic) at diagnosis in most

patients [5].

Many (but not all [23]) contemporary series suggest that the prognosis of AC is better than that of SCC, particularly in early stage disease [6, 7, 23-27]. One reason may be the lower prevalence of lymphatic spread for Barrett's-associated cancer than for SCC [6, 23]. Although SCC tend to arise 10 years earlier, on average, than AC, perioperative mortality is higher for SCC than for a Barrett's AC, likely related to associated comorbidity and tumor location [8, 28]. This was contradictory to our results that showed no difference in OS and PFS between SCC and AC.

There seems little doubt that esophageal SCC and AC represent two different diseases with characteristic pathogenesis, epidemiology, tumor biology, and outcomes. In acknowledgement of these differences, the most recent 2010 TNM staging system provides separate stage groupings for SCC and AC [29]. However, it remains unclear as to whether and how histology should dictate the therapeutic approach. Future studies in EC should analyse and report separately the results of therapeutic strategies according to histology. In our study, there was no significant difference between SCC and AC in most of their clinico-epidemiologic features except that 70% of AC were located in the lower third of the esophagus ($p=0.04$).

Out of 70 patients registered in GPBCR, only 35 patients (50%) were treated in TCC. Following patients treated outside this center is very difficult for several reasons. We are in need to increase the number of cancer centers treating patients with the updated treatment policies and provide reliable access to their clinical follow-up data. Out of 35 patients referred for TCC, Fifteen patients (43%) underwent surgery; 5 (14%) with a curative intent and 10 as a palliative measure. It means that 14% only of our cases had potentially resectable disease. Three out of the five patients that had surgery with a curative intent eventually relapsed. In many series, although only 30% to 40% of patients have potentially resectable disease at presentation, surgery has been the standard treatment for early stage EC. Data from contemporary surgical series report five-year survival rates of 15% to 20% for surgery alone [30, 31-34] and 15% for any patient with node-positive disease [35]. In a review of 49 early series involving more than 8400 patients treated with RT alone, survival rates at 1, 2, and 5 years were 18%, 8%, and 6%, respectively [36].

In TCC, only 5 patients underwent radical esophagectomy during 3 years (2000-2002). It would be better to do esophagectomy in a high-volume institution because it has superior operative mortality rates (more than 12% absolute reduction in mortality when compared to low volume centers) [37].

Our patients were treated between 2000 and 2002 with the traditional treatment at that time which was single modality treatment. The management of local-regional EC has undergone a major evolution over the past 15 years. The low cure rates after locoregional therapy alone prompted the inclusion of systemic chemotherapy in multimodality treatment regimens, to control distant micrometastatic

disease and enhance local radiation effects. The seminal RTOG 85-01 trial demonstrated a survival benefit for the addition of cisplatin-based chemotherapy to radiation therapy in non-surgically treated patients; whether induction chemoradiotherapy adds benefit to surgery for potentially resectable disease remains a controversial area. Less than one-third of all patients are cured by multimodality therapy, and distant failure accounts for three-fourths of all recurrences [30]. We encourage treating all EC patients in a dedicated oncology center applying the current multimodality treatment trying to achieve better outcome.

Although this study includes small number of patients in only one province, it adds to the very limited data available about esophageal cancer in Egypt and highlights the need for more studies including larger number of patients to get clearer picture about this disease in our country.

5. Conclusions

Esophageal carcinoma in Gharbia Governorate, Egypt represents 11% of all GIT cancers with a median age of 60 years and characterized by predominance of male gender, lower third location and squamous histology. Most patients presented with dysphagia and the disease was advanced in 47% of cases. Less than one third of patients (29%) were candidates for radical treatment while the majority of patients received palliative and supportive treatment. Radical surgery was done in 14% of patients while chemotherapy and radiotherapy were given in 34% and 20% of patients respectively. Overall and progression free survivals were dismal.

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