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Relationship Between the Degree of Radio-induced Mucositis in Patients with Head and Neck Cancer and Clinical-Pathological Characteristics and Demographics

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Dissertação apresentada à Universidade Estadual Paulista (UNESP), Faculdade de Odontologia de Araçatuba, para obtenção do título de Mestra em Odontologia.
Área de Concentração: Estomatologia e Psiconeuroimunologia

Orientadora: Profa. Dra. Aline Satie Takamiya
Coorientador: Prof. Dr. Glauco Issamu Miyahara

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“A educação tem raízes amargas, mas os seus frutos são doces.”

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RESUMO

CARVALHO, M. M. **Relação entre o grau de mucosite radio-induzida em pacientes com câncer da cabeça e do pescoço e as características clínico-patológicas e demográficas.** 2025. Dissertação (Mestrado) - Faculdade de Odontologia, Universidade Estadual Paulista (UNESP), Araçatuba, 2025.

A mucosite oral é um processo inflamatório causado pelos efeitos citotóxicos dos tratamentos antineoplásicos, sendo frequentemente observado em pacientes submetidos a tratamentos na região de cabeça e pescoço. Prejudicando significativamente os indivíduos e afetando a fala, deglutição e a mastigação. A etiopatogênese da mucosite ainda permanece bastante controversa. Os fatores relacionados ao tratamento e ao paciente têm sido apontados, como fatores causadores e modificadores das alterações de mucosites orais radio-induzidas. Assim, o propósito deste estudo foi avaliar a relação entre o grau de mucosite radio-induzida, os aspectos clínicos-patológicos e demográficos em pacientes durante o tratamento de câncer de cabeça e pescoço. Para a realização deste estudo, foram recrutados pacientes diagnosticados com câncer da cabeça e pescoço, submetidos ao tratamento de radioterapia obrigatório. Os pacientes foram avaliados clinicamente diariamente e responderam verbalmente a um questionário. Para a realização da análise estatísticas foram separados dois tempos, onde o tempo 1 foram analisados os dados em relação ao início da mucosite oral e o tempo 2 em relação ao pior grau apresentado pelos pacientes. Foram incluídos 50 pacientes, com cerca de 78% dos pacientes do sexo masculino. A quimioterapia (*P*= .034) foi associada aos pacientes que apresentaram lesões de mucosite oral até a décima sessão de radioterapia. Diabetes (*P*= .017), dermatite por radiação (*P*=.017) e dermatite por radiação moderada (*P*=.013) foram estatisticamente associadas ao grau grave de mucosite no momento de seu início. Enquanto hipertensão (*P*= .030), diabetes (*P*= .016), alcoolismo leve e moderado (*P*= .029), dermatite por radiação (*P*= .001), odinofagia (*P*= .022), ardência bucal (*P*= .003), dificuldade de higiene (*P*= .020) e uso de opioides (*P*= .045) foram associados aos graus mais severos no momento da exacerbação da lesão. Fumantes severos foram associados à maior ocorrência de lesões de mucosite na região labial nos dois tempos. Este estudo apresentou prevalência significativamente em relação a mucosite oral induzida por radiação e o seu grau com as características clínico-patológicas e demográficas. Estabelecer hábitos de vida saudáveis e manter uma higiene oral saudável são essenciais na prevenção da mucosite oral.

Palavras-chave: câncer de cabeça e pescoço; mucosite; dor; características clínico-patológicas.

ABSTRACT

CARVALHO M. M. **Relationship between the degree of radio-induced mucositis in patients with head and neck cancer and clinical-pathological characteristics and demographics**. 2025. Dissertação (Mestrado) - Faculdade de Odontologia, Universidade Estadual Paulista (UNESP), Araçatuba, 2025.

