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Incidence and Risk factors of Radiation induced Mucositis in Patients with Head and Neck malignancy undergoing radiotherapy: an observational study in a selected hospital in Mumbai, India

Rita Lakhani, Deepa Reddy
Principal, Associate Professor
D. Y. Patil University School of Nursing, Navi Mumbai

***Corresponding Author:**
Rita Lakhani
Principal, D. Y. Patil University School of Nursing, Navi Mumbai

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ABSTRACT

Background: The aim of this study was to assess the incidence of radiation induced mucositis in Head and Neck malignancy patients undergoing radiotherapy with a curative intent and characterize a patient profile, observing the individuals' habits, tumor characteristics and treatment protocol to analyse the risk and clinical consequences.

Methods: 50 patients undergoing cumulative Radiotherapy of 58 to 70 Gy with or without Concomitant chemo-radiotherapy were evaluated in this study. Weekly evaluations of the degree of mucositis were performed according to WHO scale, a four-degree ordinal scale.

Results: The current study confirms that RIM is a frequent complication in head and neck malignancy patients submitted to RT and CCRT. The respondents predominantly presented with grade 2 and 3 RIM by the last week of treatment with other associated toxicities as pain, odynophagia and eating difficulties amongst others. Oropharyngeal tumor location, a cumulative radiation dosage ≥5000 cGy, and the administration of concomitant chemotherapy were found to increase the risk of radiation induced mucositis in logistic regression models. This study constitutes secondary analysis from the main study by the researcher.

Keywords: Head and neck malignancy; Radiotherapy; Radiation induced Mucositis, risk

INTRODUCTION

Radiation induced mucositis [RIM] refers to erythematous and ulcerative lesions of the oral mucosa observed in patients with head and neck malignancy [HNM] being treated with radiotherapy [RT]. RIM develops in almost all patients receiving RT to the upper aero digestive tract [1, 2]. Patients receiving cumulative radiation doses >5000 cGy, hyper fractionation with dose escalation, accelerated radiation schedules, and/or concomitant chemo-RT [CCRT] are more likely to develop RIM lesions that are often very painful and compromise nutrition and oral hygiene as well as increase risk for local and systemic infection. RIM decreases QOL and increases morbidity. Severe RIM compromises the functional activity, affects social interaction and emotional well-being. Thus, mucositis is a highly significant and sometimes dose-limiting complication of cancer therapy [3]

Despite its ubiquitous presence and disquieting clinical impact, risk factors have not been well-predicated and the limited studies that have been done have divergent and inconsistent results. Thus, the literature supported results, that determined greater mucosal cell susceptibility to RT as age, gender, body mass index, low leucocyte count, use of tobacco/smoking and alcohol, and treatment type

[3,5]were intended to be examined for their correlation.

It is important to highlight that adequate mucosal assessment is needed before starting RT for HNM. Among the different mucositis classification scales, an analysis of 400 studies show that 43% use the scale of the National Cancer Common Toxicity Criteria [NCI-CTC], 38% use the World Health Organization [WHO] scale, 10% use specific scales and 5% use scales by collaborating groups, such as the scale the Radiation Therapy Oncology Group [RTOG] and the Eastern Cooperative Oncology Group [ECOG][5]use. In this study, the researcher used the World Health Organization scale.

In view of the importance of mucositis during RT for HNM, the overall objective of these secondary analyses was to classify the degree of mucositis according to WHO parameters in patients submitted to RT and CCRT and to verify whether the individual characteristics of patients, the disease and treatment influenced the incidence and severity of the mucositis.

METHOD:

This prospective cohort study was undertaken at the Fortis Hospitals Ltd., Mulund, India [JCI & NABH accredited Hospital] on 50 patients treated with RT [1.8–2.0 Gy/fraction to total doses of 58–70 Gy using conventional radiation techniques] on a six-MV-linear-accelerator during the period September'14 to September'15. All those patients who received concurrent chemotherapy were treated with single agent, Cisplatin at the dose of 40 mg/m^2 IV weekly for 6-7 weeks [body surface area]. Approval from the hospital's Institutional Review Board was obtained as a part of the main study.

Eligible patients were required to have histologically confirmed HNM undergoing RT, Karnofsky-performance-status≥70 with normal mucosa at baseline and consenting to sign the informed consent form. The patients who had prior irradiation of the head and neck, underlying diabetes-mellitus, history of allergy to Aloe-vera, on immunosuppressant's and HIV-positive were excluded from this study.

