

Radiation-induced Oral Mucositis in Brazilian Patients: Prevalence and Associated Factors

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Abstract. *im: To determine the prevalence of radiation-induced oral mucositis (OM) and associated factors. Patients and Methods: A cross-sectional retrospective study was performed at a reference dental care center. The medical records of patients submitted to radiotherapy for the treatment of head and neck cancer were used to collect clinical and demographic variables. The data were submitted to descriptive analysis and multivariate Poisson regression with robust variance [$p < 0.05$; 95% confidence interval (CI)]. Results: Four hundred and thirteen patients were analyzed. The mean age was 55 ± 14 years. The prevalence of OM in the overall sample was 41.9% and was higher among males (78.2%). The following variables were significantly associated with the outcome: radiation dose [prevalence ratio (PR)= 1.04; 95% CI=1.02-1.06]; concomitant chemotherapy (PR=1.48, 95% CI=1.05-2.08); oral candidiasis (PR=1.97, 95% CI=1.44-2.68); and osteoradionecrosis (PR=1.51, 95% CI=1.10-2.06). Conclusion: Radiation-induced OM was associated with radiation dose, concomitant chemotherapy, oral candidiasis and osteoradionecrosis. The rate of OM underscores the*

importance of adequate oral care prior to treatment for head and neck cancer.

Oral mucositis (OM) is one of the most significant and common complications of radio/chemotherapy for the treatment of head and neck cancer (1-3). The pathogenesis of OM is complex and related to xerostomia, which is a consequence of the impairment of the salivary glands caused by radiation. OM may occur during or after treatment, the debilitating adverse effects of which include severe pain as well as difficulties in eating and performing oral hygiene, thereby compromising quality of life and potentially leading to suspension of cancer treatment, which increases the risk of death (4, 5).

Data on the prevalence of radiation-induced OM in patients submitted to treatment for head and neck cancer are scarce in the literature and reveal considerable variation (6, 7). Recent studies have focused more on the different methods of cancer treatment rather than the causes of OM and associated factors (8, 9).

The oral regions most affected by OM are the floor of the mouth, lateral edge of the tongue, buccal mucosa and soft palate (10). Erythema is the initial manifestation, followed by the development of desquamative white plaques, which ulcerate, causing considerable pain. Poor oral hygiene and an absence of clinical follow-up before and during radiotherapy may aggravate the problem (8).

An in-depth investigation of OM would provide information for better clinical management of this complication, contributing to its prevention and improving the quality of life of patients (9, 10). Thus, the aim of the present study was to investigate the prevalence of radiation-induced OM and report its associated factors.

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Key Words: Radiotherapy, chemotherapy, epidemiology, head and neck cancer, oral mucositis.

Patients and Methods

The present study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (11).

Study design and sample characteristics. A cross-sectional retrospective study was conducted involving data from patients who received dental care at the School of Dentistry of the Federal University of Minas Gerais (UFMG), Belo Horizonte, Brazil, which is a dental care reference center for patients with head and neck cancer. Data were collected from the medical records of all patients submitted to radiotherapy for the treatment of head and neck cancer between 2008 and 2017.

Data collection. The records were examined by a trained researcher who collected data on the following variables: Age, sex, type of malignancy, location of tumor, history of alcohol and tobacco use, radiation dose, occurrence of OM and tooth extractions before and after radiotherapy.

Statistical procedures. The data were analyzed using descriptive and inferential statistics with the aid of the Statistical Package for the Social Sciences (SPSS, version 23.0; IBM, Armonk, NY, USA). After the descriptive analysis, Poisson multiple regression analysis with robust variance was performed to determine associations between the dependent variable (OM) and the independent variables, considering a 5% level of significance ($p < 0.05$). Variables with a p -value of less than 0.20 in the bivariate analysis were incorporated into the multiple analysis and those with a p -value of less than 0.05 remained in the final model. Prevalence ratios (PR) and respective 95% confidence intervals (CI) were calculated.

Ethical aspects. This study was performed in compliance with the ethical precepts stipulated in Resolution 466/12 of the Brazilian National Health Council and Declaration of Helsinki. The investigation only included information from medical records that were correctly filled out and had the patient's authorization in the form of a signed statement of informed consent. This study received approval from the Human Research Ethics Committee of the Federal University of Minas Gerais (certificate number: 47197715.0.0000.5149).

Results

A total of 413 medical records of patients submitted to radiotherapy for the treatment of head and neck cancer between January 2008 and December 2017 were evaluated. Table I displays the clinical characteristics of the patients, malignant lesions and main complications of treatment. The prevalence of OM in the overall sample was 41.9% ($n=173$) and was higher among males (78.2%). The mean age was 55 ± 14 years. Squamous cell carcinoma was the most frequent type of tumor (76.3%; $n=315$) and the oral cavity was the most frequent location (42.2%; $n=174$). The frequencies of osteoradionecrosis and oral candidiasis were 9.7% and 17.9%, respectively. The mean number of teeth extracted was 10.