Oral mucositis is an inflammatory process caused by the cytotoxic effects of antineoplastic treatments and is frequently observed in patients undergoing treatment of the head and neck region. It significantly impairs individuals and affects their speech, swallowing, and chewing. However, the etiopathogenesis of mucositis remains controversial. Factors related to treatment and the patient have been identified as factors that cause and modify changes in radio-induced oral mucositis. Thus, the purpose of this study was to evaluate the relationship between the degree of radiation-induced mucositis and the clinical-pathological and demographic aspects of patients during treatment for head and neck cancer. To conduct this study, patients diagnosed with head and neck cancer who underwent mandatory radiotherapy treatment were recruited. The patients were clinically evaluated daily and answered a questionnaire verbally. Two time points were separated for statistical analysis: Time 1 analyzed data regarding the onset of oral mucositis and time 2 analyzed data regarding the worst degree presented by the patients. Fifty patients were included, with approximately 78% of the patients being male. Chemotherapy (P= .034) was associated with patients who presented with oral mucositis lesions up to the tenth radiotherapy session. Diabetes (P= .017), radiation dermatitis (P= .017) and moderate radiation dermatitis (P= .013) were significantly associated with severe mucositis at the time of onset. Hypertension (P= .030), diabetes (P= .016), mild and moderate alcoholism (P= .029), radiation dermatitis (P= .001), odynophagia (P= .022), burning mouth (P= .003), difficulty with hygiene (P= .020) and use of opioids (P= .045) were associated with the most severe degree of lesion exacerbation. Severe smoking was associated with a greater occurrence of mucositis lesions in the lip region at two specific times. This study showed a significant prevalence of radiation-induced oral mucositis and its degree in relation to clinical-pathological and demographic characteristics. Establishing healthy lifestyle habits and maintaining healthy oral hygiene are essential for preventing oral mucositis.

Keywords: head and neck cancer; mucositis; pain; clinical characteristics; pathological characteristics.

LISTA DE TABELAS

LISTA DE ABREVIATURAS E SIGLAS

BRA	Brazil
CAPES	Coordination for the Improvement of Higher Education Personnel
COB	Oral Oncology Center
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
NY	New York
OM	Oral Mucositis
OSCC	Oral Squamous Cell Carcinoma
UICC	Union for International Cancer Control
UNESP	São Paulo State University
USA	United States of America
VAS	Visual Analog Scale
RTOG	Radiation Therapy Oncology Group
SD	Standard Deviation
SP	São Paulo
SPSS	Statistical Package for the Social Sciences
WHO	World Health Organization

SUMÁRIO

RELATIONSHIP BETWEEN THE DEGREE OF RADIO-INDUCED MUCOSITIS IN PATIENTS WITH HEAD AND NECK CANCER AND CLINICAL-PATHOLOGICAL CHARACTERISTICS AND DEMOGRAPHICS

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1 INTRODUCTION*

Oral mucositis (OM) affects 20 to 30% of patients receiving conventional chemotherapy doses, around 80% of those receiving high doses and more than 95% of patients undergoing radiotherapy in the head and neck region [1–3]. There are significant differences between OM induced by chemotherapy and radiotherapy in the head and neck [4]. Patients undergoing chemotherapy usually begin to show signs and symptoms of OM right after the end of the treatment cycles and the lesions heal within approximately two weeks [5]. Radio-induced mucositis, on the other hand, requires more time to develop and heal. The lesions usually appear up to two weeks after starting radiotherapy. Initially, they present as erythema on the oral mucosa and a burning sensation. Later, the condition evolves with the formation of extremely painful deep ulcers that coalesce and increase the risk of opportunistic infections [4,5].

The course of OM lasts an average of 7 to 98 days [4], and is characterized by five different stages corresponding to (1) the initial phase, (2) the primary damage phase, (3) the signal amplification phase, (4) the ulcerative phase (5) and healing [3–8]. The first phase begins approximately 1 to 2 weeks after the start of radiotherapy. In this phase, ionizing radiation induces inflammation and the formation of free radicals that cause DNA damage, compromising the proliferation of tumor cells and also healthy tissues in the basal layers of the epithelium [2,6–8]. In the primary damage phase, transcription factors such as NF-kβ and STAT3 are activated, stimulating the expression of adhesion molecules, metalloproteinases and pro-inflammatory cytokines [6–8]. These molecular events are capable of inducing cell death and destruction of the oral epithelium [6,8,9]. Signal amplification refers to the ability of the molecules produced in the previous phases to intensify tissue damage [4,6]. The development of ulceration is the most significant stage of OM, as it is highly symptomatic for patients. In addition, ulcerated sites become relatively neutropenic, which predisposes them to opportunistic bacterial and fungal infections. Bacterial toxins further stimulate the inflammatory state through the release of additional cytokines, exacerbating tissue damage [3,10]. The healing phase of lesions usually occurs spontaneously, begins after the end of

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radiotherapy sessions and requires a series of biological processes related to repair that take place in the submucosal layer [6,8,11].

