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A Survival Analysis of Head and Neck Cancer Patients in North East India: A Hospital-Cancer registry Based Study

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ABSTRACT

Background: The cancer cells that grow in the lip, mouth, and throat of a person is known as 'Head and Neck' cancer and the incidence of this particular type of cancer is very high in North East India due to frequent consumption of high amount of betel nut and tobacco by most of the inhabitant of the region. So this research work intends to perform a study on the survival pattern of Head and Neck cancer patients from North-East India.

Materials and Methods: This study was based on 212 Head and Neck cancer patients treated at North East Cancer Hospital & Research Institute (NECHRI), Guwahati, from 1st January 2018 to 31st December 2018. Some standard survival analysis techniques like Kaplan–Meier product limit estimator, Log-rank test, Cox proportional hazards model, etc.

Results: The present study estimated that the median survival time of Head and Neck cancer patients of Assam was 31 months (standard error = 4.115, 95% C.I. 22.93 to 39.06). The average survival time (22 months) was lower and the risk of dying was higher for the patients of the age group 60 years and above as compared to the person below 60 years. The patients who were diagnosed in stage 1 survived maximum (57 months) and those who were diagnosed in stage 4 survived minimum (12 months). Similarly, the patients from the rural area experience poor survival (24 months) and higher risk of dying as compared to the patients from urban areas.

Conclusion: The survival of Head and Neck Cancer patients of Assam was not so good. There was a need for improved health facilities to ensure better survival. Due to poor health facilities in rural areas of Assam patients experience poor survival and a higher risk of dying. The results of the present study also indicate that early detection and prompt diagnosis of the disease aid in better survival of the patients.

Keywords: Head and Neck Cancer, Survival Analysis, Kaplan–Meier product limit estimator, Log-rank test, Cox Proportional Hazards Model.

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1. INTRODUCTION:

Cancer is one of the universal leading causes of morbidity and mortality. Bray et. al. (2018) estimated 18.1 million new cancer cases and 9.6 million deaths due to this disease across the world wide for the year 2018. Globally more than 20 million new cancer cases were predicted in 2025 [Annual Report ICMR: NCDIR, Dr. B. Borooah Cancer Institute, 2021]. In India Cancer is one of the most serious public health problems, especially in North East India; in Assam, it is one of the top five leading causes of death according to a report of ICMR: NCDIR, Dr. B. Borooah Cancer Institute, 2022. In Assam's Kamrup District Urban area, the number of cancer cases has increased by around three times in the past ten years. According to the annual Report ICMR: NCDIR, Dr. B. Borooah Cancer Institute, 2021, between 2007 and 2016 in the Kamrup Urban area, there were 11013 instances of cancer diagnosed, with 6223 male and 4790 female cases, for a standardized incidence rate of 213.0 male cases and 169.6 female cases per 100,000 people. Between 2007 and 2016, Kamrup Urban District's cancer incidence rate increased from 143.0 to 234.8 per 100,000 men and 93.1 to 184.8 per 100,000 women. Barman, et. al. (2004) have done research work on the Survival of Oesophageal Cancer Patients in Assam. Kataki, et. al. (2018) have done research work on the survival of female uterine cervical patients in North East India. Krishnatreya, et. al. (2019) performed a study on the survival of hypopharyngeal cancer patients based on hospital-cancer registry data. Bhattacharjee & Deka (2022) worked on the Multivariate analysis of breast cancer patients in North-East India with the help of the Cox model. Hazarika, et. al. (2022) recently work on COVID-19 Prevalence and Survival Outcomes in Patients Cancer Patients of North-East India undergoing Chemotherapy.

According to Das et al. [2017] each year, more than 600,000 new cases of head and neck cancer (HNC) are reported worldwide, and the incidence and death rates vary depending on the nation's economic status. Every year a huge number of head and neck cancer cases are detected in India, accounting for about 20%–30% of all cancers, but in the United States, the number is only 3%. According to Addala et. al, (2012), in South Asian countries, the risk of HNC is further aggravated by smoking bidis, chewing betel quid, and areca nut. In the case of Head and Neck cancer research, Kulkarni, (2013) published a review article on Head and neck cancer in India. Saxenaet. al. (2019) have done a hospital-based research work on the Survival analysis of head and neck cancer patients of southern Karnataka. Choudhury & Ghosh (2015) performed a hierarchical clustering analysis study of Promoter hypermethylation profiling to identify subtypes of head and neck cancer patients of North-East India with viral, environmental, genetic, and survival characteristics. Baishya et. al. (2018) have done research work on Carcinoma Lower Lip on the basis of the data collected from the Regional Cancer Centre of North-East India. Bora et. al. (2022) have done a Prospective Observational Study on Nutritional Status in Head and Neck Cancer Patients Treated with Radiotherapy–A from North East India.