Table I. Clinical characteristics of patients and the main complications of the treatment of head and neck cancer from the School of Dentistry of the Federal University of Minas Gerais ($n=413$).

Variable	Value
Gender, n (%)	
Female	90 (21.8)
Male	323 (78.2)
Age, n (%)	
≤55 Years	207 (50.1)
>55 Years	206 (49.9)
Oral mucositis, n (%)	
Present	173 (41.9)
Absent	240 (58.1)
Osteoradionecrosis, n (%)	
Present	40 (9.7)
Absent	373 (78.2)
Type of cancer, n (%)	
Other	98 (23.7)
SCC	315 (76.3)
Site of tumor, n (%)	
Other	238 (57.8)
Oral cavity	174 (42.2)
History of alcohol use, n (%)	
No	
64 (15.5)	
Yes	349 (84.5)
Smoking, n (%)	
No	44 (10.7)
Yes	158 (38.3)
Stopped	211 (51.1)
Chemotherapy, n (%)	
No	200 (48.4)
Yes	213 (51.6)
Oral candidiasis, n (%)	
No	339 (82.1)
Yes	74 (17.9)
Visited the dentist before radiation, n (%)	
No	220 (53.3)
Yes	193 (46.7)
Removed teeth before radiation, n (%)	
No	2 (1.1)
Yes	186 (98.9)
Radiation dose, Gy	
Mean±SD	60.43±8.23
Number of sessions	
Mean±SD	30.53±5.36
Number of teeth removed	
Mean±SD	9.97±6.55

SCC: Squamous cell carcinoma.

The following risk factors were significantly associated with OM: osteoradionecrosis (PR=1.51, 95% CI=1.10-2.06), chemotherapy (PR=1.48, 95% CI=1.05 to 2.08), oral candidiasis (PR=1.97, 95% CI=1.44-2.68), and radiation dose (PR=1.04; 95% CI=1.02 to 1.06). The extraction of compromised teeth prior to radiotherapy was a factor protective against OM (PR=0.36; 95% CI=0.24-0.54) (Table II).

Table II. Bivariate and multivariate Poisson regression analysis regarding the association of oral mucositis and independent variables among patients undergoing radiotherapy from the School of Dentistry of the Federal University of Minas Gerais (n=413).

Independent variable	Oral mucositis		Unadjusted*		Adjusted**	
	Yes (n=173)	No (n=240)	PR (95% CI)	p-Value	PR (95% CI)	p-Value
Gender, n (%)						
Female	38 (42.2)	52 (57.8)	1.00			
Male	135 (41.8)	188 (58.2)	1.226 (0.723-2.080)	0.449		
Age, n (%)						
≤55 Years	89 (43.0)	118 (57.0)	1.252 (0.872-1.797)	0.224		
>55 Years	84 (40.8)	122 (59.6)	1.00			
Type of cancer, n (%)						
Other	37 (37.8)	61 (62.2)	1.00			
SCC	136 (43.2)	179 (56.8)	1.119 (0.693-1.808)	0.644		
Site of tumor, n (%)						
Other	94 (39.5)	144 (60.5)	1.00			
Oral cavity	78 (44.8)	96 (55.2)	1.052 (0.747-1.482)	0.771		
History of alcohol use, n (%)						
No	22 (33.4)	42 (65.6)	1.00			
Yes	151 (43.3)	198 (56.7)	1.456 (0.766-2.767)	0.252		
Smoking, n (%)						
No	13 (29.5)	31 (70.5)	1.00			
Yes	64 (40.5)	94 (59.5)	1.562 (0.628-3.889)	0.337		
Stopped	96 (45.5)	115 (54.5)	2.125 (0.881-5.123)	0.093		
Osteoradionecrosis, n (%)						
No	143 (38.3)	230 (61.7)	1.00		1.00	
Yes	30 (75.0)	10 (25.0)	1.946 (1.422-2.665)	<0.001	1.388 (1.025-1.881)	0.034
Chemotherapy, n (%)						
No	68 (34.0)	132 (66.0)	1.00		1.00	
Yes	105 (49.3)	108 (50.7)	1.611 (1.106-2.346)	0.013	1.459 (1.024-2.079)	0.037
Oral candidiasis, n (%)						
No	120 (35.4)	219 (64.6)	1.00		1.00	
Yes	53 (71.6)	21 (28.4)	2.281 (1.728-3.012)	<0.001	1.886 (1.411-2.522)	<0.001
Teeth removed before radiation, n (%)						
No	2 (100.0)	0 (0)	1.00		1.00	
Yes	76 (40.9)	110 (59.1)	0.418 (0.352-0.496)	<0.001	0.376 (0.293-0.483)	<0.001
Visited the dentist before radiation, n (%)						
No	94 (42.7)	126 (57.3)	1.00			
Yes	79 (40.9)	114 (59.1)	0.849 (0.210-3.431)	0.818		
Radiation dose						
Mean±SD	64.99±6.47	56.96±7.73	1.061 (1.037-1.085)	<0.001	1.039 (1.021-1.058)	<0.001
Number of sessions						
Mean±SD	32.72±4.93	28.86±5.075	1.034 (1.012-1.055)	0.002	1.028 (1.009-1.047)	0.004

PR: Prevalence ratio; CI: confidence interval. *Unadjusted Poisson regression analysis. **Variables incorporated in multivariate model ($p < 0.20$): osteoradionecrosis, radiation dose, teeth removed before radiation, candidiasis, number of sessions, chemotherapy, smoking, history of alcohol use.