The cellular alterations of radio-induced OM lead to clinical symptoms of incapacitating pain, dysphagia, dehydration, anorexia, weight loss and electrolyte imbalance, which contribute to a greater tendency to secondary systemic infections [12,13]. In addition, these alterations can lead to the need for changes in the radiation dose fractionation scheme or even the interruption of antineoplastic treatment, which significantly compromises the prognosis of the disease, increases the rate of cancer recurrence and decreases survival time, negatively impacting patients' quality of life, physical, emotional and social comfort [5,14]. As the severity of OM increases, more adverse consequences reducing the quality of life, and discontinuing cancer treatment occur in these patients [15]. Despite receiving equal doses of radiation, patients reacted in different ways, highlighting the importance of studies of associated factors.

In view of the above, the general objective of this study was to evaluate the relationship between the initial phase and the most critical period of radio-induced OM in patients with head and neck cancer with clinical-pathological and demographic characteristics.

2 PATIENTS AND METHODS

2.1 Study Design and Ethical Aspects

This study was approved by the Institutional Research Ethics Committee under protocol 72346123.3.0000.5420, and patients who agreed to participate in the research signed a Free and Informed Consent Term. Participants were informed about the purpose of the study and were assured of confidentiality and anonymity. All the participated voluntarily without any subsequent reward.

2.2 Characterization of the Sample and the Study

Ninety-eight patients were selected for an initial consultation, which included an analysis of their medical records, information about the study and written informed consent. Fifty adult patients (aged >18 years), all of whom had started radiotherapy treatment with curative intent, were included in the sample. The convenience sample consisted of individuals treated at Oral Oncology Center (COB), an auxiliary unit of São Paulo State University (UNESP), School of Dentistry, Araçatuba as part of an observational, prospective and longitudinal clinical study. The assessments were carried out by assessors previously calibrated for the clinical evaluations the criteria analyzed in this study. The patients included in this study underwent clinical protocol, which included preparation of the oral environment with dental cleaning, check-up and prior extraction of compromised teeth. In addition, patients were instructed on the possible transient and permanent side effects in the mouth of antineoplastic treatment with radiotherapy.

The inclusion criteria were patients diagnosed with head and neck cancer, located in the oral cavity, oropharynx or salivary glands, patients aged >18 years, undergoing radiation treatment and followed up daily in our oncology patient support center. The exclusion criteria consisted of individuals with cognitive impairment and inability to participate in the study, who had contraindications to radiotherapy, with a history of radiotherapy, who did not follow the daily follow-up at our center, who did not finish the radiotherapy treatment or who refused to sign the informed consent. All patients underwent 3D conformal radiotherapy, which consists of shaping the radiation beam to the region to be treated based on three-dimensional images from computed tomography (CT), magnetic resonance imaging (MRI) and a daily protocol of 2 Gy of radiation, not exceeding a total dose of 70 Gy.

2.3 Daily Evaluation

Laser prophylaxis was carried out on all participants daily performed with the Therapy EC (DMC®, São Carlos, SP, BRA). The following parameters were used daily from the first session until the end of the radiotherapy sessions in the regions without OM; total diode laser energy 1 J (per point) for 10 s with 1 cm a distance between points, wavelength of 660 nm, application in regions free of tumor lesions. After the first clinical sign of OM, the following photobiomodulation protocol was included in the regions where OM lesions; total diode laser energy 2 J (per point) for 20 s along the entire length of the OM lesions, wavelength 660 nm, prioritizing the repair of superficial tissue and pain control. All participants were followed up on the photobiomodulation therapy until complete resolution of the signs and symptoms of OM.

OM was classified by the World Health Organization (WHO) [16], assigning scores: (0) no mucositis; (1) irritation or erythema; (2) erythema and ulcerative lesions that still allow a solid diet; (3) ulcerative lesions in which the patient is restricted to a liquid diet; (4) when oral feeding is not possible. According to the grading scale, grades 1–2 were considered as the mild group and grades 3–4 were the severe group. Oral pain was analyzed subjectively using a Visual Analogue Scale (VAS), where “0” is the absence of pain and “10” is the maximum pain experienced by the patient. Patients were instructed to assign a score to the degree of oral pain. Two forms of evaluation were used, without pain (0) and with pain (1) and classified as (0) no pain; (1) mild pain from 1 to 3; (2) moderate pain from 4 to 7 and (3) severe pain from 8 to 10.

