ORIGINAL ARTICLE

Treatment Delay Impact on Overall Survival in Head and Neck Cancers

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ABSTRACT

Background: Head and Neck (HN) cancer is the commonly identified cancer across the globe and is considered as 8-10 % of all cancers in Southeast Asia. Early diagnosis and initiation of treatment are critical for increased survival rate among patients.
Objective: To quantify the impact of treatment initiation time post diagnosis on the survival rate outcomes of patients suffering from with head and neck cancer.
Study design: Retrospective cohort study
Place and duration of study: Department of ENT Head & Neck Surgery, Bolan Medical College, Quetta from 1st May 2023 to 1st October 2023.
Methodology: One hundred and ninety patients who were clinically diagnosed with head and neck cancers including squamous cell carcinoma of oral cavity, oropharynx, larynx, hypopharynx and under radiotherapy were enrolled. The included patients were. The patients were distributed into quartiles established on the time to start of treatment (0 to 27 days, 28 to 41 days, 42 to 60 days, and greater than 2 months). The validity of the time length between the start of treatment and diagnosis as well as impact on overall survival was investigated through multivariate cox proportional hazard regression model wherein greater than 2 month quartile served as a comparitive reference group.
Results: The mean age of the patients was 61.35±9.5 years with majority being males. Each patient was followed on a mean of 56±10.3 months. There were 26.31% those patients who were actively tobacco users while 53.68% had quitted tobacco usage. The T staging presented 31.57% patient in T2 stage while 28.94% patients were in N0 staging. There were 33.15% patients having positive results for HPV status. The most frequent treatment applied was concurrent chemoradiotherapy for cervical cancer (CCRT) of 57.36% patients. There was insignificant variance within the time of initiation of treatment with 26.84% of patients having the treatment initiated within 0 to 27 days of diagnosis. Kaplan Meier overall survival observed that those patients whose treatment was initiated within 42-60 days had most promising survival rate. Therefore, the overall survival time of the patients was not significantly different between 0-27 and 28- 41 days group in comparison to 60 days group. While the survival of patients within the 42 to 60 days group significantly higher than other groups (p vale 0.011). The similar findings were observed when the treatment initiation groups were compared for Cox proportional hazard ratio against age adjusted model and multivariant model.
Conclusion: For some patients the delay in treatment time (42-60 days) may not affect the survival rate negatively rather this time may be appropriately used for proper planning treatment Substantial delay in treatment can lead to a negative impact on survival rate.
Keywords: Treatment delay, Head & neck cancer, Survival rate

INTRODUCTION

The incidence of head and neck cancer has devastatingly increased in developed and developing countries all across the globe. An estimated 65000 novel cases of head and neck cancer has been diagnosed only a half decade before in the western world.[1] An upsurge in new cancer cases has been documented with more than a thousand cases presented annually.[2,3] The situation is critical in South Asian countries as well with increasing incidence of cases per year.

There are various protocols followed for the treatment and management of head and neck cancer. These includes surgical methods, radiation as well as chemotherapy depending upon the staging and regional involvement. The head and neck cancer diagnosis is followed by staging information for opting the ideal regimen for therapy. The consequence of various steps involved within this protocol can result in treatment delays.[4]

With advancement in technology the planning of radiotherapy and treatment delivery has turned more sophisticated. This further leads in increasing the time delay between diagnosis and actual initiation of the treatment.[5] In addition to these other various factors as advanced stage, treatment site, transferring of care brings delays in initiation of the treatment.[6,7] Reduction in smoking has also been linked with better survival rate in patients suffering from head and neck cancer.

Contrary to the above there are several studies where no association has been found between treatment delay and outcomes of the disease.[8-11] The current study was designed for estimating the impact of the treatment delay on overall survival rate

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of patients suffering from head and neck cancer. The results of this study assisted in provision of evidence-based data which elaborated the association between rate of survival and head and neck treatment delay, therefore, facilitating in survival outcomes of the patients.