From the literature survey, it is observed that the incidence of Head and Neck cancer is very high in North East India which comprises the states of Assam, Manipur, Mizoram, Tripura, and Nagaland, as compared to other parts of the country. So, in this paper, an attempt has been made to perform a study on the survival pattern of Head and Neck cancer patients from North-East India.

2. MATERIALS AND METHODS:

This study was based on a historical cohort of Head and Neck cancer patients of North East Cancer Hospital & Research Institute (NECHRI), Guwahati. The period of the study was from 1st January 2018 to 31st December 2018. All the patients who were diagnosed with Head and Neck cancer during this period of time in the institute were included in the study and they are followed up to 31st July 2022. During this period of the study, a total of 212 patients were diagnosed in the institute. A pre-designed suitable questionnaire was used for the collection of data. Some of the data like age, sex, extension of the disease at the time of diagnosis, cancer-directed treatments given, addresses, religion, place of residence, stage, treatment, and place of the treatment of the patients were collected from the official records of the institute. Some of the information related to the patient's survival was collected by communicating with them over the telephone. Also, a re-verification of the information collected from the hospital was made during this telephonic interview. Survival (in months) was estimated from the month of diagnosis until death. The patients were considered censored if they were still alive at the end of the study period, i.e., beyond 31st July 2022 or they died due to some other cause(s) or loss of follow-up. Patients are categorized into eight groups based on the cancer treatment. Those who are treated with surgery, without the combination of radiotherapy and chemotherapy are designated as "surgery". Again, in this way patients who are treated only with chemotherapy and only with radiotherapy are designated as "Chemotherapy" and "Radiotherapy" respectively. Patients who were treated with radiotherapy and chemotherapy (without the combination of surgery) were designated as "R+C". Again, patients who were treated with surgery and radiotherapy (without the combination of chemotherapy), surgery and chemotherapy (without the combination of radiotherapy), and patients who were treated with all three treatments surgery, radiotherapy, and chemotherapy were designated as "S+R", S+C" and "S+R+C" respectively. Further, the study subjects who were not treated were termed as "treatment did not continue in NECHRI". This is done with a view to studying the significance of surgery and its combinations in the survival of Head and Neck cancer patients in North-East Cancer Hospital and Research Institute, Guwahati. Patients were classified into two groups according to the place of treatment taken. Those who were treated in NECHRI were termed as "In NECHRI" while the patients taking treatment out of NECHRI i.e., in big metropolises like Delhi, Mumbai, Chennai, etc. were termed as "out of NCEHRI".

Kaplan–Meier product limit estimator (Kaplan and Meier, 1958) was employed here to estimate the survival probabilities and median survival time of the patients. The 95% confidence intervals (95% CI) of the median survival time were also calculated here and the test of statistical significance for the difference in survival time was done with the help of a log-rank test (Peto & Peto, 1972). Finally, the Cox-proportional hazard model (Cox, 1972) was fitted to estimate the unadjusted and adjusted hazard ratio of dying with respect to different covariates under study. In this study, SPSS version 17.0 (International Business Machines Corp., Chicago, IL, USA) was used for the analysis of the data.

3. RESULTS:

A total of 212 individuals diagnosed with Head and Neck cancer during the study period were included in the study. Among them, most of the patients were male (85% males against 15% females). 12% of the patients were diagnosed with stage 1, 22% were in stage 2, 37% were in stage 3 and 20% were in stage 4, and for 9% of patients, the stage at the time of

diagnosis remained unknown. Table I depicts the profiles of the subjects under study. From the study, it was observed that the median survival time of Head and Neck cancer patients was 31 months (standard error = 4.115, 95% C.I. 22.93 to 39.06). The Kaplan-Meier survival curves for overall patients and with respect to sex, location, age interval, religion, treatment, stage, and place of treatment are presented in figures from Fig-1 through Fig-8. The log-rank test and median survival time of Head and Neck cancer patients with respect to location, age, sex, religion, stage, place of treatment, and treatment are shown in Table II. The patients who were diagnosed in stage 1 survived on an average of 57 months which was the highest in comparison to patients diagnosed in stage 2 (45 months), stage 3 (33 months), and stage 4 (12 months). The patients from the urban area enjoyed better survival (44 months) than the patients from the rural areas (24 months). The average survival time for patients of the age group below 60 years was 42 months whereas for the patients of the age group 60 years and above it was 22 months.

