Research Article

A prospective study to assess the predictive factors of radiation-induced oral mucositis in head-and-neck carcinoma and its impact on treatment outcome: Long-term results and lessons learned

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Received: December 12, 2019; **Accepted:** January 21, 2020

ABSTRACT

Background: Radiation-induced oral mucositis (RIOM) is one of the major dose-limiting toxicities in head-and-neck cancer patients. It is due to normal tissue damage by radiation. It is a potential hazard to treatment delivery as it threatens to alter the therapeutic ratio. The radiation oncologist must find a way to balance between tumor control and sparing of normal mucosa to validate the age-old principle of cancer treatment. The onus lies on them to find the contributory factors to curb them accordingly. **Objective:** The objective of the study was as follows: (1) To find out the factors associated with RIOM in head-neck squamous cell cancer (HNSCC) and (2) to assess the impact of the RIOM on treatment outcome. **Materials and Methods:** This was a single-institutional, prospective, non-randomized, and open-label study. All cases were treated after informed consent and tumor board approval. This was an observational study with standard treatment according to the stage of the disease. **Results:** Tumor site, poor oral hygiene, modality of radiation, addiction, and fractionation appeared to be the significant predictive factors of RIOM in HNSCC. **Conclusion:** This study helps to identify the contributory factors and gives a comprehensive understanding of the same. More multi-institutional subsite-specific studies are warranted to validate the same.

KEY WORDS: Head-Neck Carcinoma; Radiotherapy; Mucositis; Radiation-Induced Oral Mucositis

INTRODUCTION

According to the GLOBOCAN 2018 report, oral cancers make the second place in most common cancer in India, with an annual incidence of 1.2 lakhs and more than 72,000 deaths annually. India has one-third of oral cancer cases in the world. If hypopharyngeal and laryngeal cancer are taken into account, the estimated new cases add more than 50,000/year.[1] Locally advanced head-and-neck cancers get treated by surgery and chemoradiation, while radical radiotherapy (RT) with concurrent chemotherapy is standard of care for inoperable oral cancers and pharyngeal and laryngeal cancers. Indications of post-operative radiation are close/positive margin, $pT_{3-}T_{4,}pN_{2-3}$, ECE, and any adverse factors such as depth of invasion >10 mm, lymphovascular invasion, and perineural invasion.[2-4] The use of concurrent chemotherapy with RT shortens the onset, exacerbates the severity, and prolongs the duration of oral mucositis.[5] Incidence of radiation-induced oral mucositis (RIOM) stands between 75% and 80% of head-neck cancer while crossing 95% in cases of accelerated RT. Grade 3/4 toxicity has been around 50–55% according to published literature.[6,7]

RIOM has been a challenging matter for the treating radiation oncologist as it not only impairs patient's quality of life but also jeopardizes the treatment continuity. The

Access this article online	
Website: http://www.ijmsph.com	Quick Response code
DOI: 10.5455/ijmsph.2020.12346201921012020	

unexpected gaps in treatment lead to poor tumor control due to accelerated repopulation. Around 40–50% of patients of Grade 3/4 toxicity require hospitalization and symptomatic care and around 30% of patients heal with cessation of radiation treatment.[8]

Aim and Objective

- Primary endpoint – To evaluate the risk factors of RIOM in head-and-neck cancers
- Secondary endpoint – To analyze the effect of mucositis on treatment outcome.

MATERIALS AND METHODS

Study Design

This was a prospective, non-randomized, open-label, and single-institutional study. All cases were treated after informed consent and tumor board approval. This was an observational study with standard treatment according to the stage of the disease. All the procedures followed were in accordance with the ethical standards as laid by the Indian Council of Medical Research – Ethical Guidelines for Biomedical Research on human participants.

Study Population

Patients of biopsy-proven head-and-neck cancer attending radiotherapy outpatient department (OPD) of medical college, Kolkata.

Study Duration

The study duration was from February 1, 2015, to December 31, 2018, and traced till November 30, 2019.

Inclusion Criteria

The following criteria were included in the study:
- Patients with histologically proven carcinoma of oral cavity, oropharynx, hypopharynx, larynx of locally advanced stage based on tumor-node-metastasis staging (Stage II-IVB)
- Male and female patients aged between 18 and 70 years
- No previous surgery for the disease except for biopsy
- No previous computed tomography (CT) or RT for head-and-neck cancer
- Adequate performance status (Karnofsky performance status > 60)
- Provision of informed consent
- Adequate life expectancy
- Hematological, renal, and hepatic function within normal limits.

Exclusion Criteria

The following criteria were excluded from the study:
- Cancers of maxillary antrum, orbit, brain, skin, nasopharynx, salivary glands, lymphoma
- Pregnancy and lactation
- Prior chemotherapy, RT, or surgery for the malignancy
- Evidence of uncontrolled comorbid conditions (e.g., uncompensated respiratory, cardiac, hepatic, and renal disease).

