Original Article

Radiation-Induced Oral Mucositis In Egyptian Patients: Incidence And Associated Risk Factors

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Abstract

Background:
Radiotherapy (RT) in head and neck cancer patients (HNC) can frequently and severely result in oral mucositis (OM) can lead to many comorbidities such as discomfort, infection, despair, extended hospital stays, therapeutic delays, rise in patient morbidity, and higher expenses.

Aim:
To record the incidence of oral mucositis among head and neck cancer patients, investigate the connection between risk factors and the occurrence of oral mucositis and side effect of RT reported by patients.

Methods:

The cohort study included 99 patients who had radiation for HNC. Gender, concomitant chemotherapy, history of smoking, and primary site of tumor were recorded for every patient, the patients were followed from the beginning of radiation to the end of radiation, and the occurrence of OM was assessed by using the WHO scale. Also, the association between the incidence and recorded risk factors was assessed.

Results:
The occurrence of oral mucositis was 37.4% among patients, Analysis revealed significant associations between tumor sites and incidence of oral mucositis, where most of the oral mucositis cases occurred in patients with oral tumors while no cases of mucositis occurred in patients with brain tumors ($p<0.001$), In addition, there was a significant association between the incidence of oral mucositis and concomitant chemotherapy ($P<0.0001$). Other factors showed no statistically significant association with the incidence of oral mucositis ($p>0.05$).

Conclusions:
The current study showed that certain factors may increase the risk of oral mucositis in patients receiving radiotherapy for HNC, Patients with OM are more likely to experience unanticipated radiation therapy breaks and entail hospitalization. Thus, in high-risk patients a preventive plan for oral mucositis needs to be recognized in the future before the beginning of radiotherapy.

Keywords: Oral mucositis, Risk factors, Incidence, Radiotherapy, Head and Neck cancer.

INTRODUCTION

The radiation treatments (RT) that are routinely given to patients with head and neck cancers (HNC) include a variety of side effects, such as oral mucositis (OM), xerostomia, taste abnormalities, oral candidiasis, and osteoradionecrosis of the jaw. Particularly with oral mucositis, individuals experienced difficulty in eating normally due to excruciating pain, which impairs their quality of life (QoL)[1]. The continuation of RT is often hampered by radiation-induced oral mucositis (RIOM). Despite oral mucositis's challenges during radiation therapy, no proven prevention or treatment methods are approved as the gold standard [2].

The interaction of numerous factors impacts the appearance of RIOM. Thus, the risk factors recognized as having the potential to impact OM are classified into two groups: linked to the patient and cancer therapy[3]. The factors linked to the patients are age (young, due to the rise in cell turnover, and elderly persons because of the reduction in the cure rate), gender (females have an advanced risk of OM due to hormonal factors), inadequate nutrition, and pre-existing oral lesions, bad oral hygiene habits, reduced salivary function, genetic factors (some persons appear to have a significantly lower risk of developing OM than others exposed to the same mucotoxic agents), kidney function (the rise in creatinine possibly leads to a rise in glucotoxicity and a history of OM resulting from previous anticancer treatments, Additional factors that may deteriorate the incidence of radiation-induced oral mucositis (RIOM) are the intake of alcohol and tobacco, and the presence of infections [4]

Factors linked to the treatment of RT for HNC, such as radiation techniques, area of irradiated tissue, entire and daily doses of RT, and fractionation systems, interfere with the alteration of normal irradiated tissue, in addition to these, concomitant chemoradiotherapy is added by Eilers et al. [4]

There is a deficiency of data in the literature on the frequency of RIOM in patients receiving therapy for HNC, and that information reveals a wide range of results[5]. Recent studies have concentrated more on treating oral mucositis and other cancer-treatment techniques than on RIOM etiology and related factors [6]. Therefore, the purpose of the current study was to ascertain the incidence of RIOM and list the important contributing factors.

PATIENTS:

In this cohort prospective study, 99 patients were enrolled in the Trial at the clinical oncology unit of Cairo University Hospital between November 2020 and April 2022.

The inclusion criteria were as follows: (1) The patient's consent to participate in the study, (2) patients with HNC who underwent radiotherapy (RT) or chemoradiotherapy (CRT) and had no prior history of RT in the affected area, and (3) dose of RT at the least 60Gy. The only exclusion criterion was if the patients declined to take part in the study.

