Survival Status of Oesophageal Cancer Patients in Assam, India: A Bio-Statistical Analysis

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Research Article

Abstract: **Background:** The incidence and mortality of oesophageal cancer patients are high in Assam, India. No Bio-statistical study has been conducted so far to assess the survival pattern of oesopahgeal cancer patients in the state. This research work was undertaken to study the survival pattern of the oesophageal cancer patients with respect to some factors relevant to this region. **Methodology and Findings:** An analytical study was conducted on 251 patients diagnosed between 1st January 2007 and 31st December 2008 in Assam Medical College Hospital (AMCH), Assam. The data were analysed using different techniques of survival analysis. The average survival time was estimated to be 10.33 months (95% C.I. 7.86 to 12.88). The lower socio-economic group patients experienced lowest survival of 5.53 months and also higher risk of dying in comparison to higher socio-economic group. About 13% of the patients remained untreated whose average survival time was abysmally low of 3.33 months only, significantly less than the treated patients. The adjusted hazard ratio of the untreated patients was 4.54. Patient treated in Assam was experiencing a 2-fold risk of dying than that of the patients treated in metropolies of India. **Conclusion:** The survival of patients with oesophagus cancer was low in Assam. Socio-economic status, treatment and stage of cancer were important factors influencing the survival of patients with oesophageal cancer. The performance of health services with regard to cancer care in Assam is seemed to be poor in comparison to other parts of India.

Key words: Oesophagus cancer, survival, Kaplan-Meier product limit estimator, Cox Regression.

Introduction :

Oesophageal cancer is one of the most common cancer worldwide with a very poor prognosis, responsible for 462,000 new cases (4.2% of the total) and sixth most common cause of death from cancer with 386,000 deaths (5.7% of the total) in 2002 (Parkin et al., 2005). World Health Organization (WHO) estimated that it was the fifth most common cause of death globally in 2004 among male; while in case of female it was in the seventh place (World Health Organization, 2008). Oesophageal cancer is endemic in the developing nations , it is the fourth most common cancer in men, with an annual incidence rate of 12.2 per 100,000 in developing countries, while in the developed countries it is 6.4 per 100,000 (Day and Varghese, 1994; Parkin et al., 1999). The incidence of oesophagus cancer is high in India with an age standardized incidence rate of 7.6 per 100,000 for males and 5.1 per 100,000 for females (Pfizer Facts). Reports published by National Cancer Registry Programme (PBCR) from time to time showed that with respect to incidence and mortality, it is one of the major tobacco related sites both in males and females (National Cancer Registry Programme, 2001; 2002; 2004; 2006; 2007; 2009).

The state of Assam, located in the North-Eastern part of India extending from 89 degree 42 minutes E longitude to 96 degree E longitude and 24 degree 8 minutes N latitudes to 28 degree 2 minutes N latitudes in the graticule. Assam with an area of 78,438 sq. km. accommodating about 26 million (2001 Census) of India's population having different customs, food habits, life-style and diverse ethnic groups. The incidence of oesophagus cancer is high in the state of Assam in comparison to the other places of the country. Cancer data, from population based cancer registries in India (PBCR) showed the highest incidence of oesophageal cancer occur in the state of Assam in the country (National Cancer Registry Programme, 2001; 2002; 2004; 2006; 2007; 2009). It was the leading site among males of all cases reported in Assam Medical College Hospital (AMCH), Assam, Dibrugarh and Dr. Bhubaneswar Borooah Cancer Institute (BBCI), Guwahati, Assam during 2001 to 2007. Major proportion of the deaths due to cancer during this period in both the sexes was because of oesophagus cancer. The three population based cancer registries covering the state of Assam reported age adjusted incidence rate (AAR) for males of 32.5, 15.7 and 8.3 per 100,000; while in cases of females the reported AARs were 21.1, 8.2 and 12.1 per 100,000 during the period 2003-2004. These AARs for both the sexes were quite high in comparison to the other parts of the country. Among females also this site accounted for a predominant proportion of all the reported cases. This high incidence of oesophaugs cancer in Assam may be mostly due to the typical food habit among the people residing here. Studies showed that betel nut chewing with or without tobacco, pickle

consumption and a typical locally made food named Kalakhar consumed by the indigenous population of Assam are significant risk factors for oesophagus cancer in Assam (Phukan et al., 2001; Phukan et al., 2001) .

