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RESEARCH ARTICLE

A COMPARATIVE STUDY ASSESSING THE DIFFERENT PATTERNS OF RADIATION REACTIONS IN HEAD AND NECK CANCER PATIENTS UNDERGOING RADIATION THERAPY AT DIFFERENT TIMES OF THE DAY- IN THE MORNING VERSUS EVENING

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Abstract

Background: Human oral mucosa, is a prime target for radiation induced toxicity in patients undergoing radiotherapy for head and neck cancer. The oral cavity is highly susceptible to direct and indirect toxic effects of cancer chemotherapy and ionizing radiation. In our study we investigated the role of chronotherapy with respect to radiation induced mucositis occurring in the normal oral mucosa and treatment response in tumor tissue in cancer patients undergoing radiation therapy to head and neck region.

Materials and Methods: This non-randomized clinical study was done to compare the two different timing schedules in the management of head and neck cancer by external beam radiation therapy by cobalt-60 (Theratron780C). In morning arm (arm A), Patients received external beam radiotherapy (EBRT) by cobalt-60 with SSD of 80cm with daily fractions, five days a week, between 8AM– 10 AM whereas in evening arm (arm B), patients received EBRT by cobalt-60 with daily fractions, five days a week, between 3PM– 5 PM. Both the arms received same radiation regimen.

Results: The study concluded that in the morning arm the onset of oral mucositis was observed to be significantly delayed and the duration of mucositis was also significantly shorter as compared to the evening arm. Statistically significant difference in severity of mucositis was found between the two arms.

Conclusion: Since there is no active measure to minimize normal tissue toxicity, chronomodulated radiotherapy would be a feasible and cost effective treatment strategy that can be put into clinical practice.

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Introduction:-

The term “Head and Neck Malignancies” usually refers to the variety of neoplasms arising from upper aerodigestive tract.¹Ninety percent of head and neck malignancies are squamous cell carcinomas.²Head and neck cancers represent the sixth most common cancer worldwide with approximately 650000 new patients diagnosed annually resulting in more than 330000 deaths every year. It is accounting for approximately 6% of all cancer cases and 1-2% of all cancer deaths. Oral cavity and laryngeal cancers are the most common head and neck cancers globally.³

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Historically, Head and neck squamous cell carcinoma (HNSCC) have been a disease of older males with heavy lifelong tobacco use, high alcohol consumption, poorly preserved diet, and bad dentition. As smoking increased among women, the male to female ratio of 5:1 observed in 1960s declined to 3:1 as of present. Infection with highrisk HPV has also been implicated in the pathogenesis of growing subset of HNSCCs.⁴

In patients with early stage head and neck squamous cell carcinoma, single-modality treatment with surgery or radiotherapy (RT) remains the therapy of choice. RT is an option in early stage cancer as either external beam or brachytherapy, however in this setting, RT is limited by xerostomia, mucositis, and osteoradionecrosis.

The mucosal lining of the gastrointestinal tract, including the oral mucosa, is a prime target for treatment-related toxicity. The oral cavity is highly susceptible to direct and indirect toxic effects of ionizing radiation.⁶ Acute mucositis results from the loss of squamous epithelial cells owing to the sterilization of mucosa stem cells and the inhibition of transit cell proliferation. This leads to a gradual linear decrease in epithelial cell numbers. Normally, cells of the mouth undergo rapid renewal over a 7-14 days cycle. Radiation therapy interferes with cellular mitosis and reduces the ability of the oral mucosa to regenerate.⁷

Management of oral mucositis has been largely palliative to date. Various guidelines are being followed which include Mucositis Study Group of the Multinational Association for Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) guidelines for the management of mucositis and RTOG guidelines.⁸

Chronotherapy refers to the use of circadian, ultradian, infradian & seasonal or other rhythmic cycles in the application of therapy. The goal of chronotherapy is to take into account the biological clock of various tissues in trying to schedule treatment in the most opportune time for the tumor and the least harmful time for the normal cells. Therefore, investigating the peak times of oral mucosa cells could dictate the timing of treatment to diminish side effects.⁹

