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Survival data and prognostic factors seen in Pakistani patients with esophageal cancer

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Background: Esophageal cancer is common in Pakistan. An attempt has been made for the first time to look at the survival data and prognostic factors associated with esophageal cancer in this region.

Patients and methods: We did a retrospective review of 263 cases seen at the Aga Khan University Hospital in Karachi. Data analysis was done using the Kaplan–Meier method and the Cox proportional hazard model.

Results: Squamous cell carcinoma was noted in 81% of the cases, whereas adenocarcinoma was the second most common. At the time of diagnosis, early-stage disease was found in 25%, locally advanced in 41% and metastatic in 34% of all cases. Mean age at diagnosis was 56 years, with 59% males and 41% females. Survival data were available in 89 cases. Median survival was 7 months. On univariate analysis, the following factors were of prognostic significance: obstruction, histology, albumin level at diagnosis, age and platelet count. On multivariate analysis, three factors were found prognostic: presence or absence of obstruction, squamous cell carcinoma versus adenocarcinoma and platelet count.

Conclusions: We found that patients with squamous cell carcinoma and absence of thrombocytopenia and obstruction had a better overall survival. However, this is a limited retrospective analysis; we therefore recommend that these prognostic factors be evaluated in larger studies.

Key words: histology, obstruction, prognostic factors, survival, thrombocytopenia

Introduction

Esophageal cancer is one of the 10 most common cancers and the sixth most common cause of cancer deaths worldwide. It is the third most common gastrointestinal malignancy after gastric, colorectal and hepatocellular cancers. Esophageal cancer displays unique epidemiological features that distinguish it from other malignancies. It shows marked geographical variation, with exceptionally high rates (some of the world's highest for any cancer) ranging from 3 per 100 000 per year reported in Western countries to 140 per 100 000 reported in Central Asia [1–3]. The malignancy is relatively more common in Pakistan, being the seventh most common cancer in men and the sixth most common in females in Karachi [4]. Data from Karachi show the predominant histology to be squamous cell carcinoma [5] as opposed to adenocarcinoma, which is the more common variety in the West. There have not been any studies in this region on the survival statistics and prognostic factors of esophageal cancers.

Esophageal cancer is one of the most virulent tumors with a dismal prognosis, despite the recent advances in early diagnosis and treatment. It has one of the lowest possibilities of cure, with a 5-year survival rate of approximately 10%; these rates are second only to hepatobiliary and pancreatic cancers [6]. Given this and the fact that the incidence of esophageal cancer is on the rise, further details of this malignancy are required, especially squamous cell carcinoma.

Patients and methods

A retrospective review of all the 263 cases seen at the Aga Khan University Hospital, a tertiary-care hospital in Karachi, from 1 January 1995 to 30 June 2002 was done. International Classification of Disease-10 was used for coding. Data were analyzed using SPSS (Release 10.05, standard version, copyright ©SPSS; 1989–99). Descriptive analysis was done for demographic, clinical and radiographic features. Results were expressed as means ± standard deviation and percentage. The probability curves for survival were calculated according to the Kaplan–Meier Method and compared by the log-rank test. Multivariate analysis was carried out using the Cox proportional hazard model. $P < 0.05$ was considered as statistically significant.

In this study we looked at the following parameters: signs and symptoms, risk factors, laboratory data, imaging modalities, histology, status of the disease, overall survival and various prognostic factors of the disease.

Results

Out of the 263 cases reviewed, a male preponderance was observed (59% males versus 41% females). The mean age at the time of diagnosis was 56 years. Median age was 60 years (range 22–85). See Figure 1 for age distribution.

Dysphagia was the most frequently encountered symptom at the time of presentation, seen in 97% of the cases. Obstruction, seen

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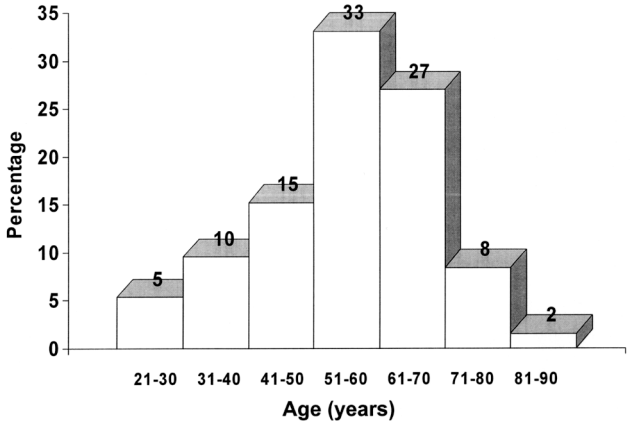

Figure 1. Age distribution of the 263 reviewed cases. Values above the bars are percentages.

