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Original Research

Survival analysis and prognostic factors of oesophageal carcinoma: a follow-up study

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Abstract

Introduction: Oesophageal carcinoma (OC) is a leading cancer in Sri Lanka. Despite the advancements in treatment, survival of patients with OC is reported to remain low. Thus, obtaining an insight into the survival and its prognostic factors is essential for policy making.

Objectives: To determine the survival and its prognostic factors among oesophageal carcinoma patients

Methods: All newly diagnosed cases of OC at the National Cancer Institute Maharagama (NCIM) during the period of May 2015 to May 2016 (n=110) were followed up for one year to assess their survival. Univariate Kaplan-Meier Survival analysis (Log Rank test) was used to assess the survival of demographic, socio-economic and clinical subgroups; and subgroups of population-specific risk factor profile for OC in Sri Lanka. In multivariate analysis, Cox-Proportional Regression was used to assess the Hazard Ratio (HR) of the prognostic factors of survival.

Results: One-year survival rate of the participants was 8.2% with median survival of four months (95% CI: 3.2, 4.8). Univariate analysis revealed that those of less than 60 years (p=0.006), with secondary or higher education (p=0.017), with monthly income >Rs. 20 000 (p=0.026), having adenocarcinoma (p=0.001), of stage I disease (p<0.001), undergone surgery (p<0.001), never smoked (p=0.044) and having high total lifetime sports and exercise activity level (p<0.001) had increased survival. Cox-Regression analysis revealed that being 60 years or older (HR=1.713; p=0.012), having primary or lower education (HR=1.702; p=0.027); with low lifetime sports and exercise activity level (HR=2.32; p=0.004); undergone palliative treatment only (HR=46.546; p<0.001), chemotherapy (HR=2.902; p=0.003) or radiotherapy (HR=6.696; p<0.001) were independent prognostic factors for survival among OC patients.

Conclusions & Recommendations: Oesophageal carcinoma is a disease with poor prognosis. Implementation of community-based novel mechanisms to improve physical activity in the general public, detection of OC early focusing on the vulnerable population and development of new treatment guidelines to improve survival of the OC patients are recommended.

Key words: *oesophageal carcinoma, survival, prognostic factors, Sri Lanka*

Introduction

Oesophageal cancer (OC) is the eighth commonest cancer in the world and is known to be highly virulent, assuming the sixth position and causing 5.5% of all cancer deaths across the globe in 2020(1). It continuously reports to be one of the five leading cancers in Sri Lanka (2-4), where it continues to be the fourth commonest cancer among males and the sixth commonest among the females, comprising 5.7% of all cancer cases in the year 2015 (4). In addition, OC had been the fourth leading cause of cancer deaths among males and the ninth among females in Sri Lanka in the year 2014 (4).

Oesophageal cancer still reports to have a higher mortality despite the recent advancements in cancer diagnosis, treatment and management. The prognosis of OC is known to be related to the disease stage (5), where the five-year survival rates for stages I, II and III are 50-80%; 30%-40% and 10-15% respectively, while stage IV has a median survival of less than one year (6). Oeophageal carcinoma is a fast-growing tumour with a high cell doubling time (7), with ability to easily metastasize. Nevertheless, the clinical diagnosis of OC is often delayed and relatively longer owing to its asymptomatic early stage of the disease. This in turn plays a crucial role for poor prognosis (6). Further, treatment of OC often requires an interdisciplinary approach. Early stages (Stage I and early-Stage II disease) of OC can be treated with radical surgery as in many other cancers. However, the locally advanced disease (Stages II and III) would require neoadjuvant chemoradiotherapy or perioperative chemotherapy, while advanced disease (Stage IV) is treated with radiotherapy and often with palliative therapy (8). Nevertheless, in addition to the tumour stage and treatment option (9), many other factors such as age, economic status and presence of comorbidities can affect the overall prognosis of a patient with OC (10) as well. Despite its importance, studies related to survival of oesophageal cancer patients and prognostic factors are scarce internationally and locally. In bridging this knowledge gap, this paper provides an insight into the survival of patients with oesphageal carcinoma and its potential prognostic factors.