In the normal human oral mucosa, a significant circadian rhythm was found for all studied proteins, with the high point of expression for p27 at 6:00 AM (early G1-phase marker), p53 at 10:50 AM (late G1- phase marker), cyclin-E at 2:50 PM (S-phase marker), cyclin-A at 4:00 PM (G2-phase marker), and cyclin-B1 at 9:10 PM (M-phase marker).¹⁰ During this time, normal cells would receive better protection, as they peak in G1.¹¹ The best treatment time for inducing apoptosis was in the late activity phase, coinciding with a time when most target cells were in the G2-M phase.¹² Henceforth the ideal time of the day to treat a tumor, would be in the morning hours, to maximize tumor kill as the cells would be more or less in the radiosensitive G2/M phase and the normal cells would be minimally affected as they would be cycling in the radio resistant G1 phase.¹³

Materials And Methods:-

A non-randomized interventional study was undertaken in the Department of Radiotherapy, Regional Institute of Medical Sciences, Imphal, Manipur for a period of 24 months starting from September 2015 to August 2017 to study the feasibility of comparison of different patterns of radiation reactions in Head and Neck cancer patients undergoing radiation therapy at different times of the day – in the Morning versus Evening. Ethical approval was obtained from Institutional Ethics Committee, RIMS, Imphal before study. Written informed consent was obtained from the participating individuals.

Patients aged between 30-70 years with histopathologically confirmed cases (epithelial tumours) of head and neck cancer with Karnofsky Performance Status (KPS) $\geq 60\%$, Haemoglobin $\geq 10\text{gm}\%$, TLC $\geq 4000/\text{mm}^3$, Platelet count $\geq 100,000/\text{mm}^3$, normal Kidney Function Test, Liver Function Test, Blood sugar, normal ECG, patients willing to remain on follow up after radiation therapy till the study is completed and willing to participate in this study were inclusion criteria for this study.

This study was done to compare the two different timing schedules in the management of head and neck cancer by external beam radiation therapy by cobalt-60 (Theratron780C). In Morning Arm (Arm A), Patients received external beam radiotherapy (EBRT) by cobalt-60 with SSD of 80cm with daily fractions, five days a week, between 8AM–10 AM whereas in Evening Arm (Arm B), Patients received external beam radiotherapy (EBRT) by cobalt-60 with SSD of 80cm with daily fractions, five days a week, between 3PM–5 PM. Both the arms received same radiation regimen. Treatment planning was done in the conventional method by using CECT neck. The head and neck radiation portals included atleast half of the oral mucosa and oropharynx. Patients received 66-70Gy in 30-35

fractions (200cGy/fraction/day) depending on the disease site by shrinking field technique. During the whole period of treatment, patients were assessed for radiation reactions every week and the tumour response was assessed 1 month post completion of treatment. Treatment related toxicities were assessed in accordance with Radiation Therapy Oncology Group [RTOG] Criteria. Tumor response was evaluated by clinical evaluation and imaging studies after 1 month of completion of treatment and late response was assessed at 6 months after the completion of treatment using RECIST Criteria and followed up till study completion.

Statistical Analysis:

Data was entered and analyzed using SPSS version 21. Descriptive statistics like age, sex etc were presented as mean and onset, grade of mucositis, etc., were presented as percentages. Chi-square was used to determine the association of the treatment regimen with the treatment response and grade of mucositis. The severity of oral mucositis was assessed by Fisher exact test. The median duration of oral mucositis was determined by independent t-test. Kaplan Meier survival analysis was used to assess the late treatment outcome. p value <0.05 was considered as significant.

Results:-

Patient's characteristics

From September 2015 to August 2017, 124 patients were recruited and randomly assigned into two treatment arms, Arm I (morning arm) with 62 patients and Arm II (evening arm) with 62 patients. The median age at diagnosis was found to be 54 years (range = 31-68 years). In regard to the age distribution among the two arms, it was found that the maximum number of patients were in the age group of 51 to 60 years, 25 (40.3%) and 23 patients (37.1%) in respective arms. The number of patients in age group 41-50 years were 18 (29%) and 19 (30.6%) patients. The number of patients in age group 31-40 years were 07 (11.3%) and 08 (12.9%) patients. The number of patients in age group 61-70 years were 12 (19.4%) in both arms (p value =0.98).