Data on feeding route (oral or nasogastric tube), type of feeding (solid, paste or liquid) or presence of oral alterations such as odynophagia, dysphagia, dysgeusia, xerostomia, burning mouth and/or difficulty with oral hygiene were collected daily from the patients. The presence of oral candidiasis or radiation dermatitis was assessed by a previously trained dental surgeon. Radiation dermatitis was classified according to the Radiation Therapy Oncology Group (RTOG) [17] scale based on the degree of toxicity, which indicates the severity of the condition. According to the grading scale, grades 1–2 were considered as the mild group and grades 3–4 were the severe group. Medications were classified as; analgesics (no opioids) or

opioids, systemic or topical antifungals. Other medications such as antibiotics, anti-inflammatories or antacids were only classified as use or non-use.

2.4 Demographic and Clinical-pathological Characteristics

Demographic and biobehavioral characteristics such as sex (female or male), age (adult patients 45-65y or elderly >65y), marital status (single, married, divorced or widowed), ethnicity (white, brown or black), smoking and alcohol consumption, were collected directly from the patients and from their medical records before the cancer diagnosis was notified. Tobacco and alcohol consumption were assessed using a scale of light to severe score according to the number of cigarettes and alcoholic drinks consumed per day. Smoking: light: less than 20 paper cigarettes or up to 4 straw cigarettes; moderate: 20-39 paper cigarettes or 5-7 straw cigarettes; severe: 40 or more paper cigarettes or 8 or more straw cigarettes. Alcoholism: mild: 1 dose of distilled alcohol or 1 bottle of beer; moderate: 2-3 doses of distilled alcohol or 2-3 bottles of beer; severe: 4 or more doses of distilled alcohol or 4 or more bottles of beer.

The clinical-pathological characteristics included the presence of comorbidities, treatment, clinical staging and tumor stage. The staging of head and neck tumors followed the criteria of TNM, (T) refers to the size of the tumor and the N was classified as (N-) without lymph node metastases and (N+) with the presence of lymph node metastases. The evidence of distant metastasis (M) was not classified as none of our patients had distant metastasis. The clinical stages were classified into I, II, III and IV.

2.5 Data Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software (version 24.0, NY, USA). All data collected were tested for normality before analysis. Descriptive data analysis was performed using mean and standard deviation (SD). The enumeration data were tested by chi-square test or Fisher's exact test to determine any statistically significant relationship between different parameters among different variables. Two time periods were separated for the statistical analysis: time 1 corresponded to the radiotherapy session in which OM began and time 2 was the radiotherapy session in which the patients started to show the worst degree of mucositis, the exacerbation of OM. These periods were selected to discover the demographic, biobehavioral and clinicopathological

characteristics associated with the onset of OM and its severity. The value of $P \leq 0.05$ was considered statistically significant.

3 RESULTS

In total, fifty adults took part in the study. Male patients constituted 78%, the mean age was 64.74 years with a range of 45 to 84 years old. In terms of ethnicity, 70% of the patients were white, 22% were brown and 8% were black. Regarding the marital status of the patients, 58% were married, 20% were divorced, 14% were single and 8% were widowed. Regarding the patients' health, 88% had some comorbidity prior to the cancer diagnosis, 46% reported having hypertension, 26% gastritis and 22% diabetes mellitus. The majority of patients, 94%, were diagnosed with squamous cell carcinoma (SCC), while 6% were diagnosed with other types of cancer. Regarding the location of the tumor, 58% of the sample had cancer in the oral cavity, 36% in the oropharynx and 6% in the salivary gland. In terms of staging, 8% of the patients were classified as T1, 24% as T2, 48% as T3 and 20% as T4. About the N, 40% of patients had some alteration in the lymph nodes. Clinical staging consisted of 8% of patients in stage I, 16% in stage II, 48% in stage III and 20% in stage IV. Concerning treatment, 76% of patients underwent radiotherapy concomitant with chemotherapy associated or not with surgery and 24% without concomitant chemotherapy, underwent radiotherapy alone or associated with surgery (Table 1).

