Frequency of Esophageal Carcinoma and Delay in Diagnostic Workup; A Multi-centre Experience from Southern Pakistan

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Abstract

Objective: Esophageal carcinoma is one of the most lethal and yet least studied malignancies in South Asian region. The aim of our study was to determine the frequency of Esophageal Carcinoma and to identify factors responsible for late stage diagnosis of this malignancy.

Methods: A multi-institutional prospective cross-sectional study was conducted at Oncology department, JPMC and Atomic Energy Medical Centre, Karachi. Association between risk factors of delayed diagnosis with ethnic groups, grade and stage of tumour was statistically assessed.

Results: A frequency of 3.83% of esophageal cancer was recorded. Squamous cell carcinoma as the most common (80.6%) subtype, moderately differentiated grade in 67.7% and lower 1/3rd involvement was noted in 53.8% cases. Representation of Sindhi speaking ethnicity was 33.3%. First visit to a general physician was within a month of onset of symptoms in 54.8% patients. In 21.5%, first visit was delayed by more than 2 months. Biopsy was delayed in 19.4% cases. Significant association was found between delayed diagnosis and late referral to oncologist (P 0.003), non-availability of laboratory (P 0.018), location of tumour (P 0.000), age and size of tumour (P 0.001).

Conclusion: Esophageal carcinoma is a common malignancy with squamous cell carcinoma as the most common subtype. Initial diagnosis of most of the patients was made in the late stage. Important contributing factors of late diagnosis were unawareness of patients, delayed initial diagnostic workup, poor socioeconomic status and late referrals to oncologists by General Physicians. No significant association was observed between ethnicity and grading or staging of tumour.

Key words: Esophageal carcinoma,
Esophageal Squamous Cell Carcinoma (SCC),
Adenocarcinoma of Esophagus (AC),
Southern Pakistan

Introduction

Esophageal carcinoma is one of the most lethal cancers worldwide, and has not been extensively studied in the Pakistani population. It is very aggressive in nature, usually diagnosed in late stages and has a poor prognosis. Esophageal Squamous cell carcinoma (SCC) and Esophageal Adenocarcinoma (AC) are its two major histological types [1, 2]. According to GLOBOCAN 2018, there are dramatic increases in the incidence of esophageal carcinoma and it is the sixth common cause of mortality, worldwide [3]. A high prevalence of this malignancy has been recorded in the Asian Belt of Esophageal cancer. This belt region expands from northern Iran to north-central China. Intermediate risk for developing Esophageal cancer exists in areas including southeast Africa, parts of South America and Western Europe. According to data, 90% of cases of esophageal cancer in the developing countries are histologically SCC [4]. Annual cancer registry report-2018, of The Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH&RC), Pakistan showed that esophageal cancer is the 10th most common malignancy in Pakistan, with a frequency of 3.2% [5].

A report published in 2004 showed that only 1/4th of patients had early stage malignancy at the time of diagnosis with locally invasive and metastatic tumours to be 41% and 34% respectively. Furthermore, statistics from the same report showed SCC is 4 times more frequent than adenocarcinoma (AC) with a median survival of 7 months [6]. Similarly, a study from Thailand reported a high frequency of late diagnoses of esophageal cancer [7].

Risk factors for esophageal carcinoma include smoking, tobacco, alcohol consumption, hot beverages. Human papilloma virus and certain driver genetic mutations are other possible factors for this malignancy. Barrett's esophagus is an important precancerous disease in which there is 50 to 100 times increased risk of developing esophageal adenocarcinoma. The association of western diet, polycyclic aromatic hydrocarbons in charcoal and mutagenic heterocyclic amines in roasted red meat with the development and progression of esophageal cancer has also been established. Diet lacking in zinc and selenium has been linked with increased risk for developing this malignancy. Common clinical features of this malignancy include dysphagia, weight loss, vomiting, dyspepsia, chest pain and hematemesis [1, 3, 7, 8, 9] .

Extensive literature review showed that substantial information regarding the possible factors contributing to delayed diagnostic workup of this malignancy is lacking in the region. Karachi is a densely populated cosmopolitan city in Southern Pakistan, where people from different regions of the country belonging to various ethnic groups, reside. They do not only differ in race and language, but also have varying dietary habits and lifestyles. The current study is an attempt to determine the frequency of esophageal cancer in different ethnic groups presenting to a public sector tertiary care hospital of Karachi. This study will also identify the possible factors involved in delayed diagnosis of esophageal carcinoma.

