

Impact of Radiation Interruption and Associated Factors on Overall Survival in Head and Neck Cancer at Tikur Anbessa Specialized Hospital. A Retrospective Study

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Abstract

Background:

Unplanned interruptions during radical radiotherapy (RT) for head and neck squamous cell carcinoma (HNSCC) are linked to poorer outcomes, particularly reduced local control and overall survival. However, evidence on the impact and contributing factors of RT interruption in Ethiopia remains limited.

Objective:

To evaluate the effect of unplanned RT interruptions and associated factors on overall survival among HNSCC patients receiving radical RT at Tikur Anbessa Specialized Hospital.

Methods:

A retrospective analysis was conducted on 126 HNSCC patients treated with radical RT using a linear accelerator between May 2021 and February 2024. Patient demographics, treatment details, and interruption data were collected. Descriptive statistics summarized baseline characteristics, and overall survival (OS) was estimated using the Kaplan–Meier method. The log-rank test assessed survival differences, and variables with $p < 0.05$ were considered significant.

Results:

Patients aged 37–61 years constituted the majority, with 64.3% males. The nasopharynx (50%) was the most frequent subsite. The mean prescribed RT dose was 68.7 Gy, and the mean delivered dose was 62.4 Gy. Concurrent chemoradiation was administered to 43% of patients. The mean RT duration was 49 days, with an average interruption of 8 days. Treatment interruption occurred in 82.5% of patients—primarily due to machine breakdown (44.5%) and holidays (34.9%). At a median follow-up of 13 months, 1-year OS was 65% (95% CI 57.2–75.3). Patients with interruptions > 5 days had significantly poorer survival (HR = 2.036, 95% CI 1.009–4.102, $p = 0.031$), and any radiation break increased mortality risk (HR = 2.654, 95% CI 1.313–6.725, $p = 0.025$).

Conclusion:

Unplanned RT interruptions—especially those exceeding 5 days—were independent predictors of poorer overall survival in HNSCC patients. Efforts to minimize treatment breaks are essential to improve clinical outcomes.

Introduction

Treatment gaps(interruptions) in radiotherapy describe unplanned breaks in a patient's treatment plans. These interruptions can be detrimental in terms of the potential for tumour control. Interruptions in radical radiotherapy for head and neck cancer have been linked to poorer treatment outcome. Short-term (2–8 days) and long-term (greater than 8 days) treatment interruptions during radical radiotherapy were each associated with absolute 5-year overall survival (OS) survival decrement of 7% and 20%, respectively. Greater number of treatment facility visits seems protective from RT breaks, particularly at centers treating greater than 15 cases per year[1].

Normally, radiotherapy interruption may be caused by Machine service/maintenance, patient related factors, treatment dose related toxicity and public holidays. These breaks in radiotherapy treatment, which thereby increase Radiation Treatment Time (RTT) [2].A traditional radiotherapy treatment schedule involves five days a week for a number of weeks but there are often breaks in this treatment and unexpected gaps in the treatment schedule are not uncommon. These breaks and interruptions in treatment regimen can result in the repopulation of tumor clonogens. Specifically, in respect to head and neck cancers for which the data best supports accelerated repopulation of clonogenic tumor cells, it is estimated that each interruption lasting 1-day and 7-day for treatment course reduces the local control rate by 0.68–1.4% and 14–20%, respectively [3–5].

Studies also reported that a substantial proportion (up to 63%) of patients with head-and-neck cancer show treatment gap at least once [6, 7]. Compensation for this loss is demanded to avoid or diminish a prolongation of the total treatment time of the patient and restore the original TCP.The latency of treatment increment delays significantly influences the strength of the treatment interruption. A current body of literature indicates that 5-year survival is decreased by 10–20% in squamous head and neck neoplasms if treatment is given for a total duration of treatment in excess of the standard schedule for up to 10 days. It is as much as 1.4% lower local control for a single-day[3, 8].To maximize patient results, radiotherapy interruptions need to be minimized during clinical practice. If the interruption is unavoidable, then the radiation doses should be appropriately corrected (dosimetrically) to maintain the treatment duration within the allowed range [9]

In our country, Ethiopia, where only three radiotherapy machines are available to care for a population of more than 120 million, interruptions in radiation therapy are not uncommon because of treatment-related toxicity, public holidays and breakdown of the machine due to overloading, lack of maintenance service and power failure. This is the first such study, with the purpose of identifying the effect of radiation interruption on overall survival and associated factors in patients with head and neck squamous cell carcinoma at TASH. The results will offer evidence-informed guidance to maximize the optimization of radiotherapy protocols and help reduce the adverse effect of interruptions on the delivery of care, and likely will initiate healthcare systems to be mindful of the need to take action regarding this problem. It will also help to overcome a knowledge and research gap in head and neck cancer, and recognize opportunities for further research & collaboration for the following step for building on this study findings.