SAMPLE SIZE:

We put a time frame to recruit the eligible patients and the recruited patients within the pre-specified period in our study sample. Every patient fulfilling inclusion criteria in the clinical oncology unit of Cairo University was recruited consecutively in a period of 18 months starting from November 2020 to April 2022.

METHODS:

The demographic data and selected variables were collected in a questionnaire that data like age, sex, primary cancer site (oral cavity or larynx, extraoral like maxillary sinus, brain cancer), concurrent cisplatin or temadol, the types of RT, including the three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT), prior history of smoking were reported. Additionally, side effects of radiotherapy and oral pain necessitating the administration of analgesics were also recorded.

The incidence of oral mucositis was noted individually. OM was categorized according to the WHO Mucositis score [7]. Oral mucositis was observed for 6-8 weeks from the beginning of radiation till the end of RT.

Oral care

Oral care by the dentist was started one week prior to beginning RT was made and performed once or twice a week. It included oral health instruction, a description of antifungal medication cleaning dentures, and the use of different anti-inflammatory mouthwash. All patients underwent dental evaluation prior to initiation of RT, and during RT. In addition, all patients got regular oral care during RT under the supervision of dentists.

Ethics Approval:

The study protocol was approved by the Research Ethical Committee of Cairo university of Dentistry with the registration code number (191113**).**

Statistical analysis:

Numerical data were represented as mean and standard deviation (SD) values. Categorical data were presented as frequency and percentage values and were analyzed using a chi-square test followed by pairwise comparisons utilizing multiple z-tests with Bonferroni correction. The significance level was set at $p<0.05$ within all tests. Statistical analysis was performed with R statistical analysis software version 4.1.3 for Windows[8]

Results:

1. **Demographic data:** cohort prospective study was conducted on 99 cases [73 (73.7%) males and 26 (26.3%) females]. The mean age of the cases was (54.49±13.48) years. There were 49(49.5%) cases that had a history of smoking, 47(47.5%) who were undergoing chemotherapy, and 37(37.4%) who had oral mucositis as shown in table (1).

Table (1): Demographic data and baseline characteristics

Parameter			**Value**
Gender	**Male**	**N (%)**	73(73.7%)
	Female	**N (%)**	26(26.3%)
Age (years)	**Mean±SD**		54.49±13.48
	IMRT	**N (%)**	93(93.9%)

Radiotherapy technique	**3D Conformal**	**N(%)**	6(6 .06%)
Smoking	**No**	**N(%)**	50(50.5%)
	Yes	**N(%)**	49(49.5%)
Chemotherapy	**No**	**N(%)**	52(52.5%)
	Yes	**N(%)**	47(47.5%)
Site of tumor	**Larynx**	**N(%)**	36(36.4%)
	Brain	**N(%)**	26(26.3%)
	Intraoral	**N(%)**	17(17.2%)
	Extraoral	**N(%)**	20(20.2%)
Oral mucositis	**No**	**N(%)**	62(62.6%)
	Yes	**N(%)**	37(37.4%)

2. **Associations with oral mucositis**: There was a significant association between the occurrence of OM and chemotherapy with a significantly higher percentage of OM occurring in patients who had chemotherapy ($p<0.001$). There was also a significant association and primary site of the tumor with a significantly higher percentage of cases of intraoral tumors 43.2%($p<0.001$). Other associations as gender and history of smoking were not statistically significant ($p>0.05$). as shown in table (2).

Table (2): Associations with oral mucositis

Parameter			**Oral mucositis**		**χ^2**	**p-value**
			No	**Yes**		
Gender	**Male**	**N(%)**	45(72.6%)	28(75.7%)	**0.11**	**0.735**
	Female	**N(%)**	17(27.4%)	9(24.3%)		
Smoking	**No**	**N(%)**	32(51.6%)	18(48.6%)	**0.08**	**0.775**