Measure of survival is a key indicator of the quality of cancer patient management. For effective formulation of a cancer control programme in a community, the information regarding the burden of the disease such as incidence, prevalence, mortality, survival, risk factors etc. are essential (World Health Organization, 2002, 2006; Yu X et al., 2004) . Dickman and Kakulimen (2003) suggested that the measure of cancer patients survival is more effective than measures of incidence and mortality in studying the overall burden of the disease. Survival of patients is a measure most often used to evaluate the effectiveness of overall cancer control programmes, early detection programmes and the effectiveness of cancer treatment together with other measures of studying cancer burden (World Health Organization, 2002; 2007; 2008). Armstrong (1992) asserted that measure of cancer patient survival is one of the most useful outcome measure for studying the components viz., screening, early diagnosis and treatment which could be undertaken with other three more components for reducing the frequency and impact of cancer.

Oesophageal cancer has an extremely poor prognosis. The average 5-year relative survival rate among adults diagnosed in 22 European countries during the early 1990s was approximately 10% (Sant et al., 2003). Sankaranarayanan et al. (1998) studied the survival status of developing regions of the world, he estimated that the 5 year survival rates of male oesophagus cancer patients ranges from 2.2% in Chaing Mai, Thailand (1983-92) to 33% in Khon Kaen, Thailand (1985-92); while in case of females the survival rates ranges from 4% in Qidong, China (1982-91) to 22.5% in Khon Kaen, Thailand (1985-92). Alidina et al., (2004) estimated that the overall median survival time for Pakistani patients with oesophageal cancer as 7 months, which was significantly varied with respect to histology, albumin level, age and stage. Tilaki (2001) estimated that the 5 year survival rate of oesophagus cancer patients in North Iran was 8%. Ries et al., (2007) estimated that in US the survival rate for whites and black oesophagus cancer patients were 18% and 11% respectively. However, the survival time of patients diagnoised with these particular cancer site has been constantly improving in developed countries like USA, Sweden etc. (Martin, 2002; National Cancer Institute, Ries et al., 2007; National Services Scotland, 2004; Cancer Statistics Group, 1982) Different sophisticated statistical methods have been developed specially to analyze survival (time-to-event) data (Kaplan and Meier,1958; Mantel, 1966; Peto and Peto, 1972; Cox, 1972)

This paper is based on a study carried out to assess the survival pattern of oeosphagus cancer patients of Assam, India and also to estimate the effects of different factors on their survival. It is first attempt, in this state of Assam, a state with high prevalence of oesophagus cancer.

Materials and Methods :

The study was taken up in a historical cohort and information from the medical charts of patients with oesophageal cancer in AMCH. The period of the study was from 1st January 2007 to 31st December 2009. All the patients diagnosed with oesophageal cancer during 1st January 2007 to 31st December 2008 were included in the study. Cases diagnosed during 2009 were excluded due to limited follow up (i.e., through 2009). During the inclusion period of the study a total of 251 patients were diagnosed with oesophageal cancer in AMCH. A pre-designed, pre-tested questionnaire was used for the collection of data. Information about age, sex, extension of the disease at the time of diagnosis, cancer directed treatments given, address of the patients were collected from the hospitals records. After collecting the hospitals records, a household survey were conducted to collect the information about the survival status of the patients, date of expired (if he/she expired), continuation of treatment and socio-economic status (Aggarwal et al., 2005) of the patients. Also, a re-verification of the information collected from the hospital was made during the household visit. The extension of the disease includes the stages : localized (confined to the oesophagus, with no evidence of spread to surrounding organs/tissues or no regional lymph nodes); regional (invasion beyond the organ to surrounding organs/tissues or no regional lymph nodes); distant/metastatic (spread to remote organs/tissues directly or by discontinuous metastasis) and unknown. Survival (in months) was estimated from the month of diagnosis until death, loss to follow up, or the end of 2009. The patients were considered as censored if they were alive beyond 31st December 2009, died due to other cause(s) or loss to follow up. Patients are categorized into three groups based on the cancer directed treatment. Those who are treated with surgery with/without the combination of radiotherapy and chemotherapy are designated as “surgery and others” while those who treated with radiotherapy, chemotherapy or both are termed as “other than surgery”. Further, the study subjects who