Methods

This was a follow-up study in which a cohort of patients who were newly diagnosed of OC (within the last three months of recruitment into the study) based on histological confirmation following upper gastrointestinal endoscopy examination, were recruited, during the period of May 2015 to May 2016. Those who were critically ill or with documented evidence of secondary carcinoma (e.g., metastasis), any other type of cancer or relapse including OC were excluded from the follow-up. Patients fulfilling these eligibility criteria were recruited from surgical and oncology wards and clinics of the NCIM, which is the premier tertiary care referral hospital in Sri Lanka dedicated for the treatment and follow-up of cancer patients who are referred predominantly from the state sector and also from the private sector hospitals. The NCIM is located in the Western Province, which reports the second highest incidence of OC in Sri Lanka (4) and represents the highest population density in Sri Lanka (11).

Data related to demographic and socio-economic characteristics (e.g., age, sex, highest level of education, income), and data related to the population-specific risk factor profile of OC for Sri Lankans (12) were obtained following an interviewer administered questionnaire. Data related to the clinical characteristics of the disease (e.g., type, grade, stage of the tumour; site of the tumour) and information related to the treatment of the patients were obtained from the clinical records. The population-specific risk factor profile for oesophageal carcinoma included age, inadequate consumption of antioxidants, inadequate consumption level of dietary fibre, over-consumption of deep-fried food, betel quid chewing, radiation exposure, family history of cancer, alcohol consumption risk level, lifetime total sports and exercise activity level, agrochemical exposure, drinking water source and tobacco smoking. Further details are published elsewhere (12). The outcome of the study was considered as death. The survival time was defined as the time lapse from the date of diagnosis to death. The last date of follow up of patients was 1st June 2017. The patients were

contacted via telephone every three months and short messages were sent every month during the period of follow-up to make sure that there was no loss to follow-up.

Data were analysed using the Statistical Package for Social Sciences (SPSS) version 22. Descriptive statistics with mean and standard deviation (SD), median and inter-quartile range (IQR), and proportions were used to describe the study sample. Kaplan-Meier survival analysis was used for the univariate analysis to assess the survival for various demographic, socio-economic and clinical subgroups. Multivariate analysis using Cox-Proportional Regression was used to assess the independent prognostic factors for survival. The level of significance was considered to be $p<0.05$.

Results

A total of 110 patients was included in the study. There was no loss to follow up. The patient characteristics are shown in the Table 1. Half of the patients (50%) were from the district of Colombo, while 32.7% were from Gampaha and 17.3% from Kalutara districts of the Western Province. The mean age of participants was 60 years (SD=11.5). Most of them were 60 years and above (51.8%), males (69.1%), with secondary education (70%), skilled workers (59.1%) and having a monthly family income of more than Rs. 20 000 (53.6%).

Majority (63.6%) of the study participants had suffered from symptoms for three months or more prior to the diagnosis. Most of the patients were diagnosed of oesophageal squamous cell carcinoma (62.7%), at the lower thoracic oesophagus and the gastro-oesophageal junction (62.7%) and having stage IV disease (42.7%), with moderately differentiated cells (65.5%). Less than half was offered radiotherapy as the main treatment modality (40%).

The median survival of the study participants was four months (95% CI: 3.2, 4.8). One year survival rate was 8.2%. The overall survival estimation curve is shown in Figure 1.