Out of 124 patients accrued for the study, 84 (67.7%) were males and 40 (32.2%) were female with a male to female ratio of 2.1:1. On sub-group analysis, there were 46 (74.2%) males and 16 (25.8%) females in the morning arm and 38 (61.3%) males and 24 (38.7%) females in the evening arm. Out of 124 patients, 85 (68.5%) were smokers or had previous history of smoking and 39 (31.5%) were non-smokers with a smokers to non-smokers ratio of 2.1:1. (p value =0.176). Maximum patients in both the arms had KPS of 80%, 31(50%) patients in the morning arm and 31 (50%) patients in the evening arm, followed by KPS 70% in 19 patients (30.6%) and 18 patients (29.0%). KPS of 90% was seen in 9 (14.5%) patients and 5(8.1%) patients. KPS of 60 % was seen 3 (4.8%) and 8 (12.9%) patients.

Tumor Characteristics:

Overall, the most common primary site was found to be carcinoma nasopharynx in 45 (36.6%) patients followed by carcinoma of oral cavity in 33 (26.6%) patients and hypopharynx in 17 (13.7%) patients. The most common histopathology found was squamous cell carcinoma in 78 (62.9%) patients followed by undifferentiated carcinoma in 31 (25%) patients.

Overall, 71 (57.3%) patients had Stage 1 disease and 53 (42.7%) patients had Stage 2 disease. In the morning arm 36 (58.1%) patients were in Stage 1 disease and 26 (41.9%) patients in Stage 2 disease. In the evening arm 35 (56.5%) patients had Stage 1 disease and 27 (43.5%) patients had Stage 2 disease.

Toxicity and treatment response:

The onset of radiation induced oral mucositis was taken as the appearance of erythema of the oral mucosa included in the radiation field as per the RTOG guidelines. Examination of the patient was done at the baseline and at the end of each week.

The development of mucositis was seen in 91.9% in the morning arm and 98.4% in the evening arm. The appearance of oral mucositis at the end of second week was seen in 32 (51.6%) patients in morning arm and 52 (83.9%) patients in the evening arm, which was found to be statistically significant (p = 0.000). By the end of the treatment 55 (88.7%) patients developed oral mucositis in the morning arm and 61 (98.4%) patients developed oral mucositis (Table 1).

The severity of oral mucositis observed during the entire period of treatment in the morning arm was 8.1% grade 0, 19.4% grade 1, 45.2% grade 2, 25.8% grade 3 and 1.6% grade 4. In the evening arm, it was 1.6% grade 0, 6.5% grade 1, 32.3% grade 2, 46.8% grade 3 and 12.9% of grade 4. The severity of mucositis was comparable

between the two arms, it was found that grade 3 and grade 4 mucositis was found statistically significant with $p=0.024$ and $p=0.017$ respectively (Table 2). The median time to develop grade 3 or grade 4 mucositis was found to 4.7 weeks in the morning arm and 5.8 weeks in the evening arm and p value was found to be statistically significant ($p=0.013$) (Table 3).

Patients who were smokers or had previous history of smoking had significant grade 3 oral mucositis and the p value was found to be significant ($p=0.005$). But for the grade 4 mucositis among smokers, the p value was not found to be significant ($p=0.115$).

Response assessment was done 1 month after the completion of treatment. Complete response was seen in 92 (74.2%) patients, partial response in 15 (12.1%) patients, stable disease 9 (7.3%) patients and progressive disease 8 (6.5%) patients. On sub-group analysis complete response was seen in 49 (79%) patients in morning arm versus 43 (69.4%) patients for evening. Partial response was achieved in 7 (11.3%) versus 8 (12.9%) patients in morning arm, evening arm respectively but the difference was statistically insignificant ($p=0.958$) (Figure 1).

In our study, 83.8% and 79% had disease free survival at the end of 6 months (Table 5). The 2- year overall survival was found to be 69.4 % in the morning arm and 53.2% in the evening arm (Figure 2).

Table 1:- Onset and duration of radiation induced oral mucositis.