Patients and Methods

A multi-institutional prospective cross sectional study was conducted at Department of oncology Jinnah Post Medical Centre (JPMC) and Atomic Energy Medical Centre (AEMC) Karachi from 1st March 2018 till 28th February 2019. The study was approved by Institutional Review Boards (JSMU/IRB/2017/93) of Jinnah Sindh Medical University, AEMC and JPMC Karachi. Non-Probability convenient sampling technique was implemented to select the study participants. The sample size was calculated using Open Epi software. Considering the annual registered number of patients at both institutes, the population size = 125, anticipated frequency = 50%, Confidence level = 95 %, confidence level as +/- percent of 100 = 5, design effect =1, the minimum sample size calculated was 95. Complete history and investigations were not available for two patients, so the final number of patients included in the study was 93.

Biopsy proven cases of esophageal carcinoma of either gender, registered in JPMC and AEMC who agreed to participate in our study after taking written or verbal consent were included in the study. Subjects who refused to participate, metastatic malignancy to esophagus or recurrent esophageal tumours cases were excluded. Data were collected using a self-structured validated questionnaire. The questionnaire was developed after extensive literature review using PubMed and Google Scholar. It was comprised of multiple choice, open and close-ended questions. The questionnaire was divided into four sections. The first part inquired about demographics, ethnicity and place of presentation. The second section included clinical features at presentation and all the possible factors leading to late diagnosis. The third and fourth sections were comprised of CT scan and biopsy findings including subtypes of cancer, grading, staging, extent, possible metastasis etc. American Joint Committee of Cancer (AJCC) criteria were followed to stage the carcinoma [10]. Stage 3 and 4 were considered late stages.

Data analysis was performed using IBM Statistical Package for the Social Sciences (SPSS), Version 25.0. Descriptive statistics were used to determine mean and standard deviation for numerical variables. Categorical variables were expressed in frequency and percentages. Chi-square/ Fisher Exact test was applied to assess the statistical difference in distribution of cases among different ethnic groups as well as to observe any association between risk factors of delayed diagnosis and ethnic groups, grade and stage of esophageal carcinoma. A P value of < 0.05 was considered significant.

Results

A total of 95 esophageal carcinoma patients presented to both institutes during the study duration. Due to incomplete data, two of them were excluded and the final number of patients remained at 93. They included 41 males and 52 females, aged between 18 to 80 years, mean age was 45.45, with Standard deviation ±14.504, (Figure 1). Out of these 93 patients, 82 were registered in Oncology ward JPMC and 11 in AEMC. SCC was the most common histological type 75 (80.6%) followed by AC 14 (15.1%) cases. Other morphological types included small cell carcinoma, signet ring cell carcinoma and large cell variety of Adenocarcinoma. Location of tumour was Upper one third in 17 (18.3%), middle one third in 26 (28%) and lower one third 50 (53.7%) cases (Table 1).

Most common presenting symptom was dysphagia in 89 (95.7%) followed by weight loss in 70 (75.3%) and Odynophagia in 41(44.1%) cases. There was significant association of dysphagia with weight loss (P=0.017), history of chronic cough (P =0.001) and history of dyspnea (P =0.000). Lack of awareness was an important contributing factor in delayed diagnosis as 87(93.5%) patients never heard about esophageal cancer before being diagnosed with it.

Positive family history of various malignancies was observed in 20 (21.5%). Sindhi population was the most commonly affected ethnic group 31 (33.3%) as shown in (Table 2). This was followed by Urdu speaking 26 (28%), Pathan and Baloch 10 (10.8%) each, respectively. Endoscopy report of only 15 patients were available where 13/15 (86.6%) patients showed an ulcerated lesion. Moderately differentiated was the most common 63 (67.7%) histologic grade. Association of grading and staging with ethnic groups is presented in detail in (Table 2).

Approximately half of the patients, 51 (54.8%) visited a physician within a month of the occurrence of first symptoms. About 26 (28%) had an appointment with a physician immediately, while 25 (26.9%) visited after 15 days. However, 20 (21.5%) patients saw a doctor about two or more months after the initial symptom. Almost all patients, 90 (96.8%) properly followed investigations and treatment as prescribed by the doctors. Biopsy of 18 (19.4%) patients was delayed. Important contributors were low socioeconomic status and unavailability of diagnostic laboratory within nearby location. (P = 0.000). Total number of patients diagnosed at late stage was 58(62.2%) [Stage 3: 26(27.8%), stage 4 31(34.4%)]. (Table 3) Significant association was found between various factors and late stage diagnosis as explained in Table 3. The majority of patients (86%) had delayed referrals by general physicians. The second most significant contributor to late diagnosis was non availability of a good diagnostic laboratory facility in the nearby vicinity in about 32% patients.