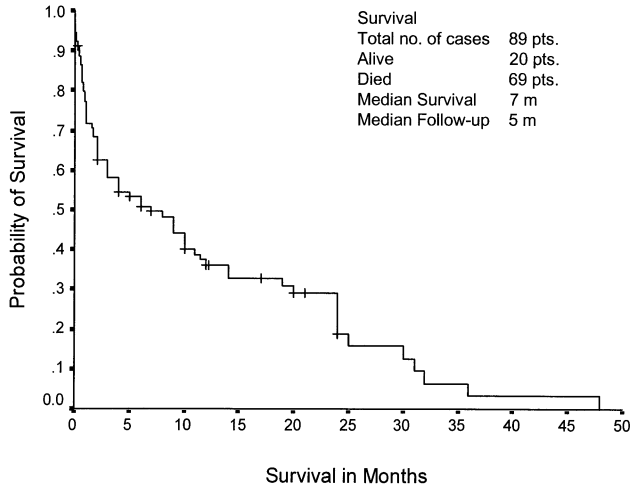

Figure 2. Survival data for the 89 patients for whom it was available. m, months; pts, patients.

Table 1. Characteristics of the 263 patients

Gender	
Male	59%
Female	41%
Age (mean years ± SD)	56.3 ± 13.0
Platelets, × 10^9/l (mean ± SD)	312 ± 141
Albumin, mg/dl (mean ± SD)	3.14 ± 0.73
Site	
Upper	25%
Middle	23%
Lower	52%
Dysphagia	97%
Obstruction	3%
Weight loss	69.5%
Alcohol/smoking/pan	
Alcohol	1%
Tobacco	35%
No identifiable risk	64%
Type	
Fungating	37%
Ulcerating	41%
Fungating and ulcerating	22%
Histology	
Squamous cell	81%
Adenocarcinoma	19%
Stage	
Early	25%
Locally advanced	41%
Metastatic	34%

SD, standard deviation.

endoscopically or on computed tomography scans, was present in 3% of patients. Seventy percent of the patients gave a history of weight loss. Tobacco use was found in 35% of the patients and 1% of the patients had a history of alcohol use.

Of the 263 patients, a histology report was available for 235 cases. Squamous cell carcinoma was seen in 81% of the patients and adenocarcinoma in 19%. Staging was primarily clinical. Early-stage (localized disease with no lymph node involvement) was seen in 25% of cases, locally advanced in 41% and metastatic in 34% of all the cases at the time of diagnosis. The most common site was the lower esophagus (52%) followed by upper (25%) and then middle esophagus (23%). Lesions were fungating in 37% of the cases, ulcerating in 41% and both ulcerating and fungating in 22% of the cases (Table 1).

Survival data were available in 89 cases. The overall median survival was 7 months (Figure 2).

According to univariate analysis, the factors influencing overall survival rate were: presence or absence of obstruction, histology (squamous cell versus adenocarcinoma), serum albumin >2.5 mg/dl on diagnosis, age <55 years at diagnosis and platelet count >150 × 10^9/l at diagnosis. Staging was borderline significant (Table 2).

Three variables were independent prognostic factors for survival as determined by multivariate analysis: presence or absence of obstruction [relative risk (RR) = 5.4; P = 0.025] (Figure 3); squamous cell carcinoma versus adenocarcinoma (RR = 2.8; P = 0.006) (Figure 4); high (>150 × 10^9/l) versus low platelet count at the time of diagnosis (<150 × 10^9/l) (RR = 6.58; P = 0.001) (Figure 5).

The following variables were not of prognostic significance in relation to survival: gender (P = 0.46); weight loss (P = 0.73); supraclavicular lymphadenopathy (P = 0.3); length of the tumor (P = 0.83); primary treatment modality, i.e. surgery versus chemotherapy (P = 0.667); and various laboratory parameters which were obtained before chemotherapy (hemoglobin, leukocyte count, blood urea nitrogen, creatinine, bilirubin and serum alanine aminotransferase).

Table 2. Factors influencing overall survival rate

	No. of subjects	Survival (months)	*P* value
Obstruction (*n* = 87)			
Present	3	1	0.031
Absent	84	9	
Histology (*n* = 77)			
Adenocarcinoma	13	6	0.034
Squamous cell	64	10	
Albumin (*n* = 40)			
≥2.5 mg/dl	31	12	0.005
<2.5 mg/dl	9	1	
Age (*n* = 89)			
≥55 years	48	2	0.016
<55 years	41	12	
Platelets (*n* = 79)			
≥150 × 10^9/l	75	9	0.003
<150 × 10^9/l	4	1	
Stage (*n* = 72)			
Early	15	14	0.056
Locally advanced	32	9	
Metastatic	25	3	