Univariate analysis indicated that age being less than 60 years (median survival=5 months; 95% CI: 3.35, 6.65; p=0.006); having a secondary or higher educational level (median survival =4 months; 95% CI: 2.69, 5.31; p=0.017); having a monthly income more than Rs. 20,000 (median survival=4 months; 95% CI: 2.55, 5.45; p=0.026); having oesophageal adenocarcinoma (median survival=6 months; 95% CI: 2.87, 9.13; p=0.001); having stage I disease (survived during the full period of follow up of 12 months; $p<0.001$) and undergoing surgery as the main treatment option (median survival=10 months; 95% CI: 9.5, 10.5; $p<0.001$) significantly improved the survival of study participants. Among the behavioural risk factors for developing OC, never smoking (median survival=4 months; 95% CI: 2.27, 5.73; p=0.044) and having a high total lifetime sports and exercise activity level (median survival=7 months; 95% CI: 1.52, 12.48; $p<0.001$) significantly influenced the survival. However, when Cox-Proportional Regression analysis was applied, it was revealed that being 60 years or older (HR=1.713; p=0.012); having a primary or lower education (HR=1.702; p=0.027); with low lifetime sports and exercise activity level (HR=2.32; p=0.004); and undergoing palliative treatment only (HR=46.546; $p<0.001$), chemotherapy (HR=2.902; p=0.003) or radiotherapy (HR=6.696; $p<0.001$) were independent factors relevant to the prognosis of patients with OC.

Table 1: Distribution and Kaplan Meier estimates for survival for demographic, socio-economic and clinical characteristics of the study sample (N=110)

Characteristic	No.	%	Significance (Log rank test)
Demographic and socio-economic characteristics			
Age			
Less than 60 years	53	48.2	$X^2 = 7.677$
60 years and above	57	51.8	df = 1
			p = 0.006
Sex			
Males	76	69.1	$X^2 = 0.022$
Females	34	30.9	df = 1
			p = 0.882
Highest level of education			
Primary education or lower	31	28.2	$X^2 = 5.696$
Secondary education or higher	79	71.8	df = 1
			p = 0.017
Monthly family income			
Rs. ≤20,000	51	46.4	$X^2 = 4.946$
Rs. >20,000	59	53.6	df = 1
			p = 0.026
Social status			
Professionals	8	7.3	$X^2 = 5.659$
Skilled workers	65	59.1	df = 2
Unskilled workers	37	33.6	p = 0.059
Clinical characteristics			
Duration of symptoms prior to diagnosis			
< 3 months	40	36.4	$X^2 = 0.358$
≥3 months	70	63.6	df = 1
			p = 0.55
Type of oesophageal cancer			
Squamous cell carcinoma	69	62.7	$X^2 = 11.737$
Adenocarcinoma	41	37.3	df = 1
			p = 0.001
Site of the tumour in relation to the oesophagus			
Upper thoracic oesophagus	25	22.7	$X^2 = 3.329$
Middle thoracic oesophagus	16	14.5	df = 2
Lower thoracic oesophagus and Gastro-oesophageal junction	69	62.7	p = 0.189
Tumour grading			
Well differentiated cells	12	10.9	$X^2 = 2.708$
Moderately differentiated cells	72	65.5	df = 2
Poorly differentiated cells	26	23.6	p = 0.258

Tumour staging			
Stage I	3	2.7	$X^2 = 96.692$
Stage II	19	17.3	df = 3
Stage III	41	37.3	**p<0.001**
Stage IV	47	42.7	
Main treatment modality			
Surgery	17	15.5	$X^2 = 96.142$
Radiotherapy	44	40.0	df = 4
Chemotherapy	33	30.0	**p<0.001**
Neoadjuvant chemoradiotherapy	9	8.2	
Palliative treatment only	7	6.4	

Table 2: Kaplan Meier estimates for survival and distribution of the population- specific risk factor profile for development of oesophageal cancer among the study sample (N=110)