	Yes	**N(%)**	30(48.4%)	19(51.4%)		
Chemotherapy	**No**	**N(%)**	42(67.7%)	10(27.0%)	**15.40**	**<0.001***
	Yes	**N(%)**	20(32.3%)	27(73.0%)		
Site of tumor	**Larynx**	**N(%)**	24 (38.7%)	12 (32.4%)	**39.65**	**<0.001***
	Brain	**N(%)**	26 (41.9%)	0 (0.0%)		
	Intraoral	**N(%)**	1 (1.6%)	16 (43.2%)		
	Extraoral	**N(%)**	11 (17.7%)	9 (24.3%)		

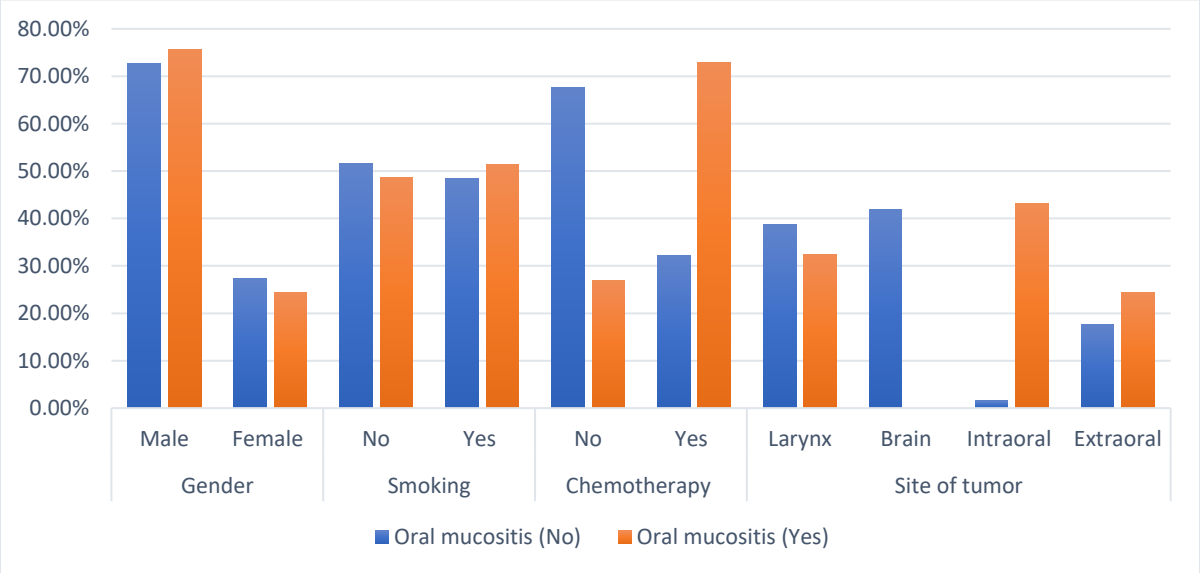

Figure (1): Bar chart showing associations with oral mucositis

3- Side effects of cancer treatment: Dysphagia, xerostomia, alteration in taste and smell sensation: side effects due to radiotherapy were detected as regards feeling of dysphagia, xerostomia, alteration in taste, and smell sensation, as shown in table (3).

Table (3): Side effects of RT reported by the patient.

parameter	**value**	
Dysphagia	N(%)	68((68%)
Xerostomia	N(%)	38(38.3%)

alteration in Taste and smell sensation	N(%)	73(73.7%)

4- Need for analgesia for oral pain & parenteral nutrition in study participants: 11% of the participant needed analgesics due to oral pain as shown in table (4). Regarding the need for parenteral nutrition, only 3 patients needed parenteral nutrition: when history was taken from those 3 patients, it was found that their insufficient food intake was mainly due to loss of appetite as a side effect of cancer therapy and not due to oral pain due to mucositis and they received only partial parenteral nutrition.

Table (4): Need for analgesia for oral pain & parenteral nutrition in study participants

Parameter	**value**	
Need for analgesia	**N(%)**	11(11.1%)
Need for parental nutrition	**N (%)**	3(3%)

DISCUSSION

RT is a common component of an HNC therapy plan. It can be used with or without chemotherapy(cisplatin) as either an initial or postoperative therapy [9].OM, xerostomia, dental caries, taste disturbance, dysphagia, trismus, and osteoradionecrosis of the jaw are among the side effects of RT[10]. A highly serious side effect of RT is OM which affects the soft tissues of the oral surfaces and can significantly impact patients' quality of life, it has not yet been successfully prevented with prophylactic measures[2].