are not treated are termed as "no treatment". This is done with a view to study the significance of surgery and its combinations in survival of oesophagus cancer patients in Assam. Patients are classified into two groups according to the place of treatment taken. Those who are treated in Assam are termed as "Assam" while the patients taking treatment in big metropolies like Delhi, Mumbai, Chennai etc. outside Assam is termed as "outside Assam".

Kaplan-Meier product limit estimator (Kaplan and Meier,1958) was used to estimate the median survival time and proportion of patients surviving at a particular time. Logrank (Mantel,1966; Peto and Peto,1972) test was used to compare the survival time of oesophagus cancer patients possessing different socio-demographic and treatment characteristics. The Cox-proportional hazard model (Cox, 1972) was fitted to estimate the unadjusted and adjusted hazard ratio of dying with respect to different characteristics. All the data were analyzed by using SPSS Ver.17.0.

Results:

A total of 251 individuals diagnosed with oesophagus cancer during the study period were included in the study. The mean and median age of the patients was 59.13 and 59.5 years respectively with standard deviation of 11.61 years. A male preponderance was observed among the patients (67% males against 33% females). Only 19% of the patients were diagnosed in localized stage, whereas 38% in the regional stage and about 28% in distant stage. The stage at the time of diagnosis remained unknown for 16% of the patients. The profile of the study subjects are presented in table I.

The median survival time of oesophagus cancer patients of Assam was found as 10.33 months (95% C.I. 7.79 to 12.88). The Kaplan-Meier survival curves for overall patients and with respect to different characteristics are presented in figures from Fig I through Fig VIII. The median survival time of oesophagus cancer patients with respect to different socio-demographic and treatment characteristics are shown in table II. The average survival time of patients belonging to the higher socio economic group was the longest (15.6 months) in comparison to lower (5.33 months) and middle (11.47 months) socio-economic group. The patients who were diagnosed in localized lesion survived on the average 18.4 months which was highest in comparison to patients diagnosed in regional stage (11.87 months) and distant stage (3 months). Patients who underwent the cancer directed treatment of surgery with/without the combination of radiotherapy and chemotherapy survive on the average about 16 months; while in case of patients administrated any one of chemotherapy, radiotherapy or a combination of them survived on the average about 9 months. Patients without any treatments survived about 3 months only. The average survival time of patients treated outside Assam was almost double (16.8 months) than patients treated in Assam (8.7 months). Although, the patients of the urban domicile enjoyed better survival (10.37 months) than rural counterpart (8.7 months), it was not statistically significant. The influence of age and sex had no statistically significant effect on the survival time of oesophageal cancer patients of Assam.

The Cox-proportional hazard model was fitted to study the effect of different variables on the survival of oesophagus cancer patients. The adjusted and unadjusted hazard ratios are presented in table III. Patients belonging to lower socio-economic group was experiencing a significantly higher risk of dying (unadjusted HR : 3.38, adjusted HR : 2.79) than higher socio-economic counterpart. The hazard of dying for patients of middle socio-economic group was not significantly different from patients belonging to higher socio-economic groups. The unadjusted hazard ratio showed that patients underwent the cancer directed treatment other than surgery experiencing a significantly higher risk of 2.29 times (95% C.I. 1.32 to 3.99) of dying than that of patients who underwent surgery with/without the other forms of treatment. But adjusted hazard ratio showed that the risk of dying was almost same for the two groups of patients. This might be because the cancer directed treatments are basically based on the stage of the disease. Thus the stage of the disease could be substantiated as a confounding factor for cancer directed treatment. The stage at the time of diagnosis was reckoned to be the prominent factor for better survival of oesophageal cancer patients of Assam. The adjusted hazard of dying for patients diagnosed with regional and distant stage was 1.87 (95% C.I. 1.06 – 3.28) and 2.46 (95% C.I. 2.46 – 7.97) times more than that of patients diagnosed in localized stage. The adjusted hazard ratio for patients treated in Assam was estimated as 2.08 (95% C.I. 1.21 – 3.57) in comparison with patients treated out side Assam.