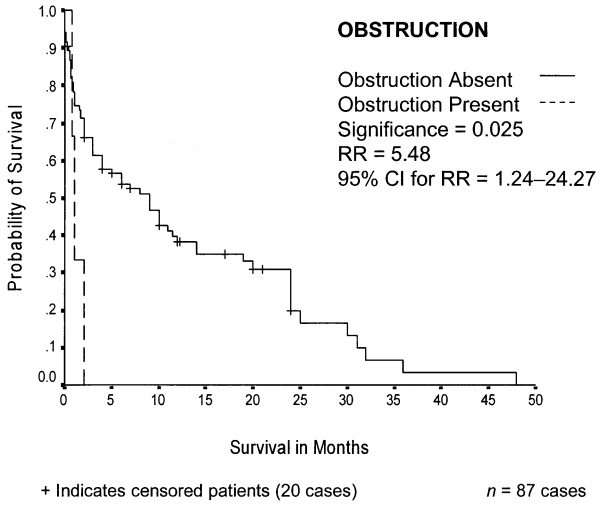

Figure 3. Presence or absence of obstruction as a prognostic factor for survival. Eighty-four cases; + indicates censored patients (20 cases). CI, confidence interval; RR, relative risk.

Discussion

This single institution study of a South-East Asian population has looked at the demographic features, risk factors, survival data and prognostic indicators of esophageal cancer. Such a study has not been reported from this region before.

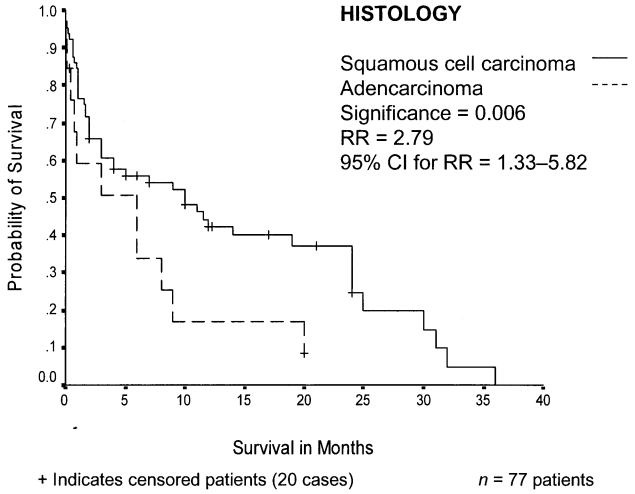

Figure 4. Histology as a prognostic factor for survival. Seventy-seven patients; + indicates censored patients (20 cases). CI, confidence interval; RR, relative risk.

Prevalence of esophageal cancer is high in Pakistan, accounting for 5% of all cancers in men within our institution, from where these data were retrieved [7]. At other places within the country, the prevalence is reportedly even higher. Quetta, a city in Northern Pakistan reports that this is the third most common cancer in men [8]. This place has close proximity to Afghanistan and Iran where this disease is endemic.

The average age at diagnosis in our patients was 56 years, median age being 60 years (range 22–85). The median age at presentation is 72 years according to data from Scotland [9]. This cancer therefore, is a disease of the younger age group in our country.

The male to female ratio was 1.4 : 1, which is similar to the results from other data from this region [5]. Male to female ratio is 3 : 1 according to data from the United States [10]. The about equal male to female ratio in our country is at least partly explained by the habits of chewing tobacco, seen commonly in both sexes here, and a risk factor for this cancer, especially squamous cell carcinoma, the more common histology here. The European data for sex ratio varied from 1.9 : 1 in Scotland to 16.3 : 1 in Calvados, France [11]. Around the rest of the world the incidence of esophageal cancer is four to six times higher in men than in women for all age groups, except is China, northern Iran and the former USSR where the ratio is 1 : 1 [12].

Dysphagia was the most common presenting complaint, seen in 97% of the patients. Weight loss was the other more common feature at presentation, notable in 70% of our patients. Data from another region [13] showed that only 42% of the patients had weight loss at presentation. Clearly, this speaks for advanced stage at presentation in our patients. Since the esophagus lacks a serosal covering, it is distensile and can accommodate considerable intramural growth before deglutition is affected. Sixty-five percent of the esophageal lumen must be involved before patients notice dysphagia [14].