Figure 1: Bar chart representing number of esophageal cancer cases in association with age groups and gender

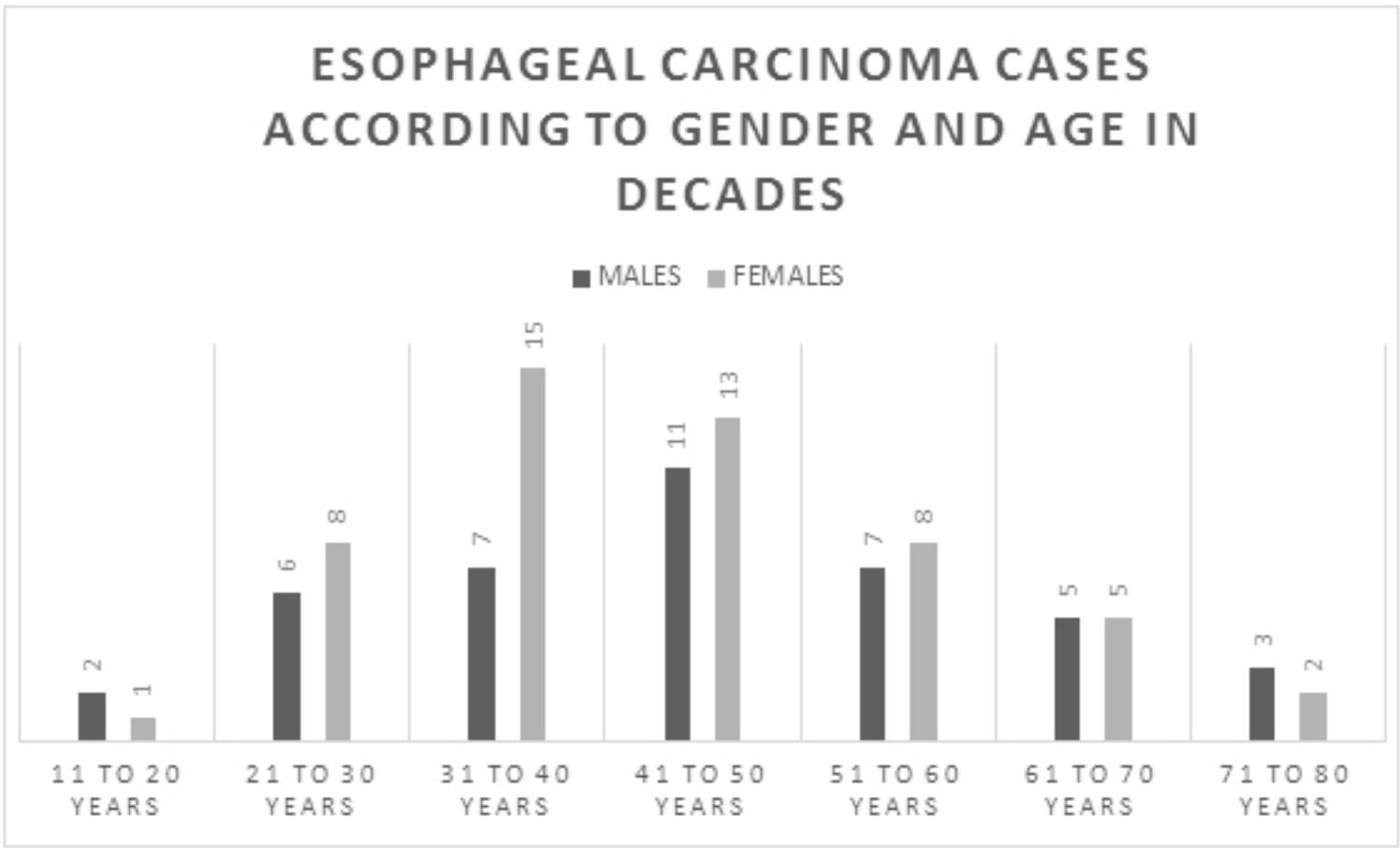

Table 1: Frequency of Esophageal Cancer according to morphological types & location