Discussion:

Patient survival is the most important single measure for monitoring and evaluating the early diagnosis and treatment components of cancer control. The present study estimated that the average survival time of oesophagus cancer patients of Assam was 10.33 months (95% C.I. 7.79 to 12.88) only. Very few studies have been conducted to assess

the survival of oesophagus cancer patient in India. Sankaranarayanan et al., (1998) estimated that the 5 year survival rate (%) of oesophagus cancer patients in Madras (1982-1996) India was 6.8% and 6.1% for male and female respectively. Sambasivaiah et al., (2004) estimated that the average survival time of oesophagus cancer patients for Andhra Pradesh, India was 12.9 months (95% C.I. 8.4 to 17.0) during 2004. In an another study, Swaminathan et. al., (2008) showed that only 3% of the oesophagus cancer patients who got registered in the population based cancer registry, Chennai during 1990-1999, survived till the end of the followed-up period (2001) which was lowest in comparison to the other leading cancer sites. In comparison to the developed countries (Martin et al., 2002; Ries et al., 2007; National Services Scotland, 2004; Cancer Statistics Group, 1982) the survival of oesophagus cancer patients in India is comparatively low (Sankaranarayanan et al., 1998; Sambasivaiah et al., 2004; Swaminathan et al., 2008). The estimated age adjusted survival (%) rate in India for males and females were 13 and 14 respectively (Parkin et al., 2005). The present study also reflected the poor survival status of the oesophagus cancer patients of Assam and in fitness of this emerging situation, certain measures are required to be taken here to ensure the better survival of the patients.

The survival time varies among patients with different socio-economic status, various forms of treatment taken, stage at the time of diagnosis and place of treatment. The adjusted effect shows that the early diagnosis of the disease is the key for better survival of the patients. Thus it can be concluded that intensive awareness programmes are required to be implemented in study area which may include measures like educating the masses and grass root level health-care personals about the disease, its risk factors, symptoms etc. This would invariably increase the early detection of the disease. World Health Organization itself in its campaign to reduce incidence, mortality and morbidity due to cancer has considered early detection as one of the major component (World Health Organization, 2007; 2007; 2008).

The present study reveals that 13% of the patients do not undergo any form of medical treatments after the diagnosis. The study results also reveal that, these groups of patients are experiencing the worst survival. A sizable portion of inhabitants of this remote part of India believe in traditional superstitions regarding cancer. These superstitions are very much penetrated in the rural population particularly among the elderly group. The prevailing belief among the population is that it occurs to a person for his sin in the past or previous birth. Some people are mortally afraid of the disease and they even do not like to utter the word "cancer". Eventually as a consequence good number of patients do not go for diagnosis or screening of the disease, and many use to go evidently for denial mode. This might have influenced their survival, which is reflected in our present study.

About 26% of the patients preferred to go out of the study area to big metropolies of India such as Delhi, Mumbai, Chennai etc. for advance treatment after the diagnosis of the disease. The study reflected a typical result that the patients who were treated outside the state have better survival than that of patients treated here in. This is confounded by socio-economic status because, poor cancer patient cannot afford for his travel or treatment of cost of expenditure outside the home state. Moreover, awareness and stage of reporting is also associated with such survival risk. These attending facts reveal that the cancer care facilities in the region are comparatively poor and in such situation intensive medical care facilities are required to be accelerated to reduce the burden of the disease in the region.