Discussion

The main objective of the most recent studies in the field of head and neck cancer has been the search for new treatment modalities and the investigation of complications (12-14). Epidemiological studies on the prevalence of complications are less common (15).

The prevalence of radiation-induced OM in the present study was 41.9%. This finding differs from rates reported in the literature, in which a frequency of nearly 100% is often reported (16, 17). While the treatment of OM is not well

established (9), individualized follow-up of patients before, during and after radiotherapy may contribute to greater control of complications stemming from treatment (18). The lower frequency of radiation-induced OM in the present study reflects the importance of adequate dental care before, during and after radiotherapy.

OM was more frequent among males. Previous studies also found a higher occurrence of OM in males, with reports of approximately 60% (17) and 89% (18). The higher prevalence in men can be explained by the greater occurrence of harmful habits attributed to this sex, such as

poor hygiene, smoking and alcohol abuse, as well as a less frequent use of dental services (19).

A further aim of the present study was to report factors associated with radiation-induced OM. The oral cavity was the site most affected by malignant tumors. Mercadante *et al.* (7) report that head and neck tumors are often related to OM due to the proximity of the oral cavity to the radiation field (20). Moreover, an association was found between the prevalence of OM and higher doses of radiation, which is similar to data reported in previous studies (9, 15, 21). This can be explained by the fact that radiation destroys epithelial cells, causing desquamation and ulceration. High doses of radiation also cause greater changes in the salivary glands, leading to hyposalivation and, consequently, OM (22).

The prevalence of OM among patients having undergone chemotherapy as adjuvant treatment was approximately 50% higher compared to those who did not undergo chemotherapy. Studies report that chemotherapy combined with radiotherapy produces better results in the treatment of head and neck cancer. However, the occurrence of side-effects is greater when the two therapies are combined. In addition to the direct aggression caused by radiotherapy, chemotherapy systematically compromises the body, leaving the patient more prone to complications (7, 15).

Good oral health status is very important prior to radiotherapy in the head and neck region (23, 24). For such, it is necessary to remove any teeth that should not remain in the oral cavity (25). A previous study reported an average of eight teeth removed per patient prior to radiotherapy (26). In the present study, a similar result was observed, with an average of 10 teeth removed. The extraction of teeth prior to the initiation of radiotherapy was a protective factor in the present study, as the prevalence of OM was lower in such cases. However, it is important to remember that individuals undergoing dental care before head and neck radiation need to have a close follow-up to avoid possible complications (10).

The prevalence of osteoradionecrosis was low (9.7%), which is similar to the rate reported in a German study (12%) (26), but much higher than that reported in a study conducted in the United States (1.2%) (27). This divergence may be explained by the different modalities of radiotherapy treatment, the presence/absence of previous oral care, the study design, sample characteristics and methods employed for diagnosing OM. In the present investigation, the prevalence of OM was 1.5-fold higher among patients with osteoradionecrosis than those without this condition. Previous studies involving patients with osteoradionecrosis have also reported a high prevalence rate of OM (25, 26). A possible explanation for this is the high doses of radiation that patients received, leading to the concomitant development of the two complications of treatment. Moreover, an association has been reported between OM and

local or systemic infection (28), which also predisposes patients to osteoradionecrosis (10).

The prevalence of oral candidiasis associated with OM ranges from 27-50% (29-31), which is higher than the rate found in the present study. Nonetheless, patients with oral candidiasis were nearly twice as likely to have OM compared to those without this condition. Oral candidiasis lesions often overlap with those of radiation-induced OM and the differential diagnosis between the two is quite difficult. Therefore, it is very common to associate these complications (31).

OM is the most common complication and one of the most debilitating side-effects of head and neck cancer treatment (3). Therefore, the investigation of predisposing factors, as well as adequate dental care before and during radiotherapy, can contribute to a reduction in the occurrence of this complication and an improvement in the quality of life of patients.

In conclusion, radiation-induced OM was associated with the radiation dose, concomitant chemotherapy, oral candidiasis and osteoradionecrosis. The extraction of compromised teeth prior to treatment was a protective factor against this complication. The lower rate of OM in the present investigation when compared to that reported in previous studies underscores the importance of adequate oral care prior to treatment for head and neck cancer.

Conflicts of Interests

IFP confirms on behalf of all the Authors that there are no conflicts of interest in regard to this work.

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