Patients who are treated with chemotherapy, without the combination of surgery and radiotherapy survive an average of about 15 months, and patients who are treated with radiotherapy, without the combination of surgery and chemotherapy survive an average of about 22 months. Patients who are treated with radiotherapy and chemotherapy (without the combination of surgery), survive an average of about 37 months. Again, patients treated with surgery and chemotherapy (without the combination of radiotherapy) survive an average of about 17 months, and patients treated with all three treatments surgery, radiotherapy, and chemotherapy survive an average of about 31 months. However, the differences are not statistically significant. The average survival time of patients treated outside NECHRI (outside Assam also) was 27 months and the survival time of the patients treated in NECHRI was 32 months, but it was also not statistically significant. Similarly, the influence of sex and religion had no statistically significant effect on the survival time of Head and Neck cancer patients at North-East Cancer Hospital and Research Institute, Guwahati.

Finally in this study, the most popular survival model, the Cox-proportional hazards model was fitted to investigate the influence of different factors on the survival of Head and Neck cancer patients. The adjusted and unadjusted hazard ratios are presented in table-III. The patients from rural background experience a higher risk of dying [unadjusted HR 1.517 (95% C.I. 1.06 - 2.15) and adjusted HR 1.315 (95% C.I. 0.903 – 1.914)] as compared to the patients from the urban background. According to both the unadjusted and adjusted hazards ratio, the instantaneous rate of dying for both male and female patients was almost the same. The unadjusted hazard ratio of death for patients of the age group 60 & above was 1.472 (95% C.I. 1.034 - 2.095) and the adjusted hazard ratio was 1.357 (95% C.I. 0.914–2.015) as compared to the patients of the age group below 60 years. The unadjusted hazard of dying for patients who belong to the Muslim and Christian religion was 0.761 (95% C.I. 0.43 - 1.33) and 1.338 (95% C.I. 0.75 – 2.38) times more than Hindu religion patients. Similarly in the case of the adjusted hazard ratio, for the patients who belong to the Muslim and Christian religions it was 0.955 (95% C.I. 0.507– 1.797) and 1.951 (95% C.I. 1.037– 3.672) as compared to the patients belongs to Hindu religion. The unadjusted and adjusted hazard ratio showed that patients treated with Chemotherapy have a higher risk of dying [unadjusted HR 2.118 (95% C.I. 0.865 to 5.187) and adjusted HR 2.281(95% C.I. 0.857– 6.074)] than those patients who underwent surgical treatment. Similarly, the patients treated with “Surgery + Chemotherapy” also have a higher risk of dying [unadjusted HR 2.209 (95% C.I. 0.77 – 6.28) and adjusted HR 1.639 (95% C.I. (0.492–5.457)] than those patients who underwent only

surgery. Those who were treated with only Radiotherapy also have a higher risk of dying [unadjusted HR 1.935 (95% C.I. 0.95 – 3.91) and adjusted HR 1.547 (95% C. I (0.733– 3.266)] as compared to the patients who underwent surgical treatment. Again those who were treated with all three types of treatments "Surgery + Radiotherapy + Chemotherapy" also have a higher risk of dying [unadjusted HR 1.804 (95% C.I. 0.79 – 4.09) and adjusted HR 1.547 (95% C. I (0.556– 3.134)] as compared to the patients who underwent only surgical treatment. The unadjusted hazard ratio of dying for the patients diagnosed with stage 2, stage 3, and stage 4 were 1.661 (95% C.I. 0.76 – 3.59), 2.084 (95% C.I. 1.01 – 4.27) and 5.093 (95% C.I. 2.44 – 10.62) times more than that of patients diagnosed in stage 1. Similarly, the adjusted hazard ratio of dying for the patients diagnosed with stage 2, stage 3, and stage 4 were 2.108 (95% C.I. 0.929– 4.768), 2.313 (95% C.I. 1.093– 4.895) and 5.822 (95% C.I. 2.688– 12.611) times more than that of patients diagnosed in stage 1. The patients treated outside the NECHRI have a higher risk of dying [unadjusted HR 1.172 (95% C.I. 0.73 – 1.85) and adjusted HR 2.875 (95% C.I 1.716 – 3.648)] as compared to the patients treated in NECHRI.