MATERIALS AND METHODS

This retrospective cohort study was conducted at Department of ENT Head & Neck Surgery, Bolan Medical College Quetta from 1st May 2023 to 1st October 2023. One hundred and ninety patients who were clinically diagnosed with head and neck cancers including squamous cell carcinoma of oral cavity, oropharynx, larynx, hypopharynx and under radiotherapy were enrolled. Those patients having distant metastases or had undergone previous treatment attempts for head and neck cancers were excluded from the study. The treatment of the patients was based on either radiotherapy unaided or in combination with surgical or chemotherapy procedure. The sample size was calculated using the prevalence of head and neck cancer as 8-10% of all cancer cases in Southeast Asia.[12] The sample size calculation software of WHO was used for sample size generation with 95% CI, 80% power of test and 5% margin of error. The diagnosis date was defined as the date when a histopathological confirmation of the malignancy was made whereas treatment date initiation was the one when treatment was started. This did include any type of curative intent such as induction definitive radiotherapy, chemo-radiotherapy surgery, or chemotherapy alone . Those patients where diagnosis was done on the surgery day were defined as zero day for imitation. Patients' complete demographic, clinic information as well as characteristics of tumor, treatment-information as well as outcomes were retrieved from medical

record of the patient. The patients were distributed into quartiles established on the time to start of treatment (0 to 27 days, 28 to41 days, 42 to 60 days, and greater than 60 days). The validity of the time length between the start of treatment and diagnosis as well as impact on overall survival was investigated through multivariate cox proportional hazard regression model wherein greater than 2 month quartile served as a comparitive reference group. The suggested models were age, gender and tumor stage adjusted. The data was analyzed using SPSS version 26.0. The Kaplan Meier survival curves were additionally made for variance determination in the overall survival within groups of treatment. P value <0.05 was taken as significant.

RESULTS

The mean age of the patients was 61.35±9.5 years with majority being males. Each patient was followed on a mean of 56±10.3 months. There were 26.31% those patients who were actively tobacco users while 53.68% had quitted tobacco usage. The T staging presented 31.57% patient in T2 stage, while 28.94% patients were in N0 staging. There were 33.15% patients having positive results for HPV status. Within the various types of treatments, the most frequent treatment applied was concurrent chemoradiotherapy for cervical cancer (CCRT) with a percentage of 57.36% patients. This was followed by 16.31% patients having CCRT and surgical combination a treatment plan. The results also interpreted that 63.15% of the patients were currently alive at the time of research publication. There was insignificant variance within the time of initiation of treatment with 26.84% of patients having the treatment initiated within 0 to 27 days of diagnosis (Table 1).

The majority of the patients were clinically diagnosed for oropharynx carcinoma followed by hypopharynx and supraglottis with a frequency of 75, 41 and 32 respectively. There was no case of lip cancer (Fig. 1). The Kaplan Meier-survival analysis between the four treatment-time groups presented a statistically significant data (p vale 0.03). Kaplan Meier overall survival of squamous cell carcinoma of the head and neck when stratified within various groups of treatment initiation from 0 to 60 and >60days it was observed that those patients whose treatment was initiated within 42-60 days had most promising survival rate. Therefore, the overall survival time of the patients was not significantly different between 0-27 and 28- 41 days group in comparison to 60 days group. While the survival of patients within the 42 to 60 days group significantly higher than other groups (p vale 0.011) [Fig. 2]

The similar findings were observed when the treatment initiation groups were compared for Cox proportional hazard ratio against age adjusted model and multivariant model (Table 2)

Table 1: Descriptive features of patients having head and neck cancer (n=190)

Characteristic	No.	%
Age at diagnosis (years)	61.35±9.5	
Mean Follow up time (months)	56±10.2	
Gender		
Male	153	80.52
Female	37	19.47
Tobacco Status		
Never	38	20.0
Former	102	53.68
Current	50	26.31
T stage (1-4)		
T1	27	14.21
T2	60	31.57
T3	55	28.94
T4	34	17.89
Others	14	8.94
N-Stage		
N0	55	28.94
N1	23	12.10
N2	95	50
N3	17	8.94
HPV status		
Negative	44	23.15
Positive	63	33.15
Unknown	83	43.68
Treatment Type		
RT	19	10.0
CCRT	109	57.36
Surgery & CCRT	31	16.31
Surgery & RT	13	6.84
CCRT&neck dissection	3	1.57
ICT & CCRT	15	7.89
Current Status		
Alive	120	63.15
Dead	70	36.84
Time to treatment initiation		
0 to 27 days	51	26.84
28 to 41 days	47	24.73
42 to 60 days	48	25.26
> 60 days	44	23.15

Table 2: Cox proportional hazard ratio models for assessing the overall survival rate