Location of Tumor	AC	SCC	Small cell carcinoma	Others	Total N (%)	P value±
Upper 1/3rd	1	14	1	1	17 (18.3%)	0.080
Middle 1/3rd	1	25	0	0	26 (28%)	
Lower 1/3rd	12	36	1	1	50 (53.8%)	
Total	14 (15.1%)	75 (80.6%)	2 (2.2%)	2(2.2%)	93 (100%)	

Table 1 shows frequency of Esophageal Adenocarcinoma (AC), esophageal squamous cell carcinoma (SCC), small cell carcinoma and other variants of esophageal cancer according to location.
±Fisher Exact Test

Table 2: Staging & Grading of Esophageal Cancer at the time of diagnosis according to ethnicity. (N=93)

Grading of esophageal cancer at the time of diagnosis according to ethnicity								
Grade at diagnosis	Sindhi	Pathan	Baloch	Punjabi	Urdu Speaking	Others	Total n(%)	P value
Well Differentiated	8	1	2	1	5	0	17 (18.2%)	0.806
Moderately Differentiated	21	7	7	3	15	10	63 (67.7%)	
Poorly Differentiated	2	2	1	1	6	1	13 (13.9%)	
Total	31 (33.3%)	10 (10.7%)	10 (10.7%)	5 (5.3%)	26 (27.9%)	11 (11.8%)	93 (100%)	
Staging of esophageal cancer at the time of diagnosis according to ethnicity								
Stage at Diagnosis	Sindhi	Pathan	Baloch	Punjabi	Urdu Speaking	Others	Total n(%)	P value
1A	1	0	2	0	0	0	3 (3.2%)	0.249
1B	3	0	1	0	2	2	8(8.6%)	
2A	9	1	2	0	5	3	20 (21.5%)	
2B	4	0	0	0	1	0	5 (5.4%)	
3A	2	1	3	1	6	2	15 (16.1%)	
3B	2	4	1	1	2	1	11 (11.8%)	
4A	5	3	0	0	7	3	18 (19.4%)	
4B	5	1	1	3	3	0	13 (14.0%)	
TOTAL	31 (33.3%)	10 (10.7%)	10 (10.7%)	5 (5.3%)	26 (27.9%)	11 (11.8%)	93 (100%)	

Table 2 shows distribution of Grades and Stage I to IV of esophageal cancer cases according to ethnicity. Stage 3 and 4 are considered advanced stage of the disease. ±Fisher Exact Test

Table 3: Possible Association of various factors with delayed diagnostic workup and late stage diagnosis of esophageal carcinoma.

Factors leading to delayed diagnosis	Number of patients n (%)	P value*
Referral by General Physician (GP) to a medical specialist		
Late Referral by GP	80 (86%)	0.003
Delayed diagnosis due to late referral	48/80 (60%)	
Availability of Diagnostic laboratory in the vicinity		
No laboratory in nearby location	30 (32%)	
Delayed diagnosis due to unavailability of early diagnostic facility	12/30 (40%)	0.018
Location of tumor in esophagus		
Upper 1/3rd	17 (18.3%)	
Middle 1/3rd	26 (28%)	0.000
Lower 1/3rd	50 (53.8%)	
Late stage diagnosis in lower 1/3rd	36/50 (72%)	
Age at diagnosis		
No. of patients in 5th, 6th, 7th decade	61 (65.6%)	
Late stage diagnosis among older age group	41/ 61 (67.2%)	0.044
Size of tumor in largest dimension (2.1 – 8 cm)	68 (73.1%)	
Late stage diagnosis according to tumor size	42/68 (62%)	0.001

Table 3 shows association of various possible factors with late stage diagnosis of EC.
*Pearson Chi-square test

Discussion

Carcinoma of esophagus is a less studied entity in the local population. The current study was designed to observe the pattern of this malignancy in a tertiary care hospital in the hub of the city. To the best of our knowledge, similar research has not been reported from this region.

A frequency of 3.83% of esophageal cancer was recorded in the current series. It is close to the annual cancer registry report 2018 of SKMCH&RC (3.2%) [5]. Most of the patients were in either 4th or 5th decade, constituting 23.6% and 25.8% respectively. Mean age was found to be 45.45 with Standard deviation ±14.504. A slight female preponderance was observed in our study (55.9% female and 44.1% male). Male to female ratio was 1:1.2. On the contrary, another tertiary care facility from Karachi reported a male majority (59%) [6]. This is an interesting finding from the subcontinent region as the GLOBOCAN 2018 also showed 70% cases of esophageal cancer in male population of Eastern and Southern Africa [3]. Sindhi and Urdu speaking were the most common ethnicities. Interestingly, no significant association was found between ethnic groups and grading (P= 0.806), and staging (P=0.249) of tumour. The reason could be the similar dietary habits, exposure to similar environmental exposure and unvarying socioeconomic conditions of all ethnic groups.