4. DISCUSSION:

Survival Analysis of the cancer patients is the most significant aspect of the cancer research. It is very beneficial for the diagnosis and treatment of the disease. From this study, it was observed that the median survival time of Head and Neck cancer patients of Assam was 31 months (standard error = 4.115, 95% C.I. 22.93 to 39.06). According to another study by Krishnatreya [2019] the median survival for hypopharyngeal cancer patients from North East India was also 31 months. In the case of Head and Neck Cancer research in India, according to a study conducted among the patients of Tata Memorial Hospital, Parel, Mumbai by Rao et. al, (1998), they estimated that the overall 5-year survival rate for oral cancer was in the range of 20-43%, 8-25% for pharyngeal cancers and 25-62% for laryngeal cancer. Another study conducted by Yeole et. al. [2000] showed that, in the case of different types of Head and Neck cancer, the 5-year relative survival rates were, 74.5% for the lip, 42.7% for the anterior tongue, 25.5% for the posterior tongue, 45.1% for the mouth, 29.7% for the oropharynx, 38.7% for the nasopharynx, 29.1% for the hypopharynx, and 41.2% for the larynx. The present study also reflects an atrocious picture of the survival of Head and Neck Cancer patients of Assam. For this, patients entail healthier facilities to ensure better survival.

From the present study, it was observed that the patients who were diagnosed in stage 1 (57 months) survived utmost as compared to patients diagnosed in stage 2 (45 months), stage 3 (33 months), and stage 4 (12 months), which indicates that prompt diagnosis of the disease aid to enjoy better survival. The present study also indicates that the average survival time of the patients of the age group below 60 years was 42 months which was almost double the same for the age group 60 years and above (22 months) and it was statistically significant. A study by Saxena et. al. (2019) also observed that, the survival for the younger age group (< 40 years) showed better survival as compared to the age group (41–50 years). However, this result was not statistically significant. Although the results were not statistically significant the present study estimated that the survival of the patients who were treated with radiotherapy and chemotherapy was maximum (about 37 months) followed by the patients treated with all three treatments surgery, radiotherapy, and chemotherapy (about 31 months). The present study also indicates better survival of patients treated in North-East Cancer Hospital and Research Institute, Guwahati as compared to patients treated outside Assam. But

it was also statistically not significant. Likewise, no significant influences of sex and religion on the survival times of Head and Neck cancer patients were observed in the present study.

The fitted Cox-proportional hazards models showed that the patients from rural backgrounds experience a higher risk of dying than their urban counterparts. This is an indication of poor health facilities in rural areas of Assam. This study establishes a better survival of the patients of the age group below 60 years as compared to the patients of the age group 60 & above. Religion-wise all the patients from the Hindu, Muslim, and Christian religions experience almost the same rate of dying. The patients treated with "Chemotherapy", "Radiotherapy", "Surgery + Chemotherapy" and "Surgery + Radiotherapy + Chemotherapy" have a higher risk of dying as compared to the patients who underwent only "Surgery". The patients diagnosed with stage 4 have a higher risk of dying as compared to the others. It is also observed that the risk of dying increases with the cancer stages. Thus early diagnosis of the disease helps in better survival of the patients. This study reveals that patients treated outside the NECHRI have a higher risk of dying as compared to the patients treated in NECHRI. This is a good indication for the institute as well for Assam and the entire North-East India.