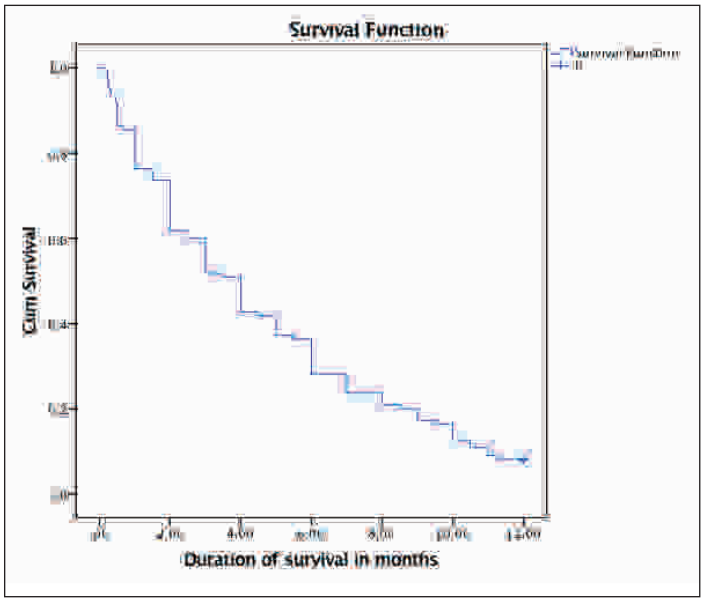
Population-specific risk factor for oesophageal carcinoma	No.	%	Significance (Log rank test)
Family history of cancer			
Yes	24	21.8	$X^2 = 2.167$
No	86	78.2	df=1
			p=0.141
Betel Quid chewing			
Ever chewed	66	60.0	$X^2=3.249$
Never chewed	44	40.0	df=1
			p=0.071
Predominant water source			
Pipe-borne water	64	58.2	$X^2=2.118$
Non-pipe borne water	46	41.8	df=1
			p=0.146
Exposure to radiation			
Yes	45	40.9	$X^2=0.289$
No	65	59.1	df=1
			p=0.591
Smoking status			
Ever smoker	60	54.5	$X^2=4.047$
Non-smoker	50	45.5	df=1
			p=0.044
Consumption of deep-fried food			
Overconsumption	53	48.2	$X^2=0.282$
Not-overconsumption	57	51.8	df=1
			p=0.595
Exposure to agrochemicals			
Yes	41	37.3	$X^2=1.621$
No	69	62.7	df=1
			p=0.203

Alcohol consumption			
High-risk consumption	59	53.6	X^2=0.139
Low-risk consumption	51	46.4	df=1
			p=0.709
Lifetime sports and exercise activity level			
Low	87	79.1	X^2=15.513
High	23	20.9	df=1
			p<0.001
Consumption of antioxidants			
Sub-optimal consumption	70	63.6	X^2=0.618
Optimal consumption	40	36.4	df=1
			p=0.432
Consumption of fibre			
Sub-optimal consumption	52	47.3	X^2=0.169
Optimal consumption	58	52.7	df=1
			p=0.681

Table 3: Cox regression analysis of independent prognostic factor survival of patients with oesophageal cancer (N=110)

Characteristic	HR (95% CI)	Significance
Age		
60 years and above	1.713 (1.125, 2.609)	**p=0.012**
< 60 years (reference)	1.00	
Highest educational level		
Primary or lower	1.702 (1.061, 2.729)	**p=0.027**
Secondary or higher (reference)	1.00	
Lifetime sports and exercise activity level		
Low	2.320 (1.318, 4.084)	**p=0.004**
High (reference)	1.00	
Main treatment modality		
Palliative treatment only	46.546 (15.252, 142.050)	**p<0.001**
Radiotherapy	6.696 (3.176, 14.114)	**p<0.001**
Chemotherapy	2.902 (1.441, 5.847)	**p=0.003**
Neoadjuvant chemoradiotherapy	1.853 (0.738, 4.651)	p=0.189
Surgery (reference)	1.00	

Figure 1: Kaplan Meier survival graph of survival of OC patients (N=110)



Discussion

Our study demonstrated poor prognosis among the patients diagnosed with OC. We found that the prognosis worsened with age being 60 years or more, with primary or lower educational level, having low lifetime sports and exercise activity level, and undergoing either palliative treatment only, chemotherapy or radiotherapy, after adjusting for confounders.