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Table I: Demographic, Treatment and Disease profile of the oesophagus cancer patients

Characteristics	Frequency (%)	Characteristics	Frequency (%)
Location		**Socio-economic Status**	
Rural	118 (47.19)	Lower	34 (13.55)
Urban	133 (52.81)	Middle	187 (74.50)
		Higher	30 (11.95)
Sex		**Cancer Directed Treatment**	
Male	169 (67.42)	Surgery and other	69 (27.53)
Female	82 (32.58)	Other Than Surgery	150 (59.55)
		No treatment	32 (12.92)
Type of Family		**Place of Treatment**	
Nuclear	157 (62.36)	Out side Assam	65 (29.68)
Joint	94 (37.64)	Assam	154 (70.32)
Age		**Continuation**	
> 50	47 (18.54)	**of Treatment**	
50 to 70	166 (66.29)	Continue	194 (88.58)
Above 70	38 (15.17)	Discontinue	25 (11.42)
Marital Status		**Stage**	
Unmarried	8 (3.14)	Localized	48 (19.10)
Married	214 (85.20)	Regional	94 (37.64)
Widow	29 (11.66)	Distant	69 (27.53)
		Unknown	39 (15.73)

Table II: Results of the logrank test, median survival time

	Average Survival time (Median)	95% Confidence Interval	Log rank	p-value
Overall	10.33	7.79 – 12.88		
Location				
Urban	10.37	6.76 – 13.98		
Rural	8.70	5.23 – 12.17	0.87	0.35
Age				
Less than 50	12.17	8.04 – 16.29		
50 to 70	9.47	6.30 – 12.63		
Above 70	7.17	6.72 – 7.62	3.78	0.15
Sex				
Female	10.00	7.64 – 12.36		
Male	10.37	6.60 – 14.13	0.27	0.60
Socio-economic status				
Higher	15.60	8.70 – 22.50		
Lower	5.53	04.37 – 6.50		
Middle	11.47	7.80 – 15.13	15.35	0.00
Cancer Directed Treatment				
Surgery & others	15.83	13.50 - 18.17		
Other Than Surgery	8.70	5.65 – 11.75		
No treatment	3.33	1.82 – 4.85	45.19	0.00
Stage				
Localized	18.40	8.26 – 28.54		
Regional	11.87	7.39 – 16.35		
Distant	3.03	1.57 – 4.50		
Unknown	7.07	4.13 – 10.01	46.98	0.00
Place of Treatment				
Out of Assam	16.83	13.95 - 19.72		
Assam	8.70	5.35 – 12.06	15.13	0.00

Table III: Unadjusted and Adjusted Hazard Ratio of dying

	Unadjusted Hazard Ratio (95% Confidence Interval)	Adjusted Hazard Ratio (95% Confidence Interval)
Location		
Urban	Reference	Reference
Rural	1.17 (0.84 – 1.63)	0.71 (0.49 – 1.02)
Age		
Less than 50 years	Reference	Reference
50 to 70 years	1.30 (0.84 – 2.01)	0.98 (0.61 – 1.58)
70 years & above	1.74 (0.99 – 3.06)	1.74 (0.95 – 3.19)
Sex		
Female	Reference	Reference
Male	0.91 (0.64 – 1.30)	0.95 (0.65 – 1.38)
Socio-economic status		
Higher	Reference	Reference
Middle	1.57 (0.87 – 2.86)	1.20 (0.64 – 2.24)
Lower	3.38 (1.67 – 6.83)	2.83 (1.32 – 6.06)
Cancer Directed treatment		
Surgery & others	Reference	Reference
Other than surgery	2.29 (1.32 – 3.99)	1.11 (0.65 – 1.90)
No treatment	6.38 (3.58 –11.35)	2.19 (1.04 – 4.62)
Stage at the time of diagnosis		
Localize	Reference	Reference
Regional	1.87 (1.09 – 3.18)	1.87 (1.06 – 3.28)
Distant	4.87 (2.84 – 8.35)	4.42 (2.46 – 7.97)
Unknown	3.38 (1.86 – 6.15)	2.63 (1.40 – 4.95)
Place of Treatment		
Out of Assam	Reference	Reference
Assam	2.34 (1.51 – 3.62)	2.08 (1.21 – 3.57)