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

Characteristics	**Frequency (%)**	**Characteristics**	**Frequency (%)**
Location		**Religion**	
Urban	119 (56.13%)	Hindu	164 (77.36%)
Rural	93 (43.87%)	Muslim	29 (13.68%)
		Christian	19 (8.96%)
Cancer Directed Treatment		**Age Interval**	
		Less than 50 years	47 (22.17%)
Surgery	28 (13.21%)	50 to 60 years	131 (61.79%)
Chemotherapy	11 (5.19%)	70 years & above	34 (16.04%)
Radiotherapy	33 (15.57%)		
R+C	75 (35.38%)		
S+R	9(4.25%)		
S+C	6(2.83%)		
S+R+C	15 (7.07%)		
Treatment did not continue at NECHRI	35 (16.50%)		

Stage		**Sex**	
Stage 1	26 (12.27%)	Male	180 (84.91%)
Stage 2	47 (22.17%)	Female	32 (15.09%)
Stage 3	78 (36.79%)		
Stage 4	42 (19.81%)		
Unknown	19 (8.96%)		
Place of Treatment			
In NECHRI	176 (83.01%)		
Out of NECHRI	36 (16.99%)		

Table II: Results of the log-rank test, median survival time

	Average Survival time (Median)	**95% Confidence Interval**	**Log-rank**	**p-value**
Overall	31.00	22.93-39.06		
Location				
Urban	44.00	40.20-47.79	5.55	0.018
Rural	24.00	16.26-29.73		
Sex				
Male	30.00	22.38-37.61	0.18	0.668
Female	38.00	28.65-47.34		
Age Interval				
Less than 60 years	42.00	38.02-45.97		
60 years & above	22.00	15.141-28.859	4.765	0.029
Religion				
Hindu	31.00	22.21-39.78	2.21	0.331
Muslim	57.00	35.09-72.56		
Christian	30.00	0.00-61.28		
Cancer Direct Treatment				
Surgery	35.10	28.15-42.06		
Chemotherapy	15.00	2.05-27.94		
Radiotherapy	22.00	0.61-43.38	6.86	0.443
R+C	37.00	19.72-54.27		
S+R	33.11	6.80-19.76		
S+C	17.00	8.59-25.40		
S+R+C	31.00	24.37-37.62		
Treatment did not continue at NECHRI	30.00	4.52-55.47		

Stage				
Stage 1	57.00	43.76-62.56		
Stage 2	45.00	38.66-52.65	34.18	0.00
Stage 3	33.00	17.91-48.08		
Stage 4	12.00	4.75-19.25		
Unknown	34.00	16.93-51.06		
Place of Treatment				
In NECHRI	32.00	23.54-40.45	0.46	0.494
Out of NECHRI	27.00	4.65-49.34		

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	1.517 (1.06-2.15)	1.315 (0.903 – 1.914)
Sex		
Male	Reference	Reference
Female	0.898 (0.54-1.48)	1.001(0.585– 1.713)
Age Interval		
Less than 60 years	Reference	Reference
60 years & above	1.472 (1.034 - 2.095)	1.357(0.914–2.015)
Religion		
Hindu	Reference	Reference
Muslim	0.761 (0.43 - 1.33)	0.955(0.507– 1.797)
Christian	1.338 (0.75 – 2.38)	1.951(1.037– 3.672)
Cancer Direct Treatment	Reference	Reference
Surgery	2.118 (0.86– 5.18)	2.281(0.857– 6.074)
Chemotherapy	1.935 (0.95 – 3.91)	1.547(0.733– 3.266)
Radiotherapy	1.323 (0.69 – 2.51)	1.248(0.638– 2.439)
R+C	1.100 (0.35 – 3.41)	0.569(0.178– 1.821)
S+R	2.209 (0.77– 6.28)	1.639(0.492–5.457)
S+C	1.804 (0.79 – 4.09)	1.320(0.556– 3.134)
S+R+C		
Treatment did not continue at NECHRI	1.640 (0.80 – 3.33)	1.977(0.904– 4.324)
Stage		
Stage 1	Reference	Reference
Stage 2	1.661 (0.76 – 3.59)	2.108(0.929– 4.768)
Stage 3	2.084 (1.01 – 4.27)	2.313(1.093– 4.895)

Stage 4 Unknown	5.093 (2.44 – 10.62) 2.309 (0.97 – 5.48)	5.822(2.688– 12.611) 1.907(0.756– 4.810)
Place of Treatment In NECHRI Out of NECHRI	 Reference 1.172 (0.73 – 1.85)	 Reference 2.875 (1.716 – 3.648)