METHODS AND MATERIALS

A retrospective study of histologically verified squamous cell carcinoma of head and neck cancer patients, registered at Tikur Anbessa Specialized Hospital Oncology department in Addis Ababa, Ethiopia, was conducted from May 2021 to February 2024. Tikur Anbessa Hospital is one of Ethiopia's leading tertiary care centers, serving as a national referral hospital for complex cases and providing specialized care to patients from across the country. At present, the majority of head and neck cancer cases are diagnosed and treated within adult Oncology units. The study population were all histologically confirmed squamous cell carcinoma of head and neck cancer patients who had received radical radiotherapy at oncology unit of TASH during the specified study period. Patients having another primary, histology other than SCC. Patients with metastatic disease, and those whose diagnosis was only documented without detailed records to diagnose and treatment criteria were excluded.

The data collection for this study was extracting from electronic medical record, the new patient registration, results, follow-up appointment forms, and Radiotherapy data (dose and fractionation, date of start and date of completion of radiotherapy) were extracted from electronic ARIA Oncology Information System (OIS). The retrieved data were thoroughly reviewed and filled by medical trained personnel using data collection formats specifically developed for this study. These formats captured socio-demographic details, clinical data, diagnostic tests, Treatment details, Radiotherapy was administered by linac using standard fractionation i.e., 1 fraction/day, 5 fractions/week. Concurrent treatment patients were treated with cisplatin-based chemotherapy infusion at the day care unit; weekly@40mg/mt2. The treatment interruptions were quantified in whole days and characterized as unscheduled interval between treatment; excluding the usual weekend break, on Saturdays and Sundays. These interruptions were logged according to the length and the reason. To complement the information, about the patients' vital status and address missing data, phone calls were made to the patients or their families to inquire. To ensure data accuracy and completeness, double data entry and cross-checking of records was implemented.

Statistical Analysis

The collected data were coded, cleaned and entered into SPSS version 25 for analysis. Various frequency tables, graphs and descriptive statistics were applied to characterize the study variables, such as patient's baseline characteristic of the overall treatment duration, cause of radiation break and cancer stage. OS is estimated by the Kaplan-Meier method and verified by the log rank test. Variables with statistically significant log-rank value < 0.05 on Kaplan Meir analysis are considered to have significant association. Predictor variables with a relationship at $p\text{-value} \leq 0.25$, determined by univariate cox-regression, were used as input in multivariate cox-regression and a $p\text{-value} < 0.05$ was considered statistically significant.

Results

Socio-Demographic and Clinical Characteristics

The median age of patients was 48.5years (IQR 37–61), with range from 19 to 83 years. The majority (64.3%) were male, and forty-four (34.3%) patients came from Addis Ababa. Regarding behavior of patients, 36(31.3%) and 7(5.9%) were smokers and alcohol drinker respectively. In this study majority (85.7%) of patients have no co-morbidity. From those who had comorbidity (14.3%), HIV and HTN being the most common. Most of the patients had ECOG performance status of I (88.9%). Nasopharynx was apparent as a primary site of cancer sub-site among 63 (50%). About histology, 72(57%) had undifferentiated SCC either NKSCC or KSCC. About 93(90.3%) patients had locally advanced stage disease at presentation, and clinical T4 and N2 disease were common accounting for 36(49%) and 31(42%), respectively. (See Table 1).

Radiation interruption and over all treatment time

Of the 126 patients with HNSCC, 104(82.5%) underwent treatment interruption. Of those, who interrupted treatment, the average day for interrupting treatment was 8 days. Fifty-eight (49.6%) had < 5 days of interruption of treatment. Whereas, 84 (72%) had both before and after 28 days of RT started as a stage in which radiation interruption occur. Machine break down and holiday was reason for treatment interruption among 44.5% and 34.86% of patients, respectively. About 50% of patients had multiple interruption, primarily due to machine breakdowns and public holidays. Compensation for interruption was done for no patient. The mean radiation dose delivered to the patient was 62.36Gy (SD $\pm$ 14.604), while the mean radiation dose prescribed to the primary target volume via ARIA Oncology Information System (OIS) was 68.71Gy (SD $\pm$ 3.262)). Only 46(37%) patients received concurrent chemotherapy.