Sample Size

Around 500 new cases of head-neck squamous cell cancer (HNSCC) attend RT OPD of medical college every year. Keeping the inclusion and exclusion criteria and about 10% drop out from the study, 250 new cases were taken every year, for 5 years and the cumulative study accrual was 1250.

Study Tools

- Patient pro forma, standard hematological, biochemical, and radiological test
- CT simulator (Brilliance CT 16-slice configuration, Philips Health Care)
- Cobalt 60 teletherapy machine (Theratron 780C), LINAC true beam
- EBRT treatment planning system with ASHA software
- Injection cisplatin with necessary premedication, fluids, etc., for administration as IV infusion
- Parameters to be studied – Baseline demographic characteristics, tumor characteristics, grades of RIOM [Table 1], and local control of tumor.

Study Technique

- Patients of HNSCC fulfilling the inclusion criteria were given RT on different fractionation regime as indicated. Patients undergoing concomitant chemoradiation (CTRT) were assigned to receive 3 weekly inj. cisplatin and every patient was assessed weekly for hematological parameters, nutrition and oral mucositis. Majority of the cases were treated in telecobalt as compared to LINAC as the latter was installed at our institution at later times.

Table 1: Oral mucositis grading scales

Grade	WHO	NCI
1	Oral soreness, erythema	Asymptomatic
2	Erythema, ulcers	Moderate pain not interfering with oral intake
3	Ulcers with severe erythema, can't swallow food	Severe pain, interfering with oral intake
4	Alimentation not possible	Urgent intervention needed
5	N/A	Death

Table 2: Demographic characteristics of the study population

Tumor site	Age (median years)	Diagnostic delay months (median)	Stage (mean)	Treatment received (%)		3-year recurrence (%)
				PORT	CTRT	
Buccal mucosa (*n*=315)	58	3	II	75	25	24
FOM (125)	52	4	III	65	35	18
Tongue (375)	49	4	III	62	38	30
RMT (125)	55	5	III	46	54	15
Hard palate (30)	58	5	II	18	82	17
Oropharynx (80)	45	6	III	10	90	10
Hypopharynx (82)	60	6	II	4	96	12
Larynx (118)	62	6	II	24	76	11
Total = 1250	58	5				

CTRT: Concomitant chemoradiation, PORT: Post-operative radiotherapy

Table 3: Multivariate analysis of predictive factors of RIOM

Variable	Hazard ratio	95% confidence interval	*P*-value
Subsite	1.2	0.8–4.6	0.01
Tobacco addiction	0.8	0.2–1.9	0.05
Treatment modality (RT/CTRT)	1.3	0.6–4.7	0.02
Fractionation schedule	0.9	0.5–2.1	0.04
RT dose (60 vs. 66 Gy)	0.6	0.2–1.3	0.34
Poor oral hygiene	0.7	0.4–1.9	0.05

RIOM: Radiation-induced oral mucositis, CTRT: Concomitant chemoradiation, RT: Radiotherapy

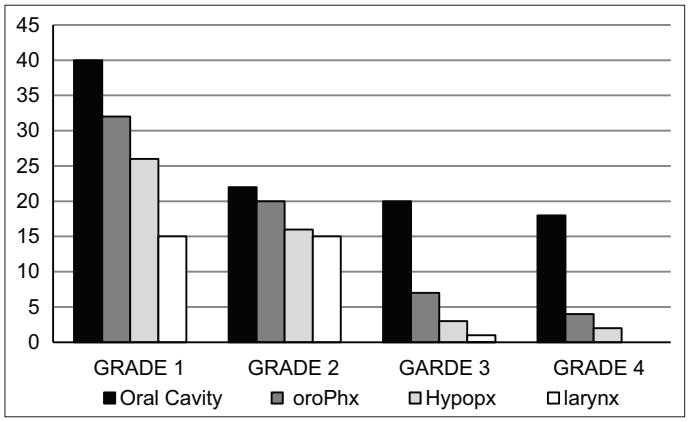

Figure 1: Bar diagram showing the association of tumor location with grades of radiation-induced oral mucositis

- Follow-up period – from treatment completion to the last day of contact or death.

Statistical Analysis

All collected and properly tabulated data are to be analyzed using standard statistical software SPSS version 20. Descriptive statistics and Chi-square test and unpaired *t*-test were used to find the correlation between the risk factors and RIOM. Significant factors were further cross-checked with multivariate Cox regression analysis.

RESULTS

The median follow-up period of the study was 49 months (20–58 months). Sex predilection was skewed to males (male:female = 2:1). The most common primary was oral cavity cancers. Subset analysis showed preponderance of oral tongue and buccal mucosa in the study population. Baseline demography was comparable [Table 2]. The median age of the population was 58 years, though oropharyngeal cases were youngest and laryngeal cases were elderly but homogeneously distributed in the study population. Patients had a median diagnostic delay of 5 months with pharyngeal and laryngeal cancers which were on the upper limit. This diagnostic delay was the summation of patient's delay, referral delay, and workup delay.