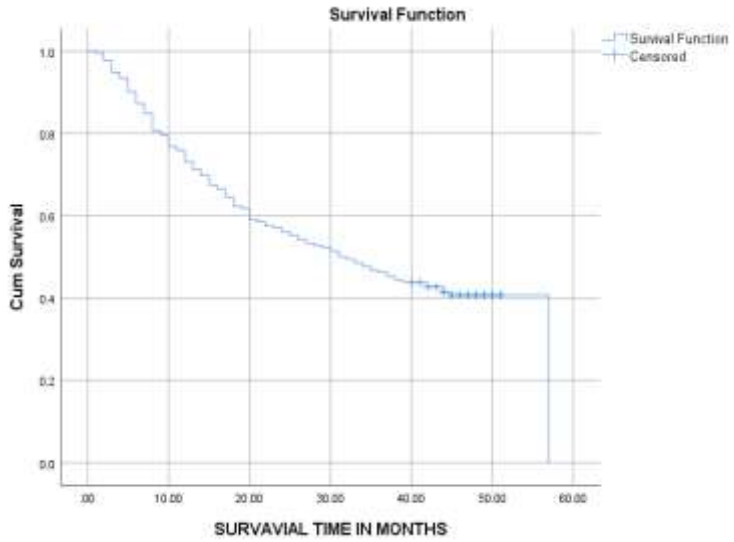

Fig-1: Kaplan-Meier survival curve for overall patients

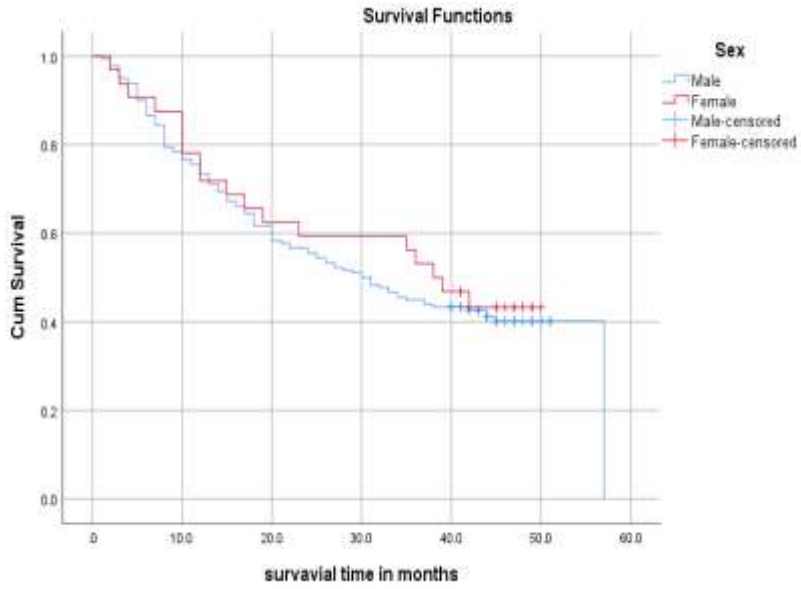

Fig-2: Kaplan-Meier survival curve with respect to sex

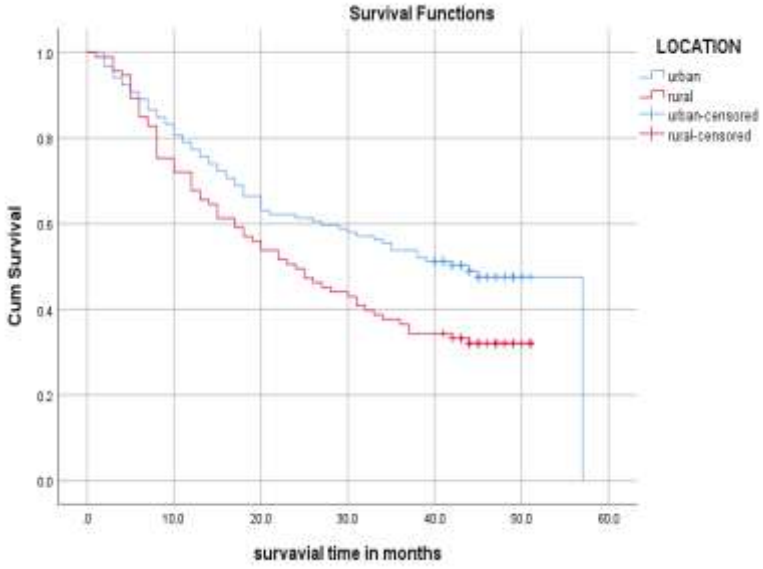

Fig-3: Kaplan-Meier survival curve with respect to location