Table 1
Sociodemographic and Clinical characteristics .

Variables	Category	Frequency (n)	Percentage (%)
Age in years (n = 126)	19–24	8	6.3
	25–29	10	7.9
	30–34	11	8.7
	35–39	9	7.1
	40–45	16	12.6
	> 45	72	57.1
Sex (n = 126)	Male	81	64.3
	Female	45	35.7
ECOG	0	8	6.3
	I	112	88.9
	II	6	4.8
Primary Cancer Sub-site	Nasopharynx	63	50
	Larynx	19	15.08
	Oral cavity	26	20.63
	Oropharynx	10	7.94
	Hypo pharynx	6	4.76
	other	2	1.59
Clinical Stage (n = 103)	Early Stage	10	9.7
	locally advanced	93	90.3
Clinical T Stage (n = 73)	T4	36	49
	T3	16	22
	T2	15	20.5
	T1	6	8.2
Clinical N Stage (n = 73)	N3	5	6
	N2	31	42
	N1	23	31
	N0	14	19

Regarding the type of treatment received, 66(53%) and 12 (10%) received definitive and adjuvant radiation alone, respectively.

The median overall treatment time i.e., first radiation treatment to date of last radiation treatment was 49 days. Also, 121 (83.3%) had an overall treatment time of ≤ 56 days.

Overall Survival and it's Predictors

In this study the median follows up time was 13months. Overall, 38 (30.4%) patients died with 95% CI (23%, 37.4%) between the time of radiation started and the time of data analysis (See Fig. 2). The minimum and maximum follow up time for patients who still alive being 5 and 27 months respectively. In our study the median survival time is not reached and the 1-year OS is 65% (95% CI 57.2, 75.3) [figure 3]

The study revealed a statistically significant difference among median survival time for those who interrupted their treatment and those who didn't. Accordingly, the median survival time for those who interrupted treatment was 18 months while not reached for those who did not have interrupted treatment (long-rank p-value = 0.013) 95% (CI: 11.485,24.515) [see Fig. 4]

The proportions of patients with treatment interruption time of < 5 days were 58 (49.6%). The study also uncovered less than 5 days of treatment interruption had better survival than their counterparts (long-rank p-value = 0.04). see Fig. 5

In this study, 46(37%) patients took concurrent chemoradiotherapy and the mean number cycles of chemotherapy was 3.61 (SD $\pm$ 1.48). There was no statistically significant difference in survival between CCRT vs RT alone (long-rank p-value = 0.1). see Fig. 6

Cox Regression model was employed to identify predictors of survival. Accordingly, different variables were entered to the univariate and multivariate cox regression model respectively. Variables with a $p \leq 0.25$, were considered as a candidate for the final model. Predictors for survival were declared at a p-value of < 0.05. Accordingly, radiotherapy interruption, primary cancer site, concurrent chemotherapy, length of treatment interruption and radiation treatment time (RTT) each were checked whether they are candidate for the final model. As a result, radiotherapy interruption, concurrent chemotherapy and length of treatment interruption were the variables which became candidate at $P \leq 0.25$. Finally, the study finds out, patients with radiotherapy interruption had a 2.65 times increased chance of poor survival/risk of death compared to those who didn't interrupt their treatment (aHR = 2.65, 95% CI 1.313–6.725, $P = 0.025$). Also, patients with more than 5 days of treatment interruption had a 2.036 times higher risk of poor survival /death than their counter parts (aHR = 2.036,95% CI,1.009–4.107, $P = 0.031$).

Discussion

In this study, 104(82.5%) patients interrupted their radiation treatment which was higher as compared to research conducted at various clinics worldwide reveals that between 45% and 77% of cancer patients

experience at least one missed radiation appointment [3, 10]. This difference might be due to presence of only one functioning machine and which is subjected to, breakdown, holidays, treatment related toxicities, and intercurrent illness.

Reasons for interruption can be broadly grouped into treatment-related toxicities, patient's personal reasons, primary disease progression during the treatment, and technical causes. Equipment's issues can also be seen in breakdowns of machine and of machine's servicing. Sometimes, it is due to the combination of the aforementioned factors, to cause interruptions. We have observed that in most case, the reason of treatment interruption from machine failures (44.5%) followed by public holidays (34.86%). In particular, 50% of our patients experienced repeated interruption during treatment at different times for reasons mainly related to machine failures and holidays. This is comparable to a national audit study conducted in the United Kingdom by James et al [11]. They reported that the machine downtime and breakdown activity led to 44% of patients' interruption and 39% of the study's interruptions were caused by public holidays.