The researcher interviewed the patients on the first day of initiation of RT. The respondents demographic, disease and treatment characteristics was collected using the constructed Interview Schedule. On this occasion, baseline mucosal assessment and pain was doneusing the WHO scale;this was repeated every week during the entire treatment schedule. The radio-oncologists also assessed the degree of mucositis. On the final day of administration of RT, data related to concomitant toxicities and any adverse health outcomes were also recorded.

The parameters for individual clinical characteristics of the disease, incidence per anatomic region, RIM grades according to weeks of treatment and main complaints reported by the patients were submitted to descriptive analysis.The statistical tests used were: Fisher's exact test and chi-square.

RESULTS:

In the present study, it was found that 82% [n=41]of the respondents were males and 78% [n=39]of them were educated ≤ 10th standard. Majority [64%] of the respondents belonged to 41-60 years; the mean age was 57.67±11.123 years [range 34-78]. The mean body weight was 69.4 kg [±16.4 kg]

90% of the respondents were ex-smokers [60%]/tobacco users [30%]. Of the 60% of the respondents who reported of smoking, 68% of them had a history of 10 pack years of smoking, the remaining [32%] had 11-20 pack years of smoking. Of the 30% of respondents who reported of tobacco use, 76% of the respondents reported of tobacco use for 11-20 years and the remaining [24%] had used tobacco for 21-30 years. 56% of the respondents reported of alcohol consumption and most [72%] were occasional consumers. 12% of the respondents did not report of any addiction.

None of the respondents were smoking or using tobacco during the treatment course. Only 15 [30%] respondents were hypertensive/CAD and 3 [6%]had hypothyroid. Diabetic patients were excluded from the study as a part of the primary study criteria.

As for the primary site, 74% of the respondents had tumor in the oral cavity 12% of them had it in larynx and 10% of them had it in nasopharynx and 4% in the paranasal sinuses. Larynx was primarily detected in respondents above 60 years of age.98% of them had SCCHN and 2% of them had poorly differentiated adenoid-cystic carcinoma. Well differentiated tumors were found in approximately 48% of the respondents and the remaining was moderately differentiated. A

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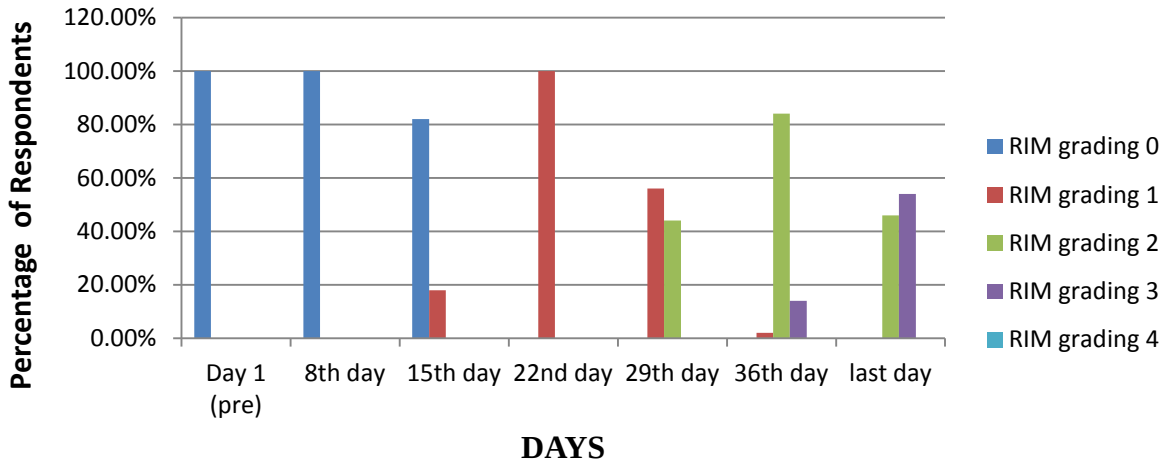
high proportion of tumors were classified as T2 [44%], followed by T3 [26%] and T4 [18%] and T1 [12%]. 34% had NO nodal staging followed by N1 38%. Remaining had N2 nodal staging.

Majority of the respondents had received a mean radiation dose of 61.26Gy for 30.8 fractionation days for a total period of 5-7 weeks. The entire respondents received standard RT.52% received CCRT. 80% had undergone a previous surgery of the primary tumor site.

All the respondents developed RIM. The mean time to the onset of RIM was 16.9±2.1 days. Figure-1 denotes the severity of RIM in the respondents during the course of RT.Predominance[98%]of grade 2 and 3 RIM was observed with higher incidence levels in the oropharyngeal region and on the tongue by the last day of the treatment.