Survival rates of the patients with OC are reported to be low, with five-year survival being less than 20% (13). However, it is reported that the survival rates of OC in developing countries are lower compared to that of the developed countries (14-15). Majority of the patients in our study were diagnosed with late stage of the disease. This could be the reason for the observed high mortality rates in this study.

Our study determined that the survival of OC patients worsens with increased age. This finding was similar to a study conducted among 10 441 OC patients in the USA which revealed that increasing age is associated with poor survival of OC irrespective of the stage of the disease (for localized OC: HR=1.27; 95% CI: 1.18, 1.37; p<0.0001; for OC with regional spread: HR=1.15; 95% CI: 1.06, 1.25; p=0.0013; for distant OC: HR=1.17; 95% CI: 1.09, 1.26; p<0.0001) (16). Similar findings were reported in a systematic review conducted using 19 studies, including 6729 elderly OC patients (aged over 65 years), which reported that the median survival rates ranged from 9.6 to 108.2 months and with 30-day mortality ranging from 3.2% to 8.1% (17). In another study conducted in China, the survival of patients who were above 45 years was relatively low (HR=1.72; p<0.04) (18). A study from Iran showed that compared to those who were 45 years or below, the patients of 45-65 years (HR=3.43; 95% CI: 1.03, 11.41; p=0.044) and patients over 66 years, HR=9.78; 95% CI: 2.93, 32.64; p<0.0001) had poorer survival (19).

Our study revealed that undergoing palliative treatment only, radiotherapy and chemotherapy have higher risk of mortality compared to undergoing surgery. These findings were similar to an Iranian study, where undergoing radiotherapy (HR=7.27; 95% CI: 1.53, 34.39; p=0.012), chemotherapy (HR=2.79; 95% CI: 1.35, 5.73; p=0.005) and palliative treatment only (HR=3.08; 95% CI: 1.5, 6.34; p=0.002) showed poor survival compared to those who underwent surgery (19). A study conducted in China reported that the 3 year- and 5-year survival rates following oesophagectomy were 43.7% and 26.2%, respectively (20). A national study conducted in Sweden (21), and a nationwide study conducted among Korean OC patients (22) also

reported that patients who underwent surgery had better survival compared to those who underwent other treatment modalities. Further, the Iranian study indicated that the survival was improved in combination therapy of surgery, chemotherapy and radiotherapy (HR=0.36; 95% CI: 0.13, 0.95; p=0.04) (19). Nevertheless, it is reported that the overall treatment plan of a patient with OC should be developed after multidisciplinary evaluation (23). However, contrasting findings had also been reported in a multinational review (15) and in other studies (24).

Survival of OC is reported to be linked to the tumour grading and stage of the OC. Tumour grading is incorporated into the staging of the cancer, which in turn precedes the treatment modality and survival. A study conducted in the USA showed that higher grading of the disease with the involvement of more than five lymph nodes, increased the risk of mortality (HR=1.29; 95% CI: 1.06, 1.56) (16). In addition, the same study revealed that having a stage IV disease with distant metastasis (HR=1.37; 95% CI: 1.37, 1.65) and tumour length (HR=1.15; 95% CI: 1.08, 1.21) have higher risk of mortality (16). In contrast, our study failed to detect tumour staging as an independent prognostic factor for the survival of patients with OC. However, since the surgery is offered as the main treatment modality to patients at early stages of OC, it could be considered as a reflection of early-stage disease. It is important to note that the current study reported undergoing surgery as an independent prognostic factor of survival, irrespective of the staging of the disease.