The analysis also revealed statistically significant difference in the median survival time between the patients interrupting versus those who were not interrupting the radiotherapy. As a result, the analysis discovered, those who did not interrupt radiation treatment the median survival time was not reached whereas the median survival time was 18 months; those with a history of interruption (long-rank p value:0.013). Additionally, interrupting radiotherapy treatment was the independent predictor of poor survival among HNSCC patients. Accordingly, the study showed patients with radiotherapy interruption had a 2.65 times increased chance of poor survival/risk of death as compared to those who didn't interrupt their treatment (HR 2.654; 95% CI 1.313–6.725 p = 0.025). This result is in line with other similar studies by Wang W et al, XU GZ et al and Kwong DL et al [12, 13]. The justification for the similarity is due to the fact that as patients are interrupting their radiation, as result the risk of repopulation of surviving tumor cells during interruption perpetuating for poor survival.

The study also, revealed that treatment interruption more than 5 days was an independent predictor of poor survival among HNSCC patients. Accordingly, the study showed patients with more than 5 days of treatment interruption had a 2.036 times increased chance of poor survival /risk of death as compared to those who had less than 5 days of radiation interruption (HR 2.036; 95% CI 1.009–4.107 p = 0.031). This finding is supported by study highlighted those interruptions exceeding 5 days were detrimental for prognosis (5-year OS: 83.4% vs. 67.8%, P = 0.007)[14, 15].

Our analysis revealed that the median overall treatment time (OTT) i.e. First radiation treatment to date of last radiation treatment was 49 days. Moreover, 83.3% completed treatment in a time $\leq$ 56 days. On the other hand, we have not observed a strong relation between treatment duration of $\geq$ 56 days and OS (P > 0.05). Importantly, our findings different from prior analyses on the impact of overall treatment time in radical treatment on survival in head and neck cancer. In one study patients treated with definitive radiation prolonged overall treatment time was linked with poorer survival (HR 1.37 95% CI 1.13–1.66 p = 0.0013). On multivariable analysis, they also reported that prolonged OTT (HR 1.25; 95% CI 1.14–1.37)

correlated with worse OS compared to standard RTT [16]. These differences are likely attributable to important variations between study population, such as not exclusion of patients who received less than 60Gy in our study and majority of our patients had less than 56 days of overall treatment time and due to multiple treatment interruption, they did not complete the prescribed radiation dose

On the other hand, in this study about 37% patients took concurrent chemotherapy and the mean and median number of weekly chemotherapy cycles were only 3.6 and 3 respectively. Furthermore, we did not find a significant correlation between concurrent chemotherapy and OS ($P = 0.1$). In contrast, the Meta-analysis of chemotherapy in head and neck cancer (MACH-NC) showed that concomitant chemotherapy was associated with increased OS ($p < 0.0001$). They reported that the absolute gain at 5 and 10 years of concomitant CT was 6.5% and 3.6% respectively [17]. These variations are mainly due to the significant difference between study population, i.e., markedly lower accumulative dose of weekly cisplatin ($< 200 \text{ mg/m}^2$) in our study. We suggest that these patients need to be given sufficient doses of cisplatin combined with radiotherapy.

Finally, this study reports a 1-year over survival was 65% which is lower than rates reported in literature [14,18,19]. These could be due to a number of reasons: First, due to multiple treatment interruption appropriate radiation dose is not received and the other reason could be inadequate cumulative dose of concurrent chemotherapy. Moreover, absence of treatment compensation after interruption could be the possible cause.

Conclusion

Significantly higher proportion of patients interrupted their radiation treatment. The study also, revealed statistically significant difference in the median survival time among those interrupting their radiation treatment as compared to those who didn't. In addition, radiation treatment interruption more than 5 days of treatment interruption are an independent predictor of poor overall survival for HNSCC patients treated with radiation therapy. Radiotherapy interruption may have different levels of involvement in patient outcomes, and therefore, the possibility of such interruptions should be avoided in clinical practice. We suggest it is essential that steps have to be taken in order to prevent it. When radiotherapy breaks were unavoidable, necessary dosimetry corrections should be done in order to not over exceed the overall treatment time.

Recommendation

To mitigate the main reasons for radiation interruptions, i.e., public holidays and machine down, we suggest the following interventions.

1. Regular maintenance: Create a maintenance schedule for routine maintenance of the machine for radiotherapy to avoid unexpected failures and uninterrupted service.
2. Measures to ensure treatment during public holidays: Define a protocol to continue treatment on public holidays, perhaps by providing incentives to staff or reorganizing work schedules.