Table 1 Demographic and clinical-pathological variables of patients

Variable	Patients
	No. (%)
Age	
Mean age (years, SD)	64,74 (SD 9,76)
Adults 45-65y	24 (48.0)
Elderly >65y	26 (52.0)
Sex	
Male	39 (78.0)
Female	11 (22.0)
Ethnicity	
White	35 (70.0)
Brown	11 (22.0)
Black	4 (8.0)
Marital status	
Single	7 (14.0)
Married	29 (58.0)
Divorced	10 (20.0)
Widowed	4 (8.0)
Comorbidity	

Yes	44 (88.0)
No	6 (12.0)
Comorbidity type	
Hypertension	23 (46.0)
Diabetes	11 (22.0)
Gastritis	13 (26.0)
Types of cancer	
OSSC	47 (94.0)
Others	3 (6.0)
Cancer localization	
Oral cavity	29 (58.0)
Oropharynx	18 (36.0)
Salivary gland	3 (6.0)
T classification	
T1	4 (8.0)
T2	12 (24.0)
T3	24 (48.0)
T4	10 (20.0)
Regional metastasis	
N0	30 (60.0)
N+	20 (40.0)
Clinical stage	
I	4 (8.0)
II	8 (16.0)
III	24 (48.0)
IV	14 (28.0)
Treatment	
Concomitant chemotherapy	38 (76.0)
Without concomitant chemotherapy	12 (24.0)

Abbreviation: SSC: squamous cell carcinoma.

About habits, 46% of the patients were smokers, 36% were ex-smokers and 18% had never smoked, and regarding alcohol, 42% of the patients were alcoholics, 32% were ex-alcoholics and 26% had never been frequent alcoholics. Regarding intensity, 22% were light smokers, 38% moderate and 20% severe, while about alcohol, 20% were light drinkers, 28% moderate and 18% severe (Table 2).

Table 2 Biobehavioral variables of patients

Variable	Patients
	No. (%)
Smoking	
No	9 (18.0)
Current smoker	23 (46.0)
Ex-smoker	18 (36.0)
Tobacco intensity*	
Non-smoker	9 (18.0)
Light	11 (22.0)
Moderate	19 (38.0)
Severe	10 (20.0)
Alcohol consumption	
Non	13 (26.0)
Current drinker	21 (42.0)
Ex-drinker	16 (32.0)
Alcohol intensity*	
Non-drinker	13 (26.0)
Light	10 (20.0)
Moderate	14 (28.0)
Severe	9 (18.0)

*Variables with missing data.

When we analyzed the clinical-pathological associations at time 1, we identified a significant association between patients who had started to show signs of OM before the tenth radiotherapy session and those who had undergone concomitant chemotherapy (*P*=.034). There was a significant association between patients who presented mucositis lesions after the tenth radiotherapy session and odynophagia (*P*=.043). The severity of the OM was significant association with diabetes (*P*=.017), radiodermatitis (*P*=.017) and mild degrees of radiodermatitis (*P*=.013). Heavy smokers had more OM lesions in the lip area (*P*=.001) than other smokers or non-smokers. Dysphagia was more significantly associated with males (*P*= 0.019), smokers and ex-smokers (*P*= 0.004), light smokers and heavy smokers (*P*= 0.002) and patients undergoing chemotherapy (*P*= 0.048). Dysgeusia was significantly associated with light smokers (*P*= 0.008). There was a significant association between odynophagia and smokers and ex-smokers (*P*=.021) and moderate smokers (*P*=.008). Patients undergoing chemotherapy were more significantly associated with oral candidiasis lesions (*P*= 0.029). None of the patients undergoing radiotherapy alone or radiotherapy associated with surgery had oral candidiasis lesions at the time of the onset of OM lesions. During the onset of OM,

xerostomia was significantly associated with females (*P*=.047), light smokers (*P*=.043) and heavy smokers (*P*=.043). N+ patients reported more pain (*P*=.010), odynophagia (*P*=.036) and burning in the mouth (*P*=.035) in the session in which OM lesions appeared than N- patients (Table 3).