SCC was the predominant morphological type. Other studies support our finding. Smoking and Betel quid chewing are regarded as important causes of increased frequency of SCC in the Western world and subcontinent respectively [3, 6, 13]. A study conducted in rural Southern province of Sindh showed frequency of SCC to be 95%, affirming 80.6% in our study [11]. Histologically, moderately differentiated tumour (Grade 2) was found in a significant number (67.7%) of patients. Well differentiated (Grade 1) and poorly differentiated morphologies (Grade 3) were 18.3% and 14% respectively. This is comparable with the findings of a German study observing grade 2 (50%) as the most frequent, followed by grade 1 (41.7 %) and grade 3 (8.3%) respectively [12]. These facts emphasize on the frequency of morphological grades of similar types, regardless of regional differences as well as higher possibility of late diagnosis of this malignancy. Lower 1/3rd of the esophagus was found to be the most common location overall as well as for both major histological types, followed by middle and upper thirds respectively (Table 1). Similar statistics regarding highest frequency of malignancy in lower third of esophagus have been reported from the region [6]. One of the possibilities of frequent involvement of lower one third of esophagus could be its association with Gastroesophageal Reflux Disease (GERD).

Most common presenting complaints of patients were dysphagia (95.7%) and weight loss (75.3%). In the majority of patients, dysphagia developed initially for solids and

subsequently for liquids. Odynophagia was the third most common symptom (44.1%), commonly in the 4th and 5th decade of life (P = 0.043). Hoarseness was found in 28%, most common with lower 1/3rd involvement. (P= 0.009). These observations are in agreement with a previous study of this region [6]. The increased severity of symptoms with time is indicative of progression to advanced stage of malignancy. This finding again indicates the fact that the delayed diagnosis of esophageal cancer is not an uncommon event.

About 61.2% patients were diagnosed either at stage 3 or 4. Table 2.0. A study conducted in Thailand reported more than 90% of the cases presented at late stage. Advanced stage disease is reported to have a poor prognosis and low survival rate [7]. Decreased awareness among masses regarding symptoms of esophageal malignancy was an important contributor to late diagnosis in the current series. Approximately 87(93.5%) of our patients did not have previous information about symptoms and signs of this disease until diagnosed. This is indicative of lack of awareness in the general population related to this ailment. Routine annual check-ups are not being offered at public sector tertiary care hospitals of the region. General physicians in the locality usually offer symptomatic treatment instead of advising early diagnostic workup including endoscopy, biopsy or referring the patients timely to medical specialists. Furthermore, this finding is supported by another study stating that the primary care physicians in the largest city of Pakistan are deficient in practicing World gastroenterology organization (WGO) practice guidelines [13]. All these factors contribute to the advancement of the disease at the time of diagnosis. In the present study, 53.8% of patients were investigated for endoscopic histological sampling after remaining on symptomatic treatment for approximately two months, by general physician (P = 0.003).

Genetic alteration is another significant contributor in development of esophageal carcinoma. Although it is not well understood but repeated chromosomal gains, losses and amplification have been reported [1, 14]. In the current study 21.5% patients had a positive family history of various malignancies at different sites. Supporting our observation, a Chinese cohort revealed 34.7% of esophageal cancer cases who had first-degree relatives suffering from cancer. Individuals with both parents affected by this malignancy were 8 times more likely to develop esophageal carcinoma. A positive family history of other types of malignancies were also found to be associated with an increased risk of this malignancy [15].

Limitation:
Loss of follow up of patients is one of the limitations of this study. No official cancer registry of the Southern province of Sindh was available for comparative analysis. Factors associated with late stage diagnosis were not compared because of lack of data in published studies.

Recommendation:
We recommend public awareness programs to spread information regarding symptoms of esophageal carcinoma. Symposiums for General physicians should be organized to increase the rate of early referrals.

Conclusion

Esophageal carcinoma is a fairly common malignancy in the region. SCC is the most common histological type. Initial diagnosis of most of the patients was made in the late stage of the disease. Important contributing factors of late diagnosis were inadequate awareness of patients, delayed initial diagnostic workup, poor socioeconomic status and late referrals to oncologist by general physicians. No significant association was observed between ethnicity and grading or staging of esophageal carcinoma.

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