Pharyngeal and laryngeal cases were mostly treated by CTRT, while oral cavity cancers were addressed by surgery and post-operative radiation. Post-operative adjuvant RT excluded concurrent chemotherapy unless margin positive or a R_2 resection. Patients who received any form of neoadjuvant chemotherapy were excluded from the study. Oral cavity cancers had the highest number of local recurrence at 3-year follow-up with tongue and buccal mucosa topping the chart. We have learnt that oral cancers (site), addiction, especially smokeless tobacco, poor oral hygiene, CTRT, and altered fractionation were significantly associated with Grade 3 and 4 RIOM [Table 3, Figure 1]. Oral hygiene was assessed with a standard chart [Table 4] with active participation from our ENT and dental colleagues. We investigated the effect of the duration of tobacco addiction, but it was not significant ($P = 0.47$). On the other hand, stage, performance status, age, and sex did not have a significant impact on RIOM.

The scores of the eight categories are summed. A normal mouth will receive a score of 8.

On treatment outcome analysis, the study showed remarkable results. Three-year progression-free survival (PFS) and 3-year

Table 4: Oral hygiene assessment guide

Category	Method of observation	Rating 1	Rating 2	Rating 3
Voice	Converse with patient. Listen to crying	Normal	Deeper or raspy	Difficulty talking or crying, or painful.
Ability to swallow	Ask patient to swallow	Normal	Some pain during swallow	Unable to swallow
Lips	Observe and feel tissue	Smooth, pink and moist	Dry or cracked	Ulcerated or bleeding
Saliva	Insert depressor into mouth, touching center of tongue, and the floor of the mouth	Watery	Thick or ropy. Excess salivation due to teething	Absent
Tongue	Observe appearance of tissue	Pink, moist, and papillae present	Coated or loss of papillae with a shiny appearance with or without redness. Fungal infection	Blistered or cracked
Mucous membrane	Observe appearance of tissue	Pink and moist	Reddened or coated without ulceration	Ulceration with or without bleeding
Gingiva	Gently press tissue	Pink and firm	Edematous with or without redness, smooth	Spontaneous bleeding or bleeding with pressure
Teeth	Observe the appearance	Clean and no debris	Plaque or debris in localized areas	Plaque or debris generalized along gum line

overall survival (OS) were not affected by Grade 3 and 4 RIOM, $P = 0.34$ and 0.54, respectively. Stage, margin positivity, radiation dose, and treatment break beyond 1 week had a significant impact on PFS ($P = 0.04$) but not on OS ($P = 0.51$). Three-year OS for our study population was 74% irrespective of subsite and stage difference. Stages 3 and 4 had poorest OS of 47% at 3 years. Three-year disease-free survival (DFS) was 86% for all cases together, laryngeal cancers fared best (90%) while oral tongue showed poorer outcome (3-year DFS 71.34%).

About 16% of cases of the analyzed population developed distant metastasis, with a major predilection for lung metastasis and few bone metastasis. About 45% of total Grade 3 and 4 RIOM cases were associated with treatment breaks more than five, but this relation was not translated into change in PFS and OS. A wide heterogeneity in the study population could be a reason for that.

DISCUSSION

Our study showed that oral cavity primary, poor oral hygiene, younger age, male sex, type of radiation, addiction, and fractionation schedule were correlated to severity of RIOM, though age had not been established as a significant factor as per data analysis. In a subset analysis, buccal mucosa cases were worst affected by RIOM.

Review of literature is also in concordance to our study findings.[9-14] Head-and-neck cancers in India are treated after a considerable delay which includes patient delay, referral delay, and treatment delay.[15] Although, this diagnostic delay was not associated with grades of RIOM. An oral assessment guide helps us to evaluate the oral hygiene status [Table 3].[16]

Management of RIOM caters around options such as povidone-iodine Gargle, Sucralfate Syrup, sodium bicarbonate solution mouthwash, and L-glutathione, but no single agent has been proven significantly efficacious till date. High-precision radiation management (intensity-modulated radiation therapy [IMRT]) with oral prophylaxis has shown a ray of hope in managing the menace of RIOM.[17-20]

Our study has few limitations such as single institutional, non-randomized, and exclusion of IMRT, and majority of the cases were treated in 780C telecobalt machine. Heterogeneity of the study population was also a noted drawback. We also excluded induction chemotherapy to remove any confounding factors. Nevertheless, this is probably the largest prospective study from Eastern India addressing the predictive factors of RIOM in head-and-neck cancers with a fairly large number of patients.

CONCLUSION

RIOM is one of the major dose-limiting toxicities while treating head-and-neck cancer patients. This study helps to identify the contributory factors and give a comprehensive understanding of the same. More multi-institutional subsite-specific studies are warranted to validate the same.

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How to cite this article: Maji A, Mandal B, Basu A. A prospective study to assess the predictive factors of radiation-induced oral mucositis in head-and-neck carcinoma and its impact on treatment outcome: Long-term results and lessons learned. Int J Med Sci Public Health 2020;9(3):209-213.

Source of Support: Nil, **Conflicts of Interest:** None declared.