3. Compensation for Interruptions: Utilize standard practice for compensating for treatment interruptions (e.g., reschedule missed sessions, adjust treatment plan/weekend treatment).
4. Working together for Further Resources: Collaborate with governmental agencies and non-governmental organizations (NGOs) to obtain funds and resources to purchase additional radiotherapy machines.
5. Departmental Protocol Development: The department should develop its own protocols to prevent or address interruptions appropriately. Through the use of these strategies, the department can guarantee more stable and good radiotherapy service, thereby ultimately promoting better patient outcomes.

The positive side of the study: This is the first study performed in our setting, using a linear accelerator (LINAC)) for the treatment of patients. It offers informative insights specific to our situation and helps to elucidate the consequences of radiation interruption in a similar

Limitation of the study:

This study has several limitations. First, as a retrospective study it is limited by direct and intrinsic limitation of biases in data collection, analysis and affected by incomplete clinical variable documentation. Second, due to the design of the study as part of a single institution; the findings could not be generalized to other populations or settings.

Declarations

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and approved by Research and Ethics Committee of Addis Ababa University, College of Health Sciences, Ethiopia before initiating the study. Due to the retrospective nature of the study and the use of anonymized patient records, the requirement for informed consent to participate was waived by Research and Ethics Committee of Addis Ababa University, College of Health Sciences. Patient confidentiality was maintained throughout the study.

Consent for publication

Not applicable

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Author Contribution

BT: Conceptualization, Formal analysis, Supervision, writing – original draft, Writing – review & editing. SW: Supervision, writing – original draft, Writing – review & editing, Methodology. FH: Data curation, Formal analysis, Writing – original draft. RT: Data curation, Investigation, Writing – review & editing. KL, WT, and MA Formal Analysis. RT:, review & editing and Manuscript Development

Data Availability

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

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Figures

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Figure 1

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Figure 2

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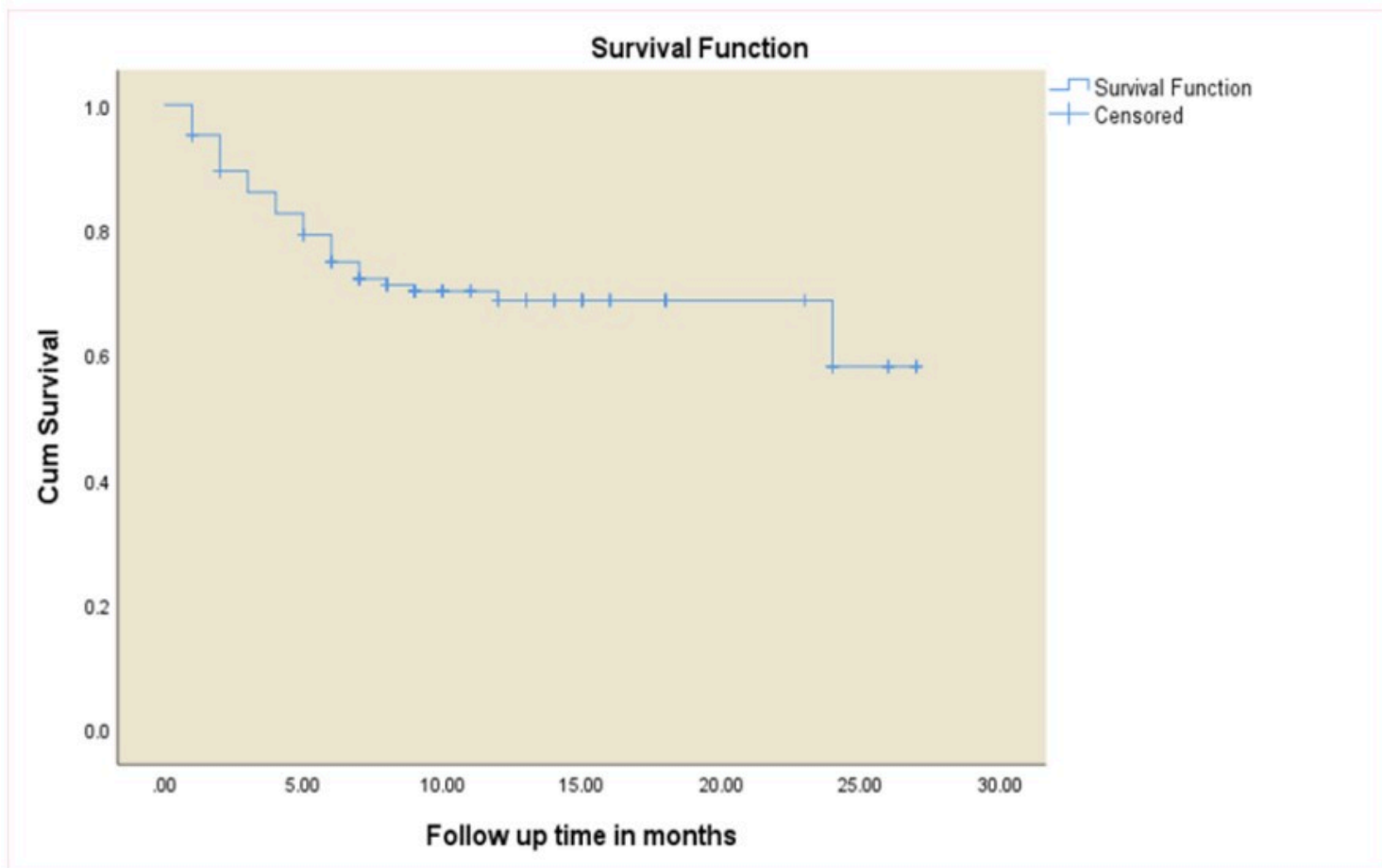


Figure 3

Kaplan Meir Survival analysis for Median Follow up time

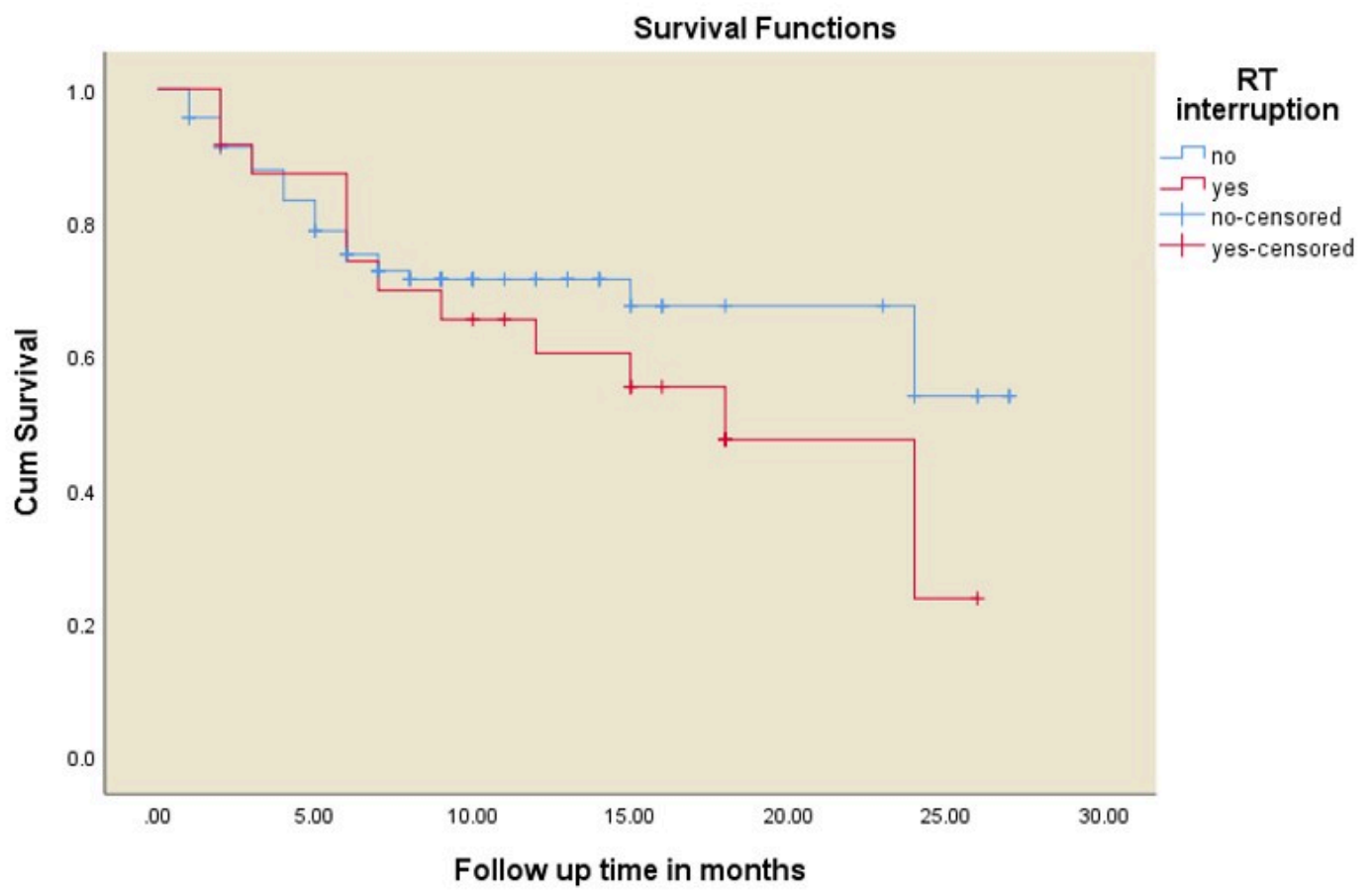


Figure 4

Kaplan Meir Survival analysis to see Differences in survivorship with treatment interruption History

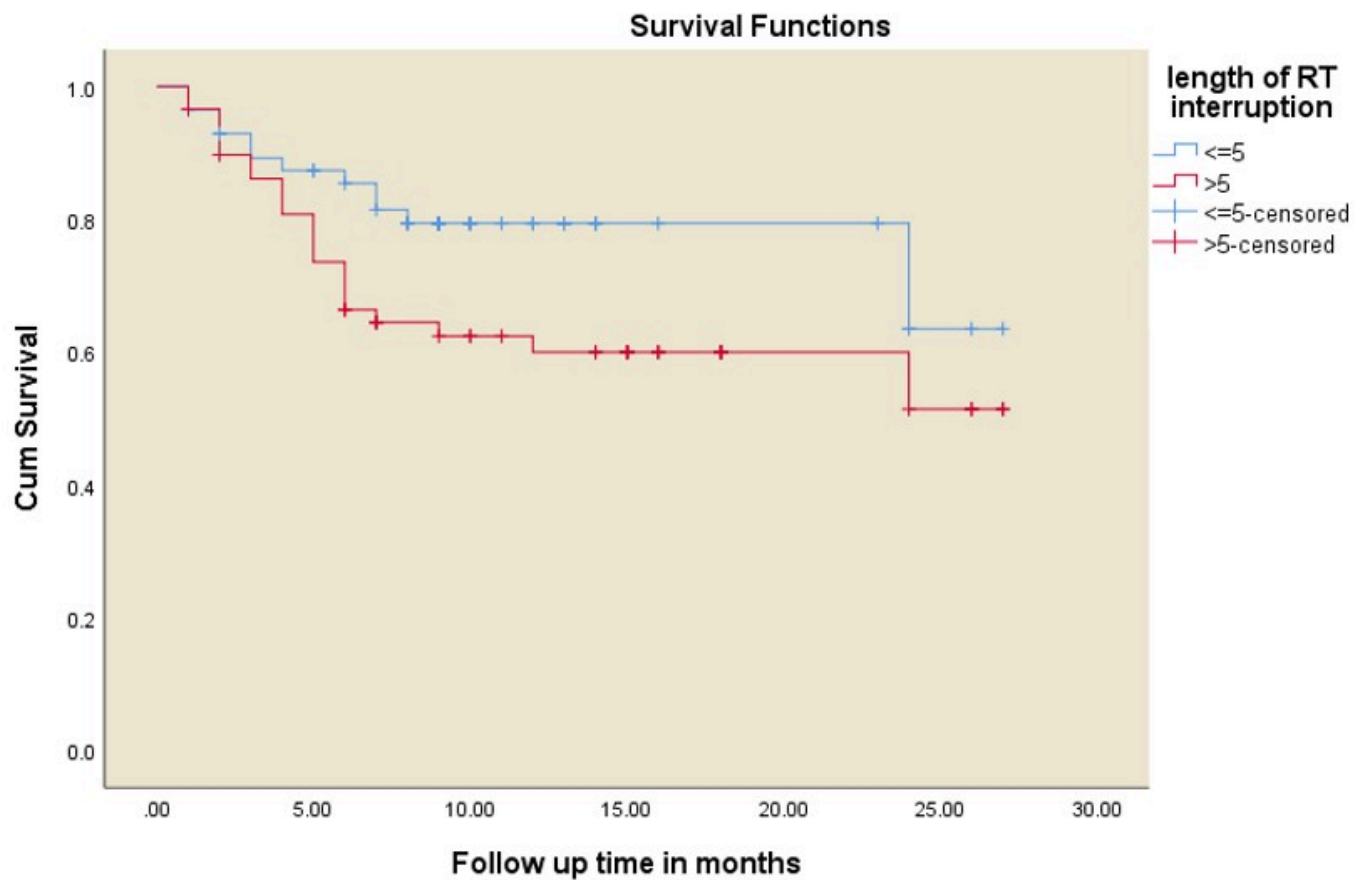


Figure 5

Kaplan Meir Survival analysis to see Differences in Survivorship with Length of radiotherapy interruption

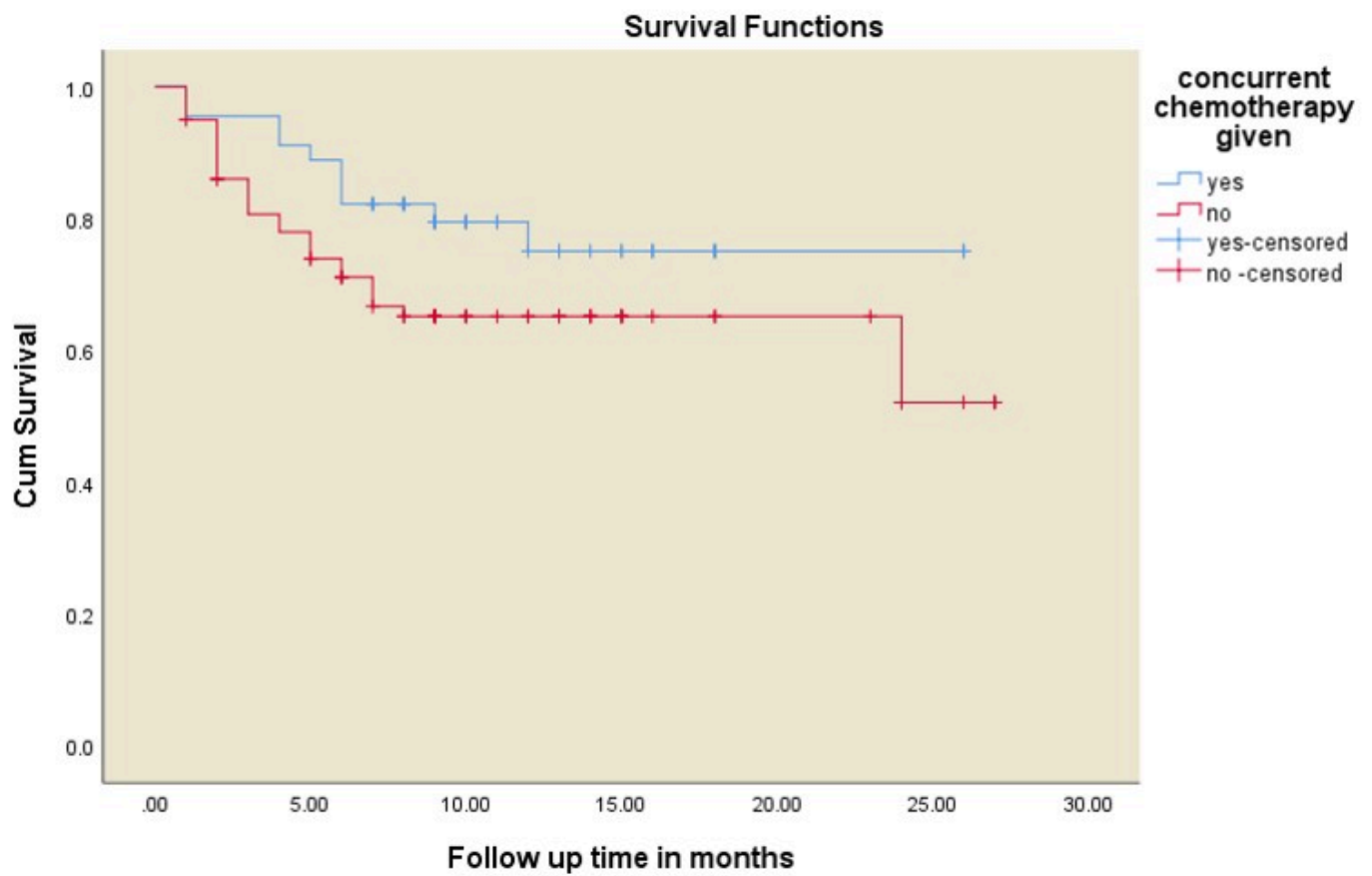


Figure 6

Kaplan Meir Survival analysis to see Differences in Survivorship with concurrent chemoradiotherapy