Table 3 Associations clinical-pathological, biobehavioral characteristics in the Time 1

Variables	Qualitative assessment (*P-Value*)
	OM before the 10th session
Chemotherapy	.034
	OM after the 10th session
Odynophagia	.043
	Severity of the OM
Diabetes	.017
Radiation dermatitis	.017
Mild degrees of radiation dermatitis	.013
	Lip mucositis
Severe smokers*	.001
	Dysphagia
Male	.019
Smokers/ Ex-smokers	.004
Light/ Severe smokers*	.002
Chemotherapy	.048
	Dysgeusia
Light smokers*	.008
	Odynophagia
Smokers/ Ex-smokers	.021
Moderate smokers*	.008
	Oral candidiasis
Chemotherapy	.029
	Xerostomia
Female	.047
Light/ Severe smokers*	.043
	N+
Pain	.010
Odynophagia	.036
Mouth burning	.035

*Variables with missing data.

At time 2, exacerbation of OM up to the twelfth radiotherapy session was significant association with trismus (*P*=.024). The variables significantly associated with exacerbation of OM after the twelfth session were the presence of radiodermatitis

(*P*=.024), odynophagia (*P*=.024), dysgeusia (*P*=.024), use of analgesics (*P*=.024) and topical and systemic antifungals (*P*=.024). The exacerbation of OM was associated significantly with hypertension (*P*=.030), diabetes (*P*=.016), light alcoholics and moderate alcoholics (*P*=.029), radiodermatitis (*P*=.001), odynophagia (*P*=.022), burning mouth (*P*=.003), oral hygiene difficulties (*P*=.020) and the use of opioids (*P*=.045). Patients who were severe smokers also had more OM lesions in the lip area (P=.017) during the time 2. Adult patients had more radiodermatitis lesions than elderly patients (*P*=.043) during the exacerbation of the OM lesion. Dysphagia was also associated significantly with male patients (*P*=.027) at time 2 and showed significant results in relation to smokers and ex-smokers (*P*=.043). Patients who did not use chemotherapy as a form of cancer treatment ate more solid foods (*P*=.030) during the exacerbation of OM. Dysgeusia was significant association with light smokers (*P*=.001). Alcoholic patients had more radiodermatitis lesions (*P*=.013) and mild degrees of radiodermatitis (*P*=.007) than non-alcoholics. There were significant results between hypertension and mild degrees of radiodermatitis (*P*= 0.047) and dysgeusia (*P*= 0.011). Patients who were N+ had a higher presence of pain (*P*=.036), radiodermatitis lesions (*P*=.003), odynophagia (*P*=.001), hygiene difficulties (*P*=.046) and used more analgesics (*P*=.011) than N- patients (Table 4).

Table 4 Associations clinical-pathological, biobehavioral characteristics in Time 2

Variables	Qualitative assessment (*P-Value*)
	Exacerbation of OM before the 15th session
Trismus	.064
	Exacerbation of OM after the 15th session
Radiation dermatitis	.000
Odynophagia	.020
Dysgeusia	.023
Analgesics	.044
Topical and systemic antifungal	.005
	Severity of the OM
Hypertension	.030
Diabetes	.016
Light/Moderate alcoholics*	.029
Radiation dermatitis	.001
Odynophagia	.022
Mouth burning	.003
Hygiene difficulties	.020
Opioids	.045
	Lip mucositis
Severe smokers*	.017
	Adult patients
Radiation dermatitis	.043
	Dysphagia
Male	.027
Smokers/ Ex-smokers	.043
	Solid food
No chemotherapy	.030
	Dysgeusia
Light smokers*	.001
	Alcoholic
Radiation dermatitis	.013
Mild degree of radiation dermatitis	.007
	Hypertension
Mild degree of radiation dermatitis	.047
Dysgeusia	.011
	N+
Pain	.036
Radiation dermatitis	.003
Odynophagia	.001
Hygiene difficulties	.046
Analgesics	.011

*Variables with missing data.

4 DISCUSSIONS

Several studies have shown that the concomitant use of the two treatment modalities, chemotherapy and radiotherapy, generally contributes to the early development and greater severity of OM lesions [15,18,19]. As shown in our study, patients who underwent chemotherapy had a higher percentage of OM lesions that started by the tenth session when compared to the group that did not use chemotherapy during treatment. The addition of chemotherapy to a standard radiation regimen has been reported to favorably affect tumor response, however, it has also been shown to cause toxicity about three times greater in relation to the development and intensity of OM [20]. The patients who did not undergo chemotherapy were able to eat more solid food at the time when they had the worst degree of OM.

OM is commonly associated with pain in the oral and/or oropharyngeal mucosa, increased consumption of opioids, discomfort, and functional impairment of eating and swallowing and therefore has a major impact on quality of life [21–23]. Our results showed no association between the presence of pain and OM, however, there was an association between the severity of OM and the use of opioids, odynophagia and burning in the mouth at the time of exacerbation of the lesions. The factors that could explain these results are the fact that the opioid drugs are masking the patients' pain, and that our sample is made up mainly of men, who find it difficult to report their feelings due to a stigma of weakness. The severity of OM lesions has also been related to the accumulated radiation dose, the dose fractionation regimen, the type of radiation and the volume of irradiated tissue. Higher daily doses of radiation (daily fractions of up to 3.5 Gy) in accelerated fractionation regimens have been shown to lead to the development of more severe OM lesions, which is the main reason for treatment interruptions and prolonged total treatment time [24,25]. In our study, all patients received daily fractions of 2 Gy, not exceeding a total of 70 Gy. There were no significant results between the degree of OM and the total amount of Gy. The severity of mucositis was associated significantly with radiation dermatitis at both times. Radiotherapy can cause sunburn-like damage to the skin, which can be further aggravated by chemotherapy. The radiation dermatitis is one of the most common side effects of radiotherapy and can cause pain and discomfort [26]. The study by Manik et al. [27] suggested that advanced age in cancer patients increases the risk of radiodermatitis, due to a decrease in the re-epithelialization process and atrophy of the dermis, resulting in a prolongation of healing

time. In our study of a sample of head and neck cancer patients, there was a prevalence of radiodermatitis in adult patients compared to elderly patients. The study by Morais-Faria et al. [28] showed higher incidences and severity of OM and trismus in sessions 21 and 35 in young head and neck cancer patients. In our study, trismus was associated with patients who had an exacerbation of OM lesions before the twelfth session, and there was no association between trismus and age. The exacerbation of mucositis lesions after the twelfth radiotherapy session was associated significantly with odynophagia, higher use of analgesics and topical and systemic antifungals. This may represent higher rates of pain and opportunistic infections after the 30 Gy dose.

Factors associated with the patient such as poor oral hygiene, alcohol consumption, smoking, xerostomia, opportunistic infections, sex, microbiome and some comorbidities can also influence the severity and incidence of radio-induced OM [29–31]. *Candida spp* are opportunistic and dimorphic fungus that causes local or systemic infections mainly in clinically compromised patients, this includes individuals undergoing chemotherapy and radiotherapy due to immunosuppressive status, induced hyposalivation and OM that lead to difficulties in establishing adequate oral hygiene and alterations in the oral microbiota [32]. This may explain the data from our study which showed that patients who underwent radiotherapy combined with chemotherapy had a significant relationship with oral candidiasis and dysphagia at the start of OM. In our study, it was shown that patients who were severe smokers had more localized lesions on the lip at the beginning of the mucositis and during the period of exacerbation of the lesions. Patients who were light and moderate smokers had a more severe degree of OM lesions at the time of lesion exacerbation, which may have been caused by the chemical substances in the cigarette and the heat source from it. The relationship between smoking before and during radiotherapy treatment and the risk of OM is still unclear. Reports of smoking having no effect on the rate of acute radiation-associated toxicity, including mucositis are contradicted by reports that tobacco use is protective [33,34] or that smoking increases the risk of OM [4,35,36]. In 2021, Pedersen et al. [37] stated that smoking influences a decrease in salivary flow, which would explain why the smokers and ex-smokers patients complained more about dysphagia at both times and odynophagia at time 1, since saliva plays a crucial role in swallowing. The study by Shoorgashti et al. [38] in 2024 revealed that xerostomia is more prevalent in smokers, which also corroborates our data, in which smokers and ex-smokers complained more of xerostomia in the session in which OM began. Nicotine is known to reduce the number of cells responsible for taste, which can

directly affect the way we perceive flavors. Research on the negative influence of smoking associated with dysgeusia in patients with head and neck cancer undergoing radiotherapy is scarce. The study carried out by Park et al. [39] did not show significant results in relation to smoking patients who received radiotherapy at higher risk and faster onset of dysgeusia. Our results showed a significant association between dysgeusia and patients who were light smokers at both times, but there was no statistical significance between severe or moderate smokers, so further studies should be carried out to prove this association. The literature shows that alcohol can alter the permeability of the oral mucosa and interfere with the tissue's repair mechanisms [40]. In our study, patients who were mild or moderate alcoholics had more severe degrees of OM when the lesion exacerbated. In addition, they were associated with radiation dermatitis and moderate degrees of radiation dermatitis. Alcohol can be an indicator of impaired wound healing, thus explaining its toxicity in relation to the side effects of head and neck cancer treatment.

Diabetics had severe degrees of OM at the beginning of the lesions and at the time of the exacerbation. The diabetes mellitus can cause changes in the microvasculature of the oral mucosa, making it more susceptible to radiation damage and hindering the healing process [41]. Frequent conditions in the oral health of diabetic individuals, such as periodontal disease and xerostomia, can increase the propensity to OM and the symptoms that accompany it [42]. Furthermore, diabetes can affect the immune system, favoring the appearance of lesions in the oral cavity of patients with OM. These wounds can act as entry routes for pathogens, potentially increasing the severity of the lesions [43]. The results in the literature regarding the association between hypertension and radio-induced OM are very scarce. Tao et al. [35] showed no significant results in relation to the acute reaction of radiotherapy-induced OM and hypertension in patients with head and neck cancer. In the sample of patients we studied, there were significant results in relation to hypertension and the most severe degrees of OM in time 2.

Sex has been increasingly studied as impacting the risk of developing radio-induced OM. Most of the time, women appear to be at greater risk than men [4,44,45]. According to Sonis [29], there is little data on sex as a risk factor for OM in the head and neck cancer population and, to date, the conclusions on gender are inconsistent with studies suggesting that gender does not significantly increase the risk or that men are more likely to be affected [46]. All the patients eligible to take part in this study had OM lesions and there were no significant results between the degree of lesions and the sex. Although male patients

complained more of dysphagia, the risk factors for the development of dysphagia during cancer treatment remain somewhat uncertain. The study by Shune et al. [47] showed a higher prevalence of dysphagia in female head and neck cancer patients. In our sample, male patients reported greater complaints of dysphagia at the onset and exacerbation of OM. With regard to the microbiome, it is known that bacterial colonization of ulcerated lesions in radio-induced OM is capable of prolonging the resolution of the lesion by exacerbating the inflammatory response [18,48–50]. Food residues create an acidic environment in the oral cavity [51]. Several studies have suggested that a series of dysbiotic alterations may affect the development, progression and severity of radio-induced OM, and that individual variations in the composition of the microbiome may be associated with variations in the course of oral mucositis [4,52–54]. Our results show that patients who had severe degrees of OM at the time of the exacerbation of the lesion had greater difficulty with hygiene. Patients with a higher N stage classification tend to have more severe oral mucosal reactions. Therefore, the irradiation dose, especially for patients with a higher N stage classification, should be the risk factor of primary concern for radiation-induced oral mucosal reactions [35]. The N+ patients in this study reported more pain and odynophagia in the two time periods analyzed. In addition, the N+ patients had more burning in the mouth at the beginning of the OM lesions, and at time 2, they had more difficulty with hygiene and the use of analgesics than the N- patients.

Guidance on quitting smoking and alcoholism, controlling diabetes mellitus and oral hygiene care before and during treatment can be extremely beneficial in preventing debilitating toxicities in the mucous membranes and skin. Patients with advanced diseases who require concomitant chemotherapy need to be monitored closely so that oral mucosal toxicity can be detected early, facilitating the adoption of appropriate preventive and therapeutic strategies. The main limitations of our study are the small number of patients, the disproportionate ratio between males and females and the fact that data on smoking and alcohol consumption were collected before the cancer diagnosed, not daily during radiotherapy treatment and univariable analysis. In addition, it was not possible to collect data on the chemotherapeutic agent used.

5 CONCLUSIONS

The interaction of clinