



Timing of Daily Radiotherapy for Cases of Head and Neck Cancer: Does It Make Difference?

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Authors' contributions

This work was carried out in collaboration among all authors. Author MSEE designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author SEA managed the analyses of the study. Author SHE managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI:10.9734/JCTI/2020/v10i130118

Editor(s):

- (1) Dr. Bing Yan, Hainan Branch of PLA General Hospital, China.
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Reviewers:

- (1) Heba Gamal Abd El-Aziz, Al-Azhar University, Egypt.
- (2) Vincent O. Imieje, University of Benin, Nigeria.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/56255>

Received 12 February 2020

Accepted 21 April 2020

Published 23 April 2020

Original Research Article

ABSTRACT

Background: Oral mucositis is a major problem affecting all head and neck cancer (HNC) patients received radiotherapy. Till now, available treatment is just symptomatic with limited effects. Preventive strategies may be better to avoid this complication. Animal models studies have illustrated that anti-cancer treatment toxicity display prominent daily variations; therefore, undesirable side effects could be significantly reduced by administration of radiotherapy at specific times when they are better tolerated.

Aim: To compare "soreness quality score" (SQS) between 2 groups of head and neck cancer patients received radiotherapy at different daily time.

Methods: 2 groups of head neck cancer patients treated at Mansoura university hospital; each group included 80 cases. Group A received radiotherapy at early morning between 6 and 8 am, while Group B received radiotherapy in the afternoon between 1 and 3 pm. Oral mucositis survey was self-reported weekly during and at the end of treatment by using "soreness quality score" (SQS).

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Results: For group A, mild mucositis (score 1 and 2) was recorded in 53 cases (66%) and severe mucositis was recorded in 27 cases (34%). For group B, mild mucositis was recorded in 29 cases (36%) and severe mucositis was recorded in 51 cases (64%). There was statistically significant difference (0.003) between both groups as regards development of severe oral mucositis.

Conclusion: Better toxicity profile as regards oral mucositis could be obtained by giving radiotherapy for (HNC) patients at early morning compared to late afternoon. Further studies are worthwhile to confirm our findings.

Keywords: Head and neck cancer; radiotherapy; oral mucositis.

1. INTRODUCTION

Head and neck cancer (HNC) has an incidence of more than 650,000 cases and 330,000 deaths per year all over the world [1]. It accounts for 3 percent of malignancies in the United States, with incidence of 53,000 new cases and 10,800 deaths per year [2]. In Europe, it accounts for 250,000 new cases and 63,500 deaths annually [3]. In Egypt, it constitutes about 17% of all malignant tumors. It affects both sexes and all races. Tobacco and alcohol continue to remain the two major risk factors of HNC [4].

This type of tumors requires a multidisciplinary team for optimal diagnosis and treatment decision including surgeons, medical and radiation oncologists, dentists, dieticians, rehabilitation therapists and psychosocial oncologist [5].

For early stage (HNC) (stage I and II) either surgery or radiotherapy is the treatment of choice in many sites, with similar cure rates. But considering complications, radiotherapy is preferred specially when the aim is organ preservation and spare function. For example, preservation of swallowing and speech in cancer tongue and larynx [6].

Oral mucositis is a common and very harmful complication of radiotherapy, occurring in nearly all (HNC) patients. It can severely affect quality of life and lead to treatment interruptions that subsequently impact clinical outcomes. With limited treatment options, there is an urgent need to develop new strategies for mucositis prevention [7].

Recent hypothesis about circadian clock and its effect on controlling daily variations in different biological processes is under research. One of most interesting of those biological processes is the effect of that circadian clock on response to genotoxic stress, such as chemotherapy and radiotherapy. Although those studies still limited to animal models, observations demonstrated

that chemotherapy and radiotherapy toxicities show daily variations, therefore by choosing specific time to give treatment with expected more tolerability, we can reduce the incidence and severity of complications [8].

1.1 Aim of the Work

The primary endpoint is to compare “soreness quality score” (SQS) between 2 groups of (HNC) patients received radiotherapy at different daily time.

2. PATIENTS AND METHODS

This study examined the associations between timing of radiotherapy (early or afternoon) and severity of oral mucositis in 2 groups of (HNC) patients treated at Mansoura university hospital with 80 cases in each group. All cases were proved pathologically to have (HNC), diagnosed in early stage (I, II) with good performance status (P.S) (ECOG 0-1), cases received weekly chemotherapy sensitizer. Cases with double malignancy, advanced or recurrent disease, were underwent surgery, or with bad P.S were excluded. Group A received radiotherapy at early morning between 6 and 8 am, while Group B received radiotherapy in the afternoon between 1 and 3 pm. Patients’ treatment time was consistent throughout a 6/7-week course, and mucositis survey was self-reported weekly during and at the end of treatment by using “soreness quality score” (SQS) which is a five-level score “0- means no, 1- little soreness, 2-moderate soreness, 3-quite a lot mucositis, and 4-severe mucositis” in assessing patients’ soreness severity for mouth and throat at the end of radiotherapy.

2.1 Statistical Analysis

Results of the study were analyzed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 24). The normality of data was first tested with one-sample Kolmogorov-Smirnov test.

Number and percent were used to describe qualitative data was tested using Chi-square test was used to test the association between categorical variables. When expected cell count is less than 5, Monte carlo test was used.

For parametric data, Continuous variables were presented as mean \pm SD (standard deviation) and for non-parametric data, were presented as median (min-max). Student *t* test was used to compare the 2 groups for parametric data and Mann Whitney test for non-parametric one.

2.2 Level of Significance

For all above mentioned tests, the threshold of significance is fixed at 5%. The results was considered non-significant when the probability of error is more than 5% ($p > 0.05$) and significant when the probability of error is less than 5% ($p \leq 0.05$). The smaller the *p*-value obtained, the more significant are the results.

3. RESULTS

160 patients with pathologically proved head and neck cancer patients, early stage (I and II)

presented to clinical oncology and nuclear medicine department at Mansoura university hospital divided blindly into 2 groups; group A includes 80 patients and received radiotherapy at early morning (6 to 8 am) and group B also includes 80 patients and received radiotherapy at afternoon (from 1 to 3 pm).

As shown in Table 1 both groups were matched as regards age (group A mean age 47.7 and group B 46.54). Male sex with the most common in both groups (50 in group A and 51 in group B) with no significant difference. As regards site of tumor, both groups were also matched with the most common sites; larynx (30% and 31.2%) and nasopharynx (26.2% and 27.5%) in both groups respectively. All cases were diagnosed with early disease (stage I and II) and were matched between both groups (stage I 34% and 36%) and (stage II 66% and 64%) in both groups respectively. All cases received radical dose of radiotherapy (65-70 Gy) concurrent with weekly chemotherapy cisplatin sensitizer 30 mg/m². Most of cases were smokers (78% in group A and 80% in group B) with no significant difference.

Table 1. Patients characteristics among the studied groups

Patients characteristics	Group A (n=80)	Group B (n=80)	Test of significance	p-value
Age/years				
Mean \pm SD	47.70 \pm 5.38	46.54 \pm 4.64	t=1.15	0.251
Min-Max	37-60	38-60		
Gender				
Male	50 (62%)	51 (64%)	$\chi^2=0.043$	0.836
Female	30 (38%)	29 (36%)		
Site				
Nasopharynx	21 (26.2%)	22 (27.5%)	MC	1.0
Oropharynx	13 (16.3%)	12 (15%)		
Larynx	24 (30%)	25 (31.2%)		
Hypopharynx	5 (6.3%)	4 (5%)		
Salivary gland	8 (10%)	7 (8.8%)		
Oral cavity	9 (11.2%)	10 (12.5%)		
Stage				
Stage 1	27 (34%)	29 (36%)	$\chi^2=0.044$	0.834
Stage 2	53 (66%)	51 (64%)		
Smoke				
Yes	62 (78%)	64 (80%)	$\chi^2=0.06$	0.806
No	18 (22%)	16 (20%)		
Soreness quality score				
Score 3 & 4	27 (34%)	51 (64%)	$\chi^2=9.01$	0.003*
Median (Min-Max)	2 (1-4)	3 (1-4)	Z=2.79	0.005*

t: student t-test, χ^2 : chi square test, MC: Monte carlo test, Z: Mann Whitney test

All cases were assessed for oral mucositis weekly and at the end of treatment according to soreness quality score and maximum score was recorded for all cases. For group A, mild mucositis (score 1 and 2) was recorded in 53 cases (66%) and severe mucositis was recorded in 27 cases (34%). As regards group B, mild mucositis was recorded in 29 cases (36%) and severe mucositis was recorded in 51 cases (64%). Significant difference (0.003) could be observed between both groups as regards development of severe mucositis.

4. DISCUSSION

Radiotherapy as a line of treatment for (HNC) may cause significant side effects. One of the most annoying is oral mucositis, which adversely affect quality of life for patients. So, it is important to search for different options for management [9].

Before starting radiotherapy, good oral care regimen should be done, including implementation of oral hygiene procedures such as brushing and the use of bland rinses. This may help in continuity of treatment without interruption by decreasing possibility of infection during treatment [10].

Oral lidocaine is useful for the treatment of oral pain and inflammation. It could be used many times per day [11].

Although all those measures, still the problem is so obvious and need more work aiming to find new strategies to overcome this complication.

Many studies were done on animals and have shown that genotoxic stress strongly depends on the time of administration of anti-cancer treatment, including radiotherapy. Therefore, giving radiotherapy at specific time every day with expected better tolerability may reduce the complication of oral mucositis [12].

This hypothesis has been confirmed by the results of many clinical studies. But despite promising results, it is not approved yet for clinical practice. This could be explained by the descriptive nature of the results which lack fixed scientific explanation of the findings. One more debate about that is the possibility of changing time of therapy which require giving treatments at non-usual times such as the so early or so late hours, which would require changes in regular working schedules of medical centers [13].

So limited studies were done to assess this hypothesis in (HNC) patients received radiotherapy, the biggest one was a multivariate analyses done by Fangyi GU et al, which revealed better tolerability of radiotherapy when given in early morning (8:30-9:30am), with lowest maximum SQS (MSQS) (mean=2.26, ste=0.18). MSQS increased in patients treated at later times, with highest peak in the early afternoon (12:00-13:30pm) (mean=2.92 (ste=0.21), then decreased for patients treated in late afternoon (mean=2.37, ste=0.25) (p-value=0.025). Among patients treated between 8:30-<9:30am, 43.2% developed severe oral mucositis (SQS grade 3 or 4), compared to 69.2% among those treated in the afternoon [12]. This result is matched with our study where only 34% of patients treated between 6-8 am developed severe oral mucositis, compared to 64% among patients treated between 1-3 pm with statistically significant difference.

5. CONCLUSION

Our study suggests that there is significant variation of oral mucositis severity according to treatment time of radiotherapy; the variation shows better toxicity profile when giving radiotherapy for (HNC) patients at early morning compared to late afternoon. Due to relatively small number of cases, Further studies are worthwhile to confirm our findings. Also, more researches are required to identify an optimal time of a day for treatment with radiotherapy.

CONSENT AND ETHICAL APPROVAL

This study protocol had ethical approval from Medical Research Ethics Committee, Faculty of Medicine, Mansoura University. Every patient gives the written and informed consent.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:

*The peer review history for this paper can be accessed here:
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