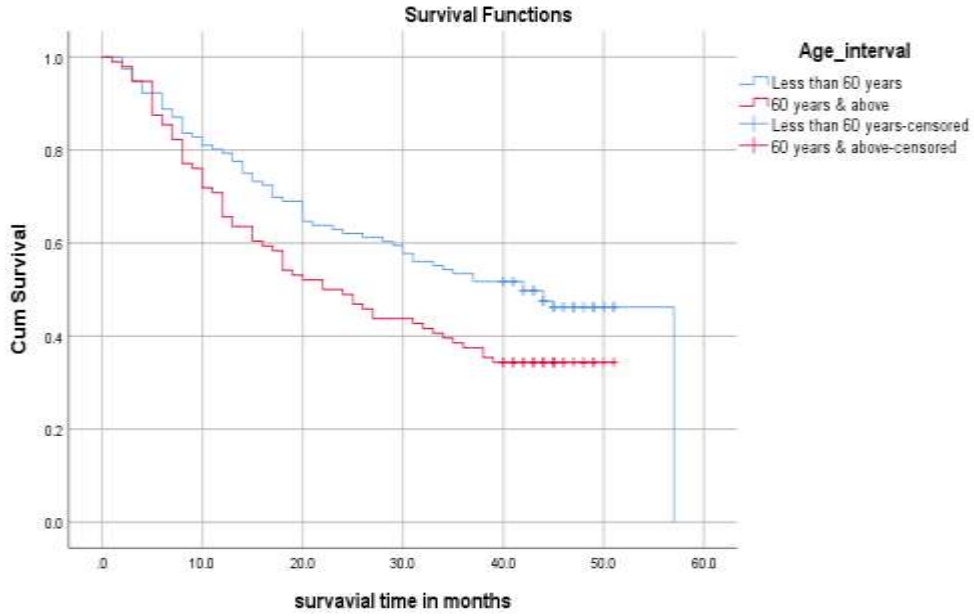

Fig-4: Kaplan-Meier survival curve with respect to age interval

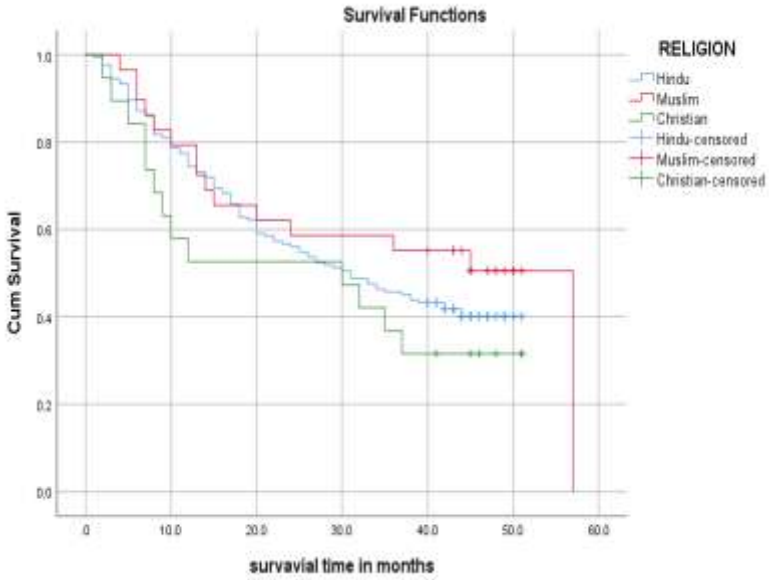

Fig-5: Kaplan-Meier survival curve with respect to religion

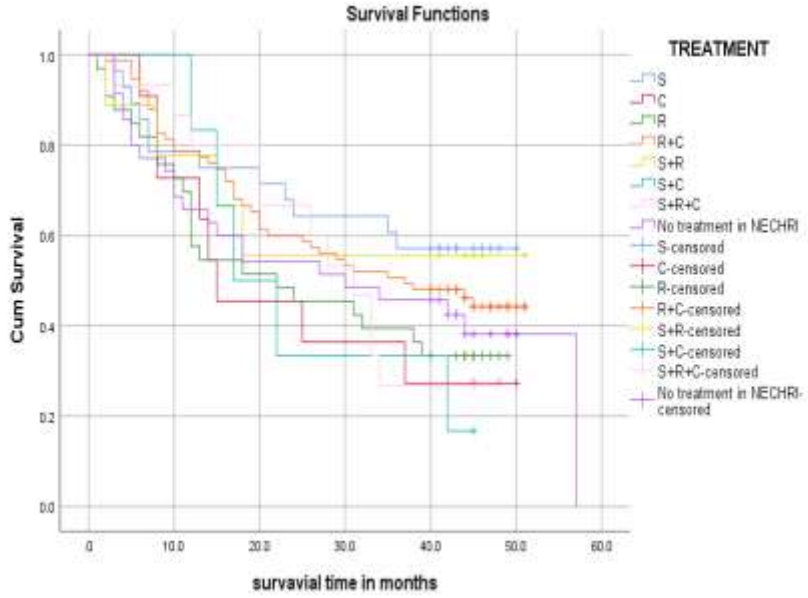

Fig-6: Kaplan-Meier survival curve with respect to treatment

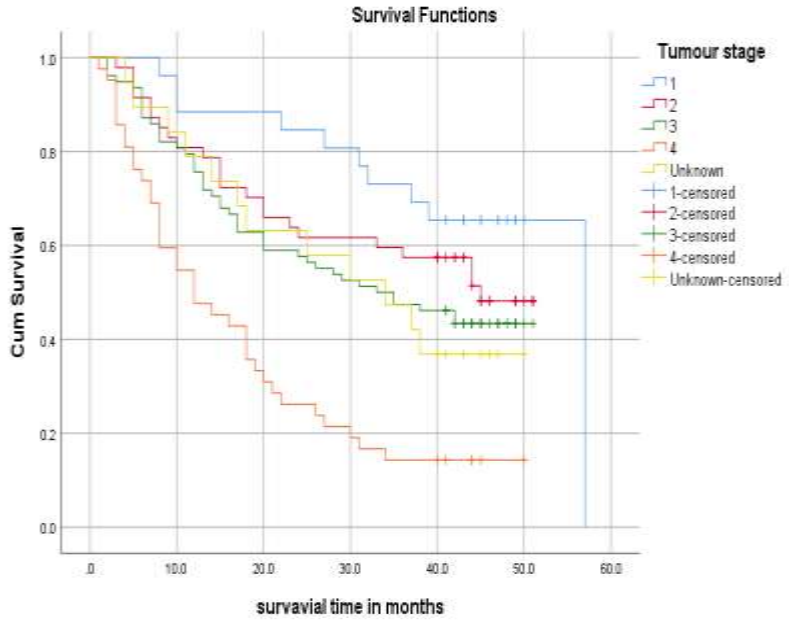

Fig-7: Kaplan-Meier survival curve with respect to stage

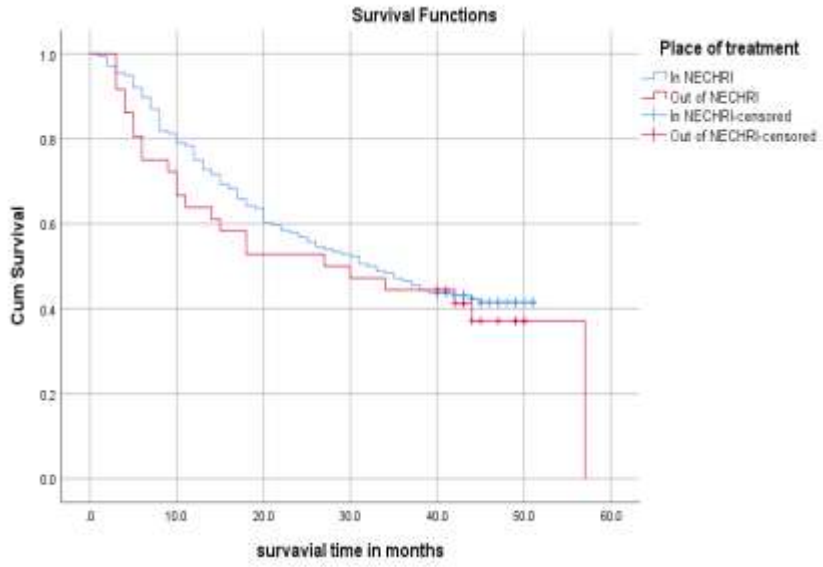

Fig-8: Kaplan-Meier survival curve with respect to the place of treatment

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