Figure 1: Severity of RIM



On the last day of RT, the clinical problems associated with RIM included xerostomia [mild to moderate], fungal and/or bacterial infections, lack of taste, lack of appetite, pain, eating problems [difficulty in eating hard food, mastication, eating/drinking food/fluids with extreme in temperature and restrictions in eating certain foods] and odynophagia [Figure 2]. Because of RIM and xerostomia the respondents also verbalized difficulty in speaking. All the respondents were prescribed antacids [Syrup form] and oral anaesthetics [mean 16.9 day], antifungal [mean 29.04 day]and antibacterial [mean 29.9 day]oral gel applications. All the respondents reported moderate intensity of pain on the VAS scale on the last day of administration of RT [Figure 3]. A comparative picture of RIM grading and intensity of pain experienced by the respondents on the last day of RT is depicted in Table I. Most of the respondents experienced pain before the clinical presentation of RIM. None of the respondents had a break in their RT regimen either due to RIM or any other reason. The mean weight loss was 4.47 kgs in the respondents.

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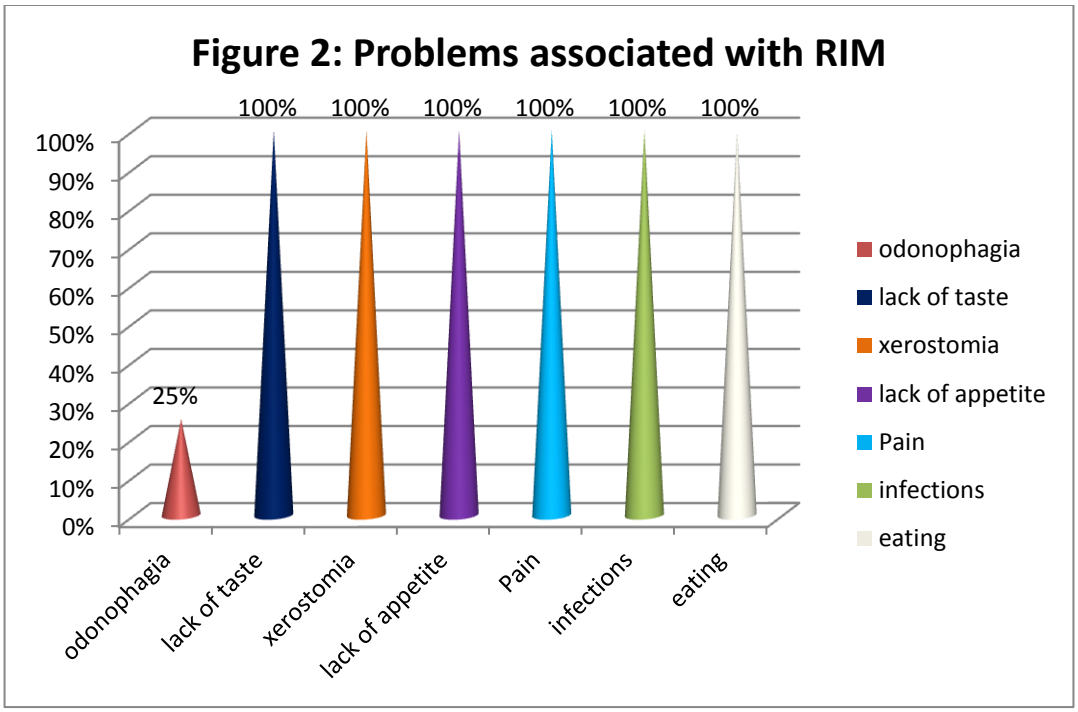

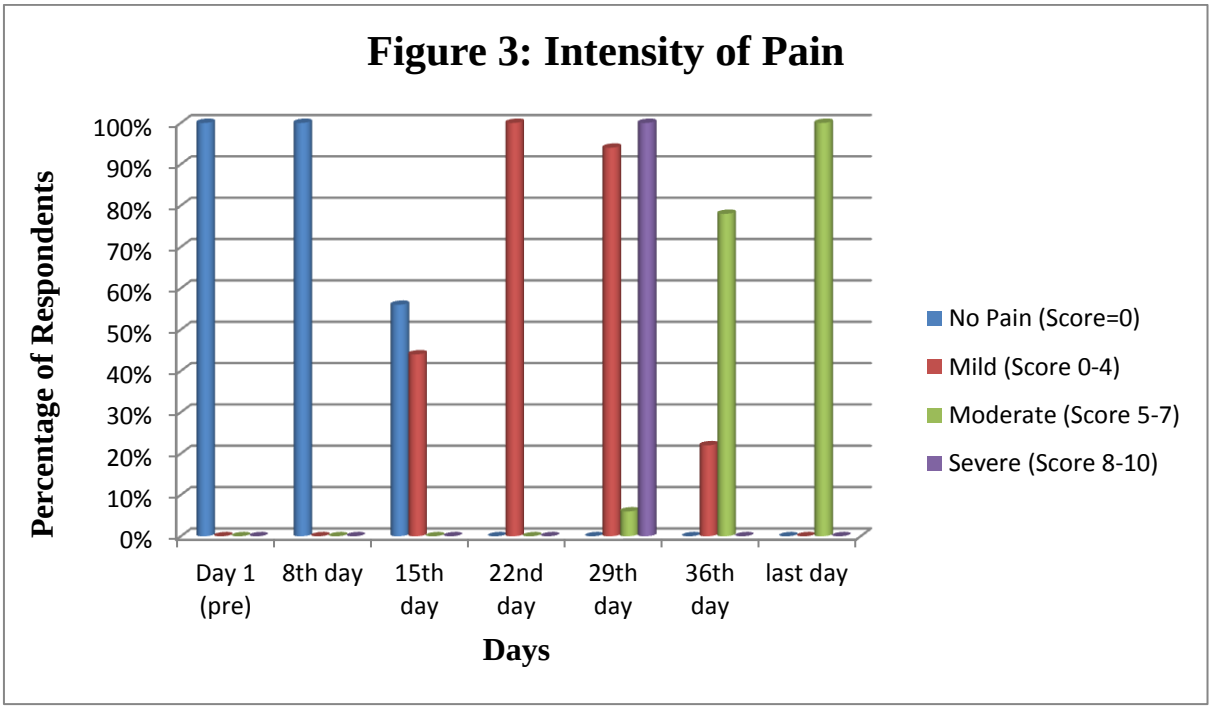

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Table I: Comparison of Severity of RIM and the Intensity of Pain experienced by the respondents on the last day of RT

N=50

Day	Grades of RIM					Grades of Pain			
	0[%]	**I[%]**	**II[%]**	**III[%]**	**IV[%]**	**No**	**Mild**	**Moderate**	**Severe**
Day 1	100	0	0	0	0	100	0	0	0
8th day	100	0	0	0	0	100	**0**	**0**	**0**
15th day	82	18	0	0	0	56	44	100	0
22nd day	0	100	0	0	0	0	100	0	0
29th day	0	56	44	0	0	0	94	6	0
36th day	0	2	84	14	0	0	22	78	0
last day	0	0	46	54	0	0	0	100	0

Table II: Characteristics of Respondents who Received RT for HNC by highest Severity of RIM

N=50

Outcome	**Grade II RIM [n= 23]**	**Grade III RIM[n= 27]**	**P value**
Mean age in years	58.60 [11.0221]	56.73 [11.2247]	0.43591
Gender [% of males]	4 [81.8%]	5 [81.4%]	1
History of smoking/tobacco chewing			
Yes	20 [86.91%]	25 [92.59%]	0.65
No	3 [13.09%]	2 [7.41%]	
History of smoking/tobacco use			
Never	3[13.09%]	2[7.41%]	0.6507
Currently	0[0.00%]	0[0.00%]	
Prior to current treatment	20[86.91%]	25[92.59%]	
History of alcohol consumption			
Yes	18 [78.26%]	17 [62.96%]	0.354
No	5 [21.74%]	10 [37.04%]	
History of alcohol consumption			
Never	5 [21.74%]	10[37.04%]	0.354
Currently	0 [0.00%]	0 [0.00%]	
Prior to current treatment	18 [78.26%]	17 [62.96%]	

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Mean Weight [kgs]	67.6 [15.6]	71.2 [17.2]	0.1576
Primary tumor location			
Oral Cavity	17 [73.9%]	20 [74.07%]	0.73
Larynx	3 [13.04%]	3 [11.11%]	
Nasophrynx	2 [8.69%]	3 [11.11%]	
Paranasal	1 [4.35%]	1 [3.71%]	
Past surgical history of the primary tumor site			
Yes	18 [78.26%]	22 [81.48%]	1
No	5 [21.74%]	5 [18.52%]	
AJCC staging			1
II	12 [52.17%]	14 [51.85%]	
III	3 [13.05%]	4 [14.82%]	
IV	8 [34.78%]	9 [33.33%]	
Mean cumulative dose of RT in cGy	5780 [±1104]	6473 [±987]	0.0051
Concomitant Chemotherapy	12 [52.17%]	14 [51.85%	1
White blood cell count [Mean]	7567±1235 cells/ cmm	8167±2035 cells/ cmm	0.92

As depicted in Table II, the severity of RIM did not appear to vary significantly with respect to patient gender or body weight, history of alcohol or tobacco use, tumor stage, or treatment characteristics between the two groups on the last day of RT [Groups with Grade 2 RIM and Grade 3 RIM]. The cumulative radiation dosage was found to increase the risk of RIM in the respondents [$P<0.05$].

Logistic regression analysis controlled for respondents age, gender, weight and tumor stage revealed that oropharyngeal tumor location [AOR: 5.1, 95% CI: 1.2-20.7], a cumulative radiation dosage 5000 cGy [AOR: 4.75, 95% CI: 1.69-13.31], and the administration of CCRT[AOR: 10.4, 95% CI: 2.9-37.1] increased the risk of RIM

DISCUSSION:

The study cohort can be characterized as heterogeneous, in terms of participant age, smoking and alcohol intake, primary tumour location, TNM cancer stage, surgical excision, use of CCRT and Dosage of RT. To clarify to what extent these factors individually or in concert influence the development of RIM during cancer therapy can only be determined in a far larger study. The size of the current sample is small and was not originally designed to test correlation between these variables and development of RIM. Besides on the last day of RT respondents did not present with varying grades of RIM to analyse the risk factors amongst them. Therefore, with specific regard the analysis done here is related to only two sub cohorts: Grade 2 and Grade 3 RIM and the researcher caution the reader to a risk of spurious association. This may perhaps also explain partly why the ranking of the most significant risk factors for RIM is quite conflicting in the current literature [Dodd et al. 1999; Trotti et al. 2003]

In this research, all the respondents had varying grades of RIM; the predominance of grade 2 [44%] and 3 [54%] mucositis was observed on the last day of RT with the oropharynx as the main site [oropharyngeal and oral cavity tumors predominated in this study]. In literature, a study on HNM patients submitted to different treatment types concluded that

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83% of patients presented with some grade of mucositis; the moderate grade predominated in 35% [3]. In another study of HNM patients submitted to different treatment modes, 91% of patients developed some grade of mucositis, but grade 3 [60%] predominated[4]. Another study revealed higher incidence levels of mucositis between the third and seventh week of treatment, with a predominance of grade 3, when patients were treated with CCRT and chemotherapy, but with altered fractionation; which could justify the higher incidence level of grade 3[1,4]

The clinical problems associated with RIM in the respondents included xerostomia [mild to moderate], fungal and/or bacterial infections, lack of taste, lack of appetite, pain, eating problems and odynophagia. The researcher needs to acknowledge that individuals differ with regard to their responsiveness to tissue damage and thus reporting of these symptoms. Investigators have reported that these signs and symptoms are common in patients with HNM. Estimates suggest that about 50% of patients prior to the cancer therapy, 81% during therapy, 70% at the end of therapy, and by 36% at 6 months after treatment have pain. Interestingly, approximately one third of patients still report pain up to 6 months post-therapy [Epstein et al. 2010]. These figures are lower than observed in the current study where the incidence was 0% at start, 100% on the last day of administration of RT.

The incidence of RIM has been reported to vary not only by treatment but also in relation to various patient characteristics, consumption of alcohol, usage of tobacco, altered oral intake, pre-existing periodontal disease, low body mass index, poor functional status, low leukocyte count, advanced disease and stage, a prior history of severe mucositis, and various comorbid conditions. However, the data supporting each of these potential risk factors are uneven. Logistic regression analysis revealed that oropharyngeal tumor location, a cumulative radiation dose of ≥5000 cGy and the administration of CCRT increased the risk of RIM. Literature proves that specifically concerning RT, some factors can influence mucositis severity, including total dose, treated volume, fractioning and treatment time [12].

CONCLUSION

The current study confirms that RIM is a frequent complication inHNM patients submitted to RT and CCRT; they predominantly presented with grade 2 and 3RIMby the last week of treatment. They had other adverse clinical consequences as pain, odynophagia, eating difficulties amongst others. It is important for nurses to heed to these parameters, considering that, in view of their presence at the radiotherapy and chemotherapy sectors, they can collaborate to enhance treatment and improve patients' quality of life.

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