This implies the overall importance of early detection of OC for better survival. However, a study conducted among OC patients at the National Hospital Colombo revealed that the median delay from the appearance of the first symptom to the diagnosis of OC following upper gastro-intestinal endoscopy (UGIE) and histological diagnosis - which is the main mode of diagnosis - was 14.9 weeks, with the majority (83.3%) having more than one month delay in diagnosis (6). The authors also reported that the patient delay from the point of appearance of the first symptom to the first contact with the free healthcare system of the country accounted for 82.2% of this delay. This indicates the importance of educating the general population on OC, identification of risk factors and early symptoms of OC, and the importance of seeking medical care soon. Further, our study revealed that the overall survival of a patient with OC is highly influenced by the educational level of the patient. In concurrence, a Swedish population-base cohort study revealed that compared to the patients who had 'high education' (13 years or more of formal education, including post-secondary education), the 'intermediate educated group'(10-12 years of formal education, including upper secondary education) (HR=1.29; 95% CI: 1.07, 1.57) and the 'compulsory educated group' (9 years of education or less, including primary and lower secondary education) (HR=1.42; 95% CI: 1.17, 1.71) had higher mortality following surgery for OC (25). Low education, resulting in poor health seeking behaviour, in turn resulting in delayed diagnosis of the disease could be the explanation for this observation, highlighting the importance of educating the general public on symptoms suspicious of OC.

Subasinghe & Samarasekara (2010) also reported that delay in UGIE also accounted for 7.1% of the delay between the appearance of the first symptom to the histological diagnosis following UGIE (6). Although, community screening of high-risk individuals for OC by UGIE would be ideal to reduce the burden on the secondary and tertiary care level hospitals to minimize the delays and for early diagnosis of the disease, it is not feasible especially in a low-resource country like Sri Lanka owing to its high cost and limited availability of human resources and equipment. As an alternative, this delay could be minimized by the introduction of a simple, low-cost screening tool as a secondary prevention strategy to identify the high-risk individuals for developing OC, and thereby prioritize the most at-risk persons for endoscopic confirmatory diagnosis, for early detection of OC.

Among the population-specific risk factor profile for OC for Sri Lanka (12), only low lifetime sports and exercise activity level was found to be influencing the survival of patients with OC. A study conducted among 303 OC patients who had undergone

oesophagectomy reported that postoperative leisure time physical activity (≥9 MET hours per week) reduced the risk of mortality by 23% (HR=0.666; 95% CI: 0.481, 0.921; p=0.014) (26). Considering other behavioural risk factors, smoking is reported to increase the mortality among patients with OC (27-29). However, the current study failed to identify smoking as an independent prognostic factor on survival of OC patients.

Conclusions & Recommendations

This study revealed that the one-year survival rate of patients with OC residing in Western Province is relatively low. The study also revealed that being 60 years or more, having primary or lower education, history of low lifetime total physical activity level, and undergoing palliative treatment only, chemotherapy or radiotherapy are independent factors influencing the survival of patients with OC. Therefore, community-based programmes should be implemented to improve physical activity in the general public. Further, novel community-based mechanisms such as application of low-cost simple risk prediction models by field-based healthcare staff should be implemented to detect OC early especially among the vulnerable population in low-resource settings. New treatment guidelines should also be developed to improve the survival of patients with OC.

Public Health Implications

- Having an insight on the survival rates would be an eye opener for the care providers and policy makers to act promptly for improving the survival of patients with OC. Also, insight on the prognostic factors of survival of OC will provide evidence for the policy makers to expedite the implementation of mechanisms for early detection of OC, development of guidelines and implementation of novel population-based mechanisms for healthy life-style promotion.

Author Declarations

Competing interests: The authors declare that they have no financial and non-financial competing interests.

Ethics approval and consent to participate: Ethics clearance was obtained from the ethics review committee of the Faculty of Medicine, University of Colombo, Sri Lanka (EC-15-019). The study was conducted in accordance with the Declaration of Helsinki. Administrative clearance was obtained from the Director and the relevant Specialists of the NCIM. Informed written consent was obtained from each participant prior to data collection.

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