Smoking increases the risk of developing squamous cell carcinoma of the esophagus by five-fold to 10-fold, and of devel-

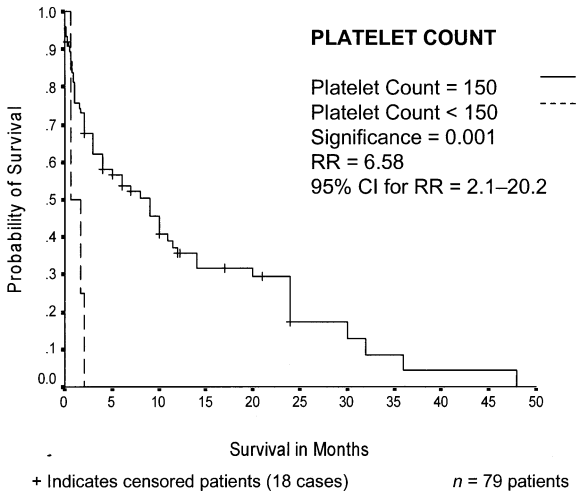

Figure 5. High versus low platelet count as a prognostic factor for survival. Seventy-nine patients; + indicates censored patients (18 cases). CI, confidence interval; RR, relative risk.

oping adenocarcinoma by two-fold. Alcohol has an additive, and perhaps synergistic effect, where the risk increases to as high as 100-fold [15–18].

Tobacco use, seen in 35% of our patients, is a major risk factor for esophageal cancer. This is in contrast to the European data, as Negri et al. [19] reported that 61% of esophageal cancer was attributable to smoking in Italy. The forms of tobacco are different here; these include chewing tobacco and bidi smoking, which are common in Pakistani and Indian populations and are considered a risk for developing this malignancy [20, 21]. Drinking alcohol is not common in our part of the world. Only 1% of our cases had a history of alcohol usage. This is much less than in Italian data, where it accounted for 39% of the cases. It is also possible that other dietary factors may be playing a role in the high incidence of esophageal cancer, like drinking of very hot beverages such as tea and Kawa, which are again extremely common in Pakistan. These have been described in other studies done in India [22, 23], which has a lifestyle and dietary practices similar to those in Pakistan.

Endoscopically, ulcerative appearance (41%) was the most common followed by fungating (37%) and a combination of both ulcerative and fungating (22%). There appeared to be no obvious histological or prognostic correlation in any of these findings.

Squamous cell carcinoma of the esophagus (81%) was the predominant histology seen in our study, with adenocarcinoma (19%) being less in proportion. These data are consistent with data from most of Asia [24, 25]. These figures are different from those found in the developed countries where adenocarcinoma is the more abundant type, primarily because of a high frequency of Barrett's esophagus [26]. Adenocarcinoma constitutes about 50–60% of the cases of esophageal carcinoma in the West [27, 28].

The most common site of malignancy was the lower esophagus (52%). The middle esophagus was involved in 23% and the upper esophagus in 25% of cases. Despite the most common site being the lower esophagus, the most common histology was squamous cell carcinoma; this speaks for the low probability of Barrett's esophagus as an etiology of esophageal carcinoma in our population. Western data show that the lower esophagus was involved in 30% of cases, whereas 60% and 10% arise from the middle and upper third of the esophagus, respectively [29, 30].

Survival data were available for 89 patients. The overall median survival was 7 months. Median survival is 14 months, 9 months and 3 months for early disease, locally advanced and metastatic disease, respectively. This is comparable with the Western data, where early disease had a median survival of 1.4 years for locoregional disease in one study [31].

In our study, on univariate analysis, the following were found to be favorable: absence of obstruction, squamous cell carcinoma, normal albumin levels, age <55 years and platelet count $>150 \times 10^9$/l. On multivariate analysis, three factors were found prognostic: obstruction, thrombocytopenia and histology. Prognostic factors described in the literature include the depth of invasion, lymphatic spread, venous invasion and distant metastasis. Other factors such as DNA ploidy status, tumor differentiation, oncogenes, growth factors and other markers are under study as prognostic indicators. Whereas in colorectal cancer, Chen et al. [32] have described obstruction as a poor prognostic sign, this has not been reported in esophageal cancer. Histology has also not been described to be prognostic in most large studies. In one study, T1 adenocarcinoma appeared to be more favorable than T1 squamous cell carcinoma [33–36]. And in another study, resected adenocarcinoma did better than resected squamous cell carcinoma [37]. As well, thrombocytopenia has not been described as prognostic in esophageal cancers. Rather, we find reports that thromobocytosis is associated with poor prognosis in other gastrointestinal cancers, including gastric, hepatocellular and colorectal cancers [38–40]. We caution, however, that the numbers of patients with adencarcinoma, obstruction and thrombocytopenia in our study were small.

Conclusion

The predominant histology in our patients with esophageal carcinoma was squamous cell carcinoma (81%). The overall median survival was 7 months. Our patients with squamous cell carcinomas had a better overall survival. Those with thrombocytopenia and obstruction had an unfavorable outcome. We recommend that the results of this retrospective analysis of a small number of patients be evaluated in larger prospective studies.

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