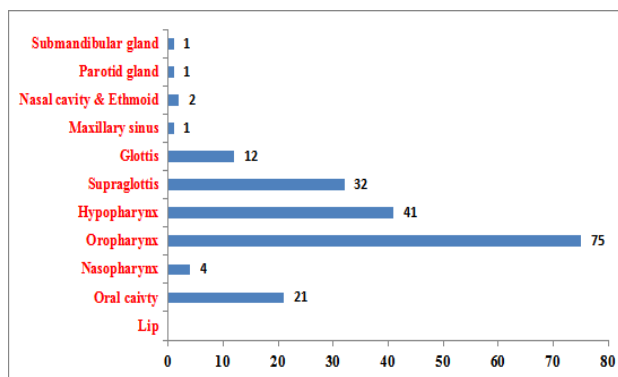| Groups	Age Adjusted-Model		Multivariate-Model	
Initiation Days	HR (95% CI)	P-value	HR (95% CI)	p-value
> 60 (ref)	1.00		1.00	
42 to 60	0.498 (0.345, 0.712)	<0.01	0.548 (0.367, 0.819)	<0.05
28 to 41	0.731 (0.51, 1.0444)	0.086	0.791 (0.544, 1.149)	0.23
0 to 27	0.730 (0.512, 1.040)	0.08	0.757 (0.523, 1.088)	0.14

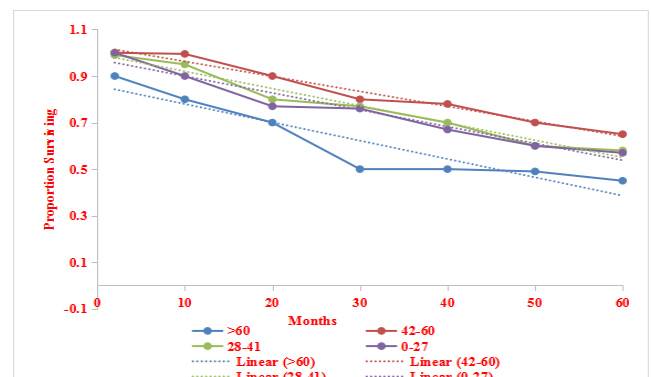Fig. 1: Distribution of head and neck cancers among patients

Fig. 2: Kaplan Meier overall survival of squamous cell carcinoma of the head and neck

DISCUSSION

The current study results shows that patients suffering from head and neck cancer when provided with treatment with a delay of only 42-60 days post diagnosis had a significantly higher impact on survival rate than those treated pre or prior to that. DeGraaff et al[13] also elaborated similar finding through its mega cohort with more than 600 patients enrolled of head and neck carcinomas. Considering the analysis in context of tumor site, type stage and HPV status stratification it was observed that no significant variance within overall survival rate was observed for majority of the analytical subtypes.[13,14]

Scientist has elaborated that among the various time groups observed the stage T3 and T4 tumors were only found to be significantly variant.[9,15] The present study has also found T3 and T4 to be significantly variant tumor staging when correlated with time of treatment initiation. Improvement in overall survival at 42 to 60 days post diagnosis was also seen by other scientist as van Harten et al[9] who elaborated in their research that patient who were treated within 30 days of their diagnosis has a comparatively poor survival rate than those treated post 30 days.[15] On the contrary larger delays also results into negative outcomes as mentioned by van Harten et al.[9]

For head and neck cancer patients, an extensive delay in treatment can lead to a 1.06 to 1.08 increased hazard ratio for mortality.[16,17] This means that the risk of death from any cause increases by 6-8% for patients experiencing treatment delays. The factors contributing to delayed treatment includes diagnostic delays such as time taken to diagnose head and neck cancer, referral delays such as me taken to refer patients to specialized treatment centers. Treatment initiation delays including time taken to start treatment after diagnosis. It is essential to prioritize timely treatment for head and neck cancer patients. By minimizing delays, healthcare providers can improve survival outcomes and reduce mortality rates.[18,19] In present study it was also observed that treatment initiation post 60 days was linked with worse outcomes and was not recommended.

In present study treatment initiation 42 days post diagnosis may have provided more progressively rapid symptomatic tumor identification and treatment which was not possible on time below the aforesaid as the symptoms were yet progressing in patients and treatment planning may have been required more aggressive in case the of appropriate cases diagnosis and presentation. Research has evidently proven that patients having more aggressive tumors experiences escalated symptoms requiring more rapid treatment and consequently decreased survival rate presentation in first quartile.[20]

CONCLUSION

Delays in starting treatment had no effect on radiation therapy. The 42–60 day treatment delay for certain individuals may not affect the survival rate negatively rather this time may be appropriately used for proper planning treatment, minimizing smoking, anxiety and malnourished risk factors. Substantial delay in treatment can lead to a negative impact on survival rate.

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