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# Influence of Circadian Rhythm In Radiation Induced Mucositis In Head And Neck Malignancies

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**ABSTRACT:-**

More than 60% of head and neck cancers in India are locally progressed. Treatment based on chemotherapy has been the mainstay for the last 30 years. Normal tissue toxicity, manifesting as mucositis, has remained a constraint despite the multimodal therapy.WHOLE SETTING AND APPROACH: Using data from patients undergoing radiation therapy for head and neck cancers, we looked at the possible links between the normal mucosal circadian cycle and the onset and progression of mucositis. We reviewed the records of 142 individuals diagnosed with squamous cell carcinoma of the head and neck (stage II to IVA) between time. There was a grading of patients according to whether they had EBRT first thing in the morning (8-11am) or last thing at night (5-8pm). Both groups exhibited a reasonable degree of homogeneity in clinicopathological features.

## INTRODUCTION :

More than a third of all cancer diagnoses in India occur in the head and neck region. The development of head and neck cancers is mostly caused by tobacco use, whether it's smoking or chewing [1]. More than 60% of these cases have progressed locally and show involvement of regional cervical lymph nodes.Research has shown that combining chemoradiation with Cisplatin as the radiosensitizer drug improves locoregional control (LRC) and overall survival (OS) compared to radiation treatment alone [2]. While LRC and OS have improved, toxicity rates have risen, with acute Grade 3 or 4 toxicities such as skin toxicity, mucositis, dysphagia, and a decrease in haematological parameters increasing by up to 43% compared to RT alone.Sections 3–8,Concerning side effects of head and neck radiation include acute mucositis, which has persisted and is still a concern today.Mucositis of varying degrees develops in almost all patients undergoing radiation therapy to the head and neck. However, the risk of severe mucositis rises substantially at

radical doses of around 66–70 Gy, as with traditional fractionation, and this risk grows in direct proportion to the dosage. This may lead to less oral intake, worse quality intake, more hospitalisations, more costs, and most importantly, treatment interruptions, which reduces projected locoregional control. sections 9–15] Pharmacological approaches to reduce this noticeable adverse effect have had little success with medications such as palifermin and benzydamine, and studies in this field have essentially come to a halt. from 16 to 18The pathophysiology of mucositis seems to entail processes that are far more intricate than the direct damage to epithelium hypothesis, even when including radiation- and chemotherapy-induced pathways.

thought to have a similar aetiology to mucositis. This involves the intricate web of relationships between cytokines, innate microbes, and local immunological effects, all of which contribute to tissue injury in one way or another.in references 18–20

The idea that almost every biological process in humans is governed by a circadian rhythm—the cycle of the day and the night—has been extensively researched and recorded. Sleep, emotions, cellular proliferation, hormone release, and many other biological activities are regulated by these circadian rhythms, which are overseen by the hypothalamic suprachiasmatic nucleus. Based on preclinical research, it seems that clock genes such as PER1, PER2, CLOCK, BMAL1, etc., interact with cell cycle progression. items 21–25

Treatment techniques have been created to find the optimal time of day to treat, maximising the impact on cancer cells and minimising the same on normal cells, by using the notion of an existing circadian rhythm. The term "chronotherapy" describes this treatment approach that makes use of the natural circadian cycle.The diurnal cycle of DNA synthesis and cellular proliferation seems to vary between normal cells and cancer cells, according to preclinical experimental findings. well referenced in [26,27]. Therefore, to get the most out of radiation therapy for tumours, it's best to administer it first thing in the morning when the cells are still in the radiosensitive G2/M phase and normal cells are still cycling through the radioresistant G1 phase.28 and 29By looking back at the cases of radiation-induced mucositis, we tested the hypothesis of chronotherapy and found no correlation between the time of radiation and the severity of the condition.

## MATERIALS AND METHODS

From January 2014 through June 2014, 208 patients with head and neck squamous cell carcinoma confirmed by histopathology were registered with our institution's Department of Radiotherapy and Oncology. All three of these subsites—the mouth, throat, and nose—were considered for the research. Stage II, III, or IVA patients were all accounted for in the research. In the end, we didn't include 66 individuals who didn't get the full 60-66 Gy in 30–33 fractions, had treatment interrupted for personal reasons, had hypopharynx or larynx subsites, or received radiation therapy between 11 am and 4 pm. All things considered, 142 patients' records were usable for the study, regardless of whether they had RT in the morning (8 am - 11 am) or the evening (5 pm - 8 pm). Both the regional ethics committee and the institutional review board gave their stamp of approval to the study's methodology and design.In order to reach the final analysis, all patients were given a 60-66Gy dose in 30-33 fractions, with 2 Gy per fraction. They were treated once a day, five fractions a week, and the radiation was directed at the head and neck primary site and regional lymph node stations using a lateral parallel pair/unilateral field and a low anterior neck field. A weekly review is conducted on all RT patients with head and neck conditions in accordance with departmental practice. Each patient's master record includes a grading of the toxicities according to the Radiation Therapy Oncology Group's (RTOG) toxicity guidelines. Researchers used information on mucositis grade, highest grade of mucositis, time to development of highest grade of toxicity, and treatment interruptions caused by toxicity in each review.Statistical analyses were conducted using the descriptive analysis approach in SPSS version 18.0. We used either a Chi-square test or an independent t-test to compare the groups' acute mucositis. It was deemed significant when the p-value was less than 0.05.

## RESULTS:

For the final tally, 142 patients were considered. Each group had a similar mix of patient, tumour, and therapy variables. 73 patients (51.4%) got RT in the morning arm, whereas 69 patients (48.5%) received RT in the evening arm. Both the morning and evening groups had similar mean ages: 56.57 and 55.61 years, respectively.As is typical for malignancies of the head and neck in India, the majority of patients were men (n=130), making up more than 90% of the total. The majority of cases (57%, n=81) were Stage III illness, while the subgroup with the most instances was oropharyngeal malignancies (52.8%, n=75). Concurrent chemoradiation was administered to 76 out of 142 patients (53.5%). Forty-seven percent of patients in the final study (n=67) reported using tobacco products even while undergoing radiation treatment. FIGURE 1There was a significant increase in the incidence of severe mucositis, defined as Grades 3 or 4, among the study population as a whole (51.4%). Specifically, in the morning arm (42.47% of patients) and the evening arm (60.9%), this condition was seen. There was a statistically significant difference (p=0.028) in this case. Consequently, a greater proportion of patients treated in the evening arm had severe mucositis when contrasted with the morning arm. In the morning group, it took 5–6 weeks longer to develop Grade 3 or 4 mucositis, compared to the evening group (TABLE 2). Severe mucositis was independently predicted by current smokers and the use of concomitant treatment (TABLE 2). Severe mucositis occurred in 62.7% of RT-smoking individuals (n=67) vs to 41.3% of nonsmoking patients (p = 0.011). In a study with 76 patients, 68.4% of those who had concurrent chemotherapy also experienced severe mucositis, compared to 31.8% of those who did not. very significant (p= 0.0001)

A statistically significant increase in treatment interruptions and discontinuation of concomitant chemotherapy owing to increased mucosal toxicity and worse overall condition was related with the evening arm RT. In terms of treatment interruptions, the morning RT arm had a 17.8% advantage over the afternoon arm (p=0.002), and in terms of patients who had to skip weekly chemotherapy, the morning RT arm had a 21.2% advantage over the afternoon arm (p=0.409).* (p=0.028) (3rd Table)

## DISCUSSION

We looked examined the possibility that the severity of mucositis after radiation treatment for head and neck cancers was related to when the radiation was administered. Overall, 51.4% of cases were Grade 3 or 4, which is comparable to the reported rate of severe mucositis in the literature.[30]Results from our research showed that morning radiation (8am-11am) considerably reduced the incidence of severe mucositis compared to evening radiation (5pm-8pm). Our findings are in line with those of Bjarnson et al., who presented research supporting the idea that radiation administered in the morning is preferable than that administered in the afternoon with regard to the preservation of normal tissue toxicity.When comparing male patients undergoing radiation in the morning to those undergoing radiation in the afternoon, his prospective randomised experiment found that the former group lost more weight and had a lower incidence of oral mucositis (49.4% vs. 64.1%). [30] Also, Bashir et al. evaluated the difference in normal tissue toxicity when radiation was given to the head and neck using the Intensity Modulated Radiation Therapy (IMRT) approach in a nonrandomized prospective way. Similarly, 28.6% of morning group patients and 43.7% of evening group patients had Grade 3 mucositis, and the severe mucositis free interval (SMFI) for the morning group was 33 days, while the evening group's was 22 days.[31] inIn a similar vein, Goyal M et al. shown, using a randomised design, that those exposed to radiation in the evening were more likely to develop higher grade mucositis (38% vs. 26%).[32]Other sections of this site include clinical evidence showing how chronotherapy reduces typical tissue toxicity and how chemotherapy works in a 24-hour cycle.

The effects of drugs on the body's circadian rhythm seem to vary, according to both preclinical and clinical research. The most delicate tissues, including bone marrow components and renal tissue, are less vulnerable to the toxicity of cisplatin when given in the evening, according to the research. Focan et al.[39] in patients with esophageal cancer and Verma et al. in patients with head and neck cancer provided clinical support for this.[38]Similar findings were seen in a retrospective study of breast irradiation patients at one institution; the frequency of acute skin toxicity was greater in the evening arm compared to the morning arm, and the degree of skin toxicity was also higher.[33]Confirming the existence of a diurnal regularity to the cell cycle of the

intestinal mucosal cells, Shukla et al. clinically demonstrated a reduction in diarrhoea incidence in cervical cancer patients who received radiation in the morning.[37]

The results suggest that the oral mucosa cells undergo a circadian rhythm, which causes a time-bound variation in their radiation response. One possible explanation is that most cells are in the more radioresistant G1 phase in the morning, compared to the more radiosensitive G2 phase in the evening. Bjarnason et al. provided the experimental evidence supporting the results. They used immunohistochemistry to examine the nuclear expression of cell cycle proteins in oral mucosa samples taken from healthy male volunteers at different times of day. For every protein that was examined, there was a clear circadian rhythm. For example, p27, which is a marker for early G1-phase, peaked at 6:00 am, p53 at 10:50 am, cyclin-E at 2:50 am, cyclin-A at 4:00 pm, and cyclin-B1 at 9:10 pm, all of which are markers for M-phase. on page 34Previous research has shown that smoking and concurrent chemotherapy increase the likelihood of getting mucositis; our new study confirms this by finding a substantial increase in the incidence of severe mucositis.The rate of treatment interruptions in the evening arm was 42.0%, which is significantly greater than the morning arm's 17.8%. There was a significant increase in the proportion of patients in the evening arm who required discontinuation of concomitant treatment.Evidence from randomised trials shows that treatment interruptions significantly reduce locoregional control and overall survival rates in head and neck cancers.35 and 36 We found that RT administered in the evening led to more severe mucosal toxicity and treatment interruptions, which in turn affected the treatment success

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## CONCLUSION

Our study's findings corroborate previous research showing a correlation between morning radiation treatments and fewer treatment interruptions and Grade 3 or 4 mucosal toxicities. There is enough clinical data to support the use of chronotherapy as a crucial therapeutic approach, even if large randomised studies are not yet available. A practical and economically viable therapeutic option would be chronomodulated radiochemotherapy, as no active interventional or pharmaceutical technique exists to reduce normal tissue toxicity.

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