The incidence of OM has been described to vary not only by cancer therapy but also relative to numerous patient characteristics, including old age, gender, smoking and alcohol intake, inadequate oral intake, presence of periodontal disease, low body mass index, poor functional status, oral microbiome, low leukocyte count, and numerous comorbid conditions[11]. However, the information supporting each of these possible risk factors is uneven. Although we did not assess all of the above-mentioned factors, in our present study, we found a relatively lower incidence of oral mucositis (37.4%) compared to other studies which found a higher incidence of oral mucositis[12], [13]. this may be due to several factors including the high percentage of patients with brain tumors (26%) and larynx cancer (36%) and the use of the IMRT technique in 93% of the participant which helps decrease the period of RT sessions and spares healthy tissues[14]. In addition, all patients use anti-inflammatory mouthwashes which play role in decreasing the incidence of oral mucositis [15]

Based on the results of our trial, two main clinical parameters were significantly associated with a higher incidence of OM: concomitant chemotherapy and the site of the tumor, The incidence of OM was greater in patients receiving concomitant chemotherapy with RT (73%) than in those receiving RT alone (27%), according to our findings, Concomitant chemotherapy has been shown to predict OM in HNC patients, the increase in the incidence of OM is because of the increased toxicity levels of chemo-radiotherapy than RT only, this finding is consistent with many studies in the literature[16]–[20]. About the site of the tumor, as expected in the present study, brain cancer with no incidence of oral mucositis followed by an extraoral site (such as maxillary sinus, external auditory meatus) had the lowest incidence of OM (24%), followed by the larynx (32%). While the intraoral site (tongue, palate, floor of the

mouth) was the site that showed the highest incidence (43%), in accordance with this, Mercadante et al. report that the site of HNC is often linked to OM due to the closeness of the oral cavity to the radiation field [21].

Regarding smoking there was no significant association between smoking and the incidence of OM, the oral mucosa is prone to inflammation as a result of smoking, and the underlying mechanisms may be direct oxidative stress and/or signal transduction pathway activation [24].In contrast to our findings, Goldberg et al. (2004) and Patussi et al reported that smoking history was found to be strongly linked with the occurrence of OM [25], [26]. This may be because the sample size in our study was small compared to the studies indicated, and most of the patients with a history of smoking had stopped smoking for at least two months before undergoing radiation therapy.

Data obtained through subjective assessment in the present study included that 68% of patients complained of dysphagia, 38% of xerostomia, and 73 % of alteration in taste and smell sensation. These complaints are most likely related to the cancer therapy taken., 3 patients needed parenteral nutrition. Noteworthy, all of the 3 patients received chemoradiation and gave a history of having loss of appetite, not oral pain, as the reason for insufficient food intake.

Pain management is a crucial component of oral mucositis treatment. The majority of individuals needed both systemic and topical analgesics[16]. One of the problems we faced in pain control was patients' lack of detailed coherent feedback prevented us from conducting an analysis of the data related to the level of analgesic intake and type of analgesic if mild or moderate or strong, as previously encountered by other authors [30].

Limitations of the study

Each patient receives a particular course of treatment (radiotherapy, chemoradiotherapy), and each person has a unique way of caring for themselves (different anti-inflammatory mouthwashes), the present study's relatively small sample size is seen to be one of its main limitations.

CONCLUSIONS

We found that half of all patients who underwent Chemo-radiotherapy had OM, the incidence of mucositis was 37.7% and the important risk factors for OM development were tumor site and concomitant chemotherapy.

For all affected patients, RIOM remains a significant therapeutical challenge: as HNC prevalence rises in the general population, the importance of prevention and management of RIOM in this patient should not be undervalued, So The study's conclusions will help to advance cancer patient care through designed preventive plans implemented before the beginning of RT in patients with addressing risk factors that can predict OM, we recommend future research with higher sample numbers, in addition, we recommend other possible risk factors need to be assessed in further studies as the oral microbiome.

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CONFLICT OF INTEREST

There were no conflicts of interest to disclose.

AUTHORSHIP STATEMENT

We confirm that all listed authors meet the authorship criteria and that all authors agree with the manuscript’s content.

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