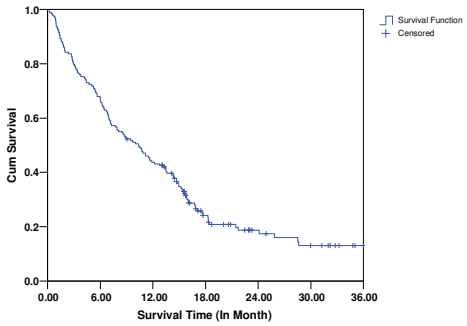

Fig I. : K-M survival curve for overall patients

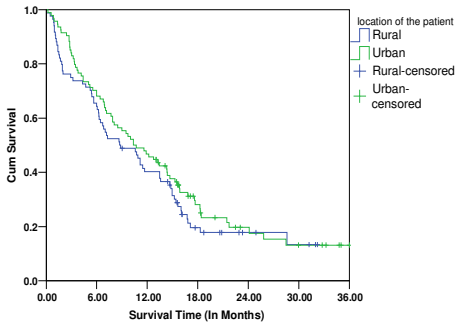

Fig II : K-M survival curve w.r.t location

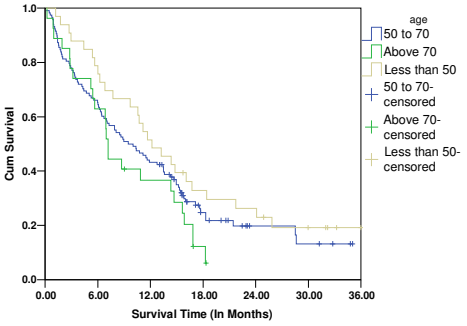

Fig III : K-M survival curve w.r.t age

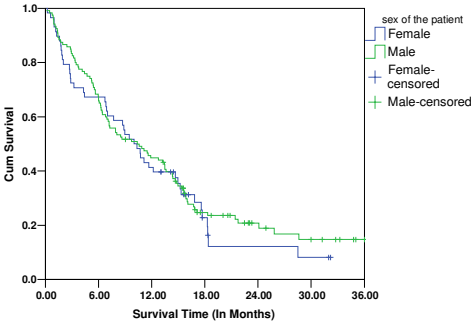

Fig IV : K-M survival curve w.r.t sex

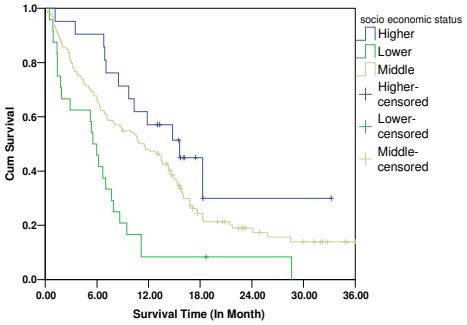

Fig V: K-M survival curve w.r.t SES

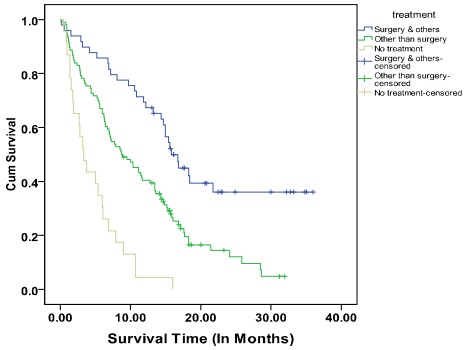

Fig VI : K-M survival curve w.r.t treatment

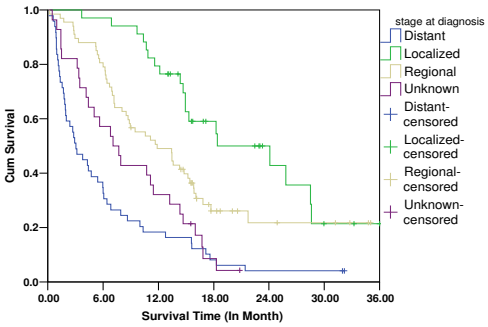

Fig VII: K-M survival curve w.r.t stage

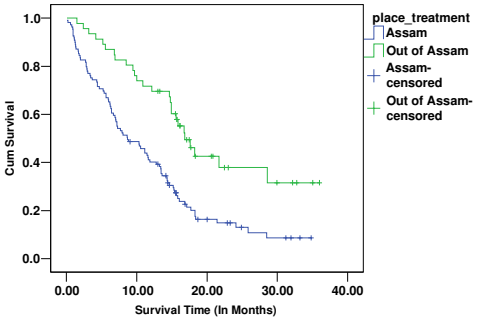

Fig VIII: K-M survival curve w.r.t place of treatment