Onset of Mucositis	Morning Arm n (percentage)	Evening Arm n (percentage)	p- value
Week 1	0 (0%)	0 (0%)	-
Week 2	32 (51.6%)	52(83.9%)	0.000
Week 3	42 (67.7%)	56 (90.3%)	0.002
Week 4	53 (85.5%)	57(91.9%)	0.256
Week 5	56 (90.3%)	60(96.8%)	0.144
Week 6	57(91.9%)	60(96.8%)	0.243
Week 7	55 (88.7%)	61(98.4%)	0.028

Table 2:- Severity of oral mucositis at the end of treatment.

Severity of Mucositis	Morning Arm n=62 (percentage)	Evening Arm n=62 (percentage)	p- value*
Grade 0	05 (8.1%)	01 (1.6%)	0.207
Grade 1	12 (19.4%)	04 (6.5%)	0.058
Grade 2	28 (45.2%)	20 (32.3%)	0.197
Grade 3	16 (25.8%)	29 (46.8%)	0.024
Grade 4	01 (1.6%)	08 (12.9%)	0.017

*Fisher Exact Test

Table 3:- The median time to develop Grade 3 or 4 oral mucositis.

	Morning Arm n=62 patients	Evening Arm n=62 patients	p-value*
Median Time	5.8 weeks	4.7 weeks	0.013

*Independent t-test

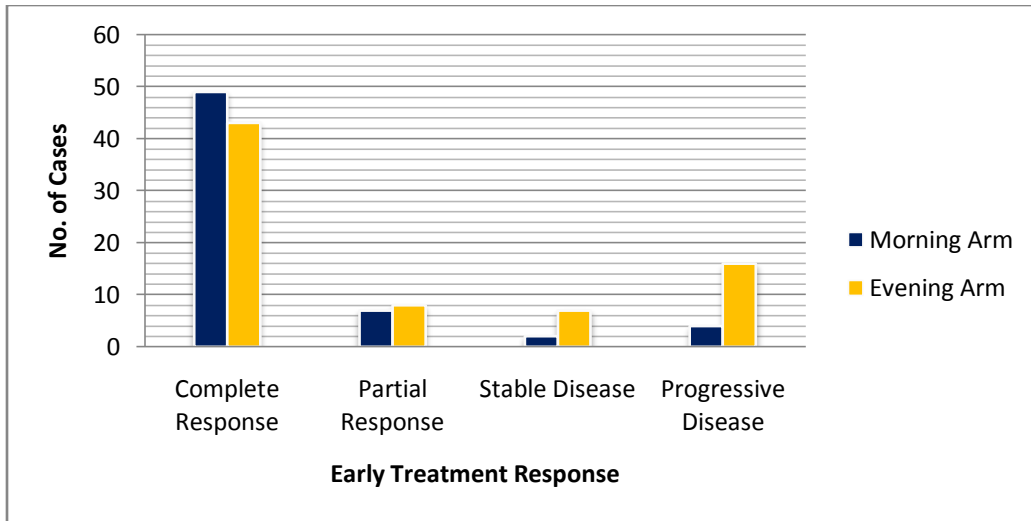


Figure 1:- Early Treatment Response between the two arms (1 month post RT).

Table 4:- Late Treatment Response at 6 Month Post RT.

Type Of Response	Morning Arm No. of patients (%)	Evening Arm No. of patients (%)
Disease Free Survival (DFS)	52 (83.8%)	49 (79.0%)
Survival with Disease (SWD)	03 (4.8%)	05 (8.0%)
Overall Survival (OS)	55 (88.6%)	54 (87.0%)

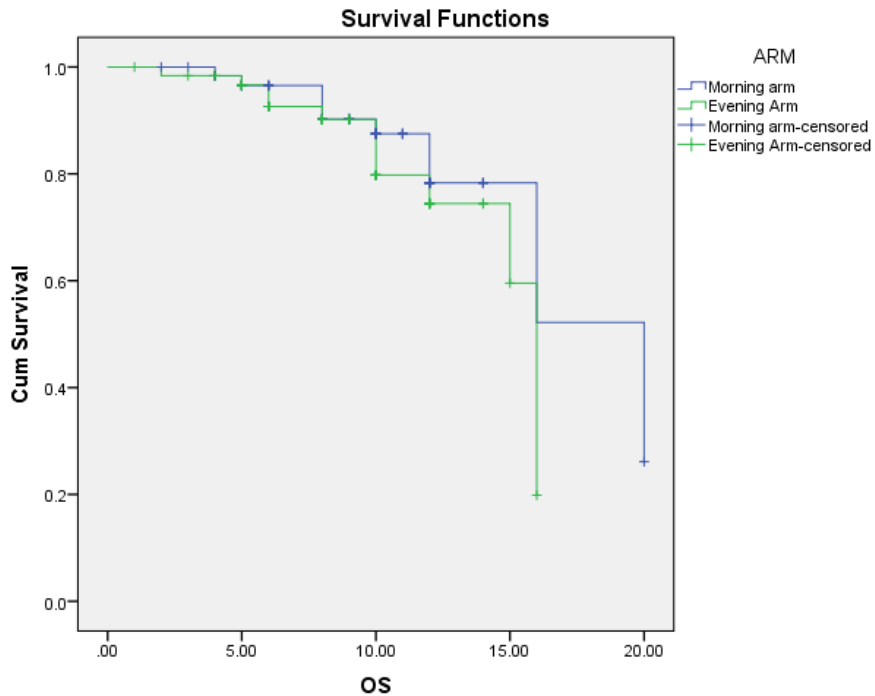


Figure 2:- Kaplan Meier overall survival curves at 2 years between the two arms.

Discussion:-

Patient and tumor characteristics:

In the present study the median age at diagnosis of head and neck cancer was found to be 54 years (range = 31-68 years). The median age for male patients being 52 years and female patients being 60 years. The analysis of study done in US population by Vigneswaran N et al showed that the median age at diagnosis of head and neck was 58

years for men and 61 years for women.¹⁴ In regard to the age distribution among the two arms, it was found that the maximum number of patients were in the age group of 51 to 60 years which was found similar to the study conducted by Sheno R et al (38.7% and 27.8% respectively).¹⁵

Out of 124 patients accrued for the study, 84 (67.7%) were males and 40 (32.2%) were female with a male to female ratio of 2.1:1. In both the arms male predominance was seen (p value =0.124). Pinholt et al observed almost equivalent numbers between men and women (1.2:1).¹⁶

In the present study 68.5% patient were smokers or had previous history of smoking and 31.5% were never smokers (p value =0.176). Koyanagi YN et al analyzed systematic review of previous epidemiological studies for cigarette smoking and head and neck cancer. Four of five cohort studies and 11 of 12 case-control studies showed a strong positive association between cigarette smoking and head and neck cancer.¹⁷ In contrary to the study in Southern India by Rekha R showed 60.4 % of head and neck cancer associated with patients having no habits or risk factors.¹⁸

In this study the median Karnofsky performance status was found to be 80 % which was similar to the study conducted by Visacri MB et al where the median KPS was found to 90% in these patients.¹⁹

In the present study the most common primary site was found to be carcinoma nasopharynx 36.6% followed by carcinoma of oral cavity 26.6% and hypopharynx 13.7%. A study by Kataki et al, showed that nasopharyngeal carcinoma is uncommon in the Indian subcontinent except in the Northeastern part of the country.²⁰

Treatment Toxicity :

In the present study the onset of radiation induced mucositis began at the end of second week, 51.6% in the morning arm and 83.9 % in the evening arm. The results were found to be statistically significant. (p=0.000). The peak of radiation induced oral mucositis was seen at the end of 5 weeks in the morning arm and 7 weeks in the evening arm. This is in consistent with the observation by Mohanti BK et al, that the radiation starts appearing towards 2nd and 3rd week of conventional radiotherapy and reach the maximum at a cumulative dose of 50Gy and gradually decline in classical shrinking field technique.²¹ A study by Baker DJ observed that that mucosal erythema occurs in the first week in patients treated with standard 200 cGy of daily fractionated radiotherapy programs, patchy or confluent mucositis peaks during the fourth to fifth weeks of treatment with the same dose of radiation. With daily fractionated programs of <200 cGy, the severity of mucositis is expected to be low. However, in accelerated radiotherapy programs, mucositis peaks within 3 weeks of the radiation therapy.²²

In this study the severity of radiation induced oral mucositis was found in the morning arm with 8.1% grade 0, 19.4% grade 1, 45.2% grade 2, 25.8% grade 3 and 1.6% grade 4. In the evening arm, it was 1.6% grade 0, 6.5% grade 1, 32.3% grade 2, 46.8% grade 3 and 12.9% of grade 4. The results with the published work of Bjarnason et al demonstrated a significant reduction of incidence of oral mucositis for the morning group (p=0.024) when compared to patients receiving radiotherapy in the afternoon.²³ The results of the study by Bashir et al were similar with 28.6% patients in the morning group compared to 43.7% patients in the evening group developing grade 3 mucositis and the severe mucositis free interval (SMFI) was 33 days compared to 22 days in favour of the morning arm.²⁴ Chan S et al in their meta-analysis showed morning treatment was significantly associated with a 19% decreased risk of developing grade III/IV oral mucositis (risk ratio 0.81, 95% confidence interval 0.66-0.99, p=0.04).²⁵

In the present study the median time to develop Grade 3 or 4 mucositis was found to be 5.8 weeks in the morning arm and 4.7 weeks in the evening arm. The similar results was seen in the study conducted by Kuriakose et al, the median time to develop grade 3 or 4 oral mucositis was found to be 6 weeks in the morning arm and 5 weeks in the evening arm.²⁶

The impact of smoking on oral mucositis has been studied extensively. In our study, it was found that patients who were smokers or had previous history of smoking had significant grade 3 oral mucositis and the p value was found to be significant (p=0.005). This was in contrary to the study by Bjarnason et al where it was seen that there was apparent reduction in oral mucositis in patients who smoked during therapy.²³ This discrepancy may be due to the westernized life style in developed countries and lack of oral hygiene in developing country like India. A study conducted by Szeszko B et al showed that Grade III/IV acute mucositis was observed in 43.5% of patients and the percentage of patients with grade III/IV acute mucositis was similar in smokers and non-smokers (46% vs. 42%, p = 0.71).²⁷

Treatment Response:

In our study early response assessment was done 1 month after the completion of treatment, which showed patients with Stage 1 and 2, complete response was seen in 92 (74.2%) patients, partial response in 15 (12.1%) patients, stable disease 9 (7.3%) patients and progressive disease 8 (6.5%) patients. The overall survival at the end of 2 years was 85%. Truong MT et al analyzed the outcome and survival in 15 head and neck cancer carcinoma patients in early stage undergoing definitive RT, with a median follow-up of 28 months (range, 6–44 months), 13 patients achieved loco regional control. Four of 15 patients developed distant metastases. The overall survival rate at 1 and 2 years was 93% and 86%, respectively.²⁸ This is contrary to a study conducted by Krstevska V et al where complete primary response was achieved in 31 of 51 patients treated with conventional fractionation. The 2-year loco regional control rate was 41.0%, overall survival rate at two years was 50.2%.²⁹

In our study, complete response was seen in 26 (41.9%) patients in morning arm versus 28 (45.2%) patients for evening. Partial response was achieved in 16 (25.8%) versus 14 (22.6%) patients in morning arm, evening arm respectively but the difference was statistically insignificant ($p=0.958$).³⁰ A study by Bjarnason et al showed that the loco regional control was achieved in 68.5% of patients in the morning arm and 62.9% in the evening arm and 2-year overall survival was found to be 61.1% and 64.1% respectively. In our study the 2-year overall survival was found to be 69.4% in the morning arm and 53.2% in the evening arm.²³ There is lack of studies on tumor response with respect to chronobiology.

Conclusion:-

In the morning arm the incidence of oral mucositis was observed to be significantly delayed and the duration of mucositis was also significantly shorter as compared to the evening arm with statistically significant difference in severity of mucositis between the two arms. Past history of smoking increases the severity of oral mucositis. The results of this study substantiate the fact that the radiation treatment delivered in the morning hours is associated with lesser incidence of Grade 3 or 4 mucosal toxicities. After treatment number of the morning arm patients' complete response was higher than evening arm patients. Through large randomized trials are lacking, there is sufficient clinical evidence signifying the importance of utilizing chronotherapy as an important treatment strategy. Since there is no active interventional or pharmacological measure to minimize normal tissue toxicity, chronomodulated radiotherapy would be a feasible and cost effective treatment strategy that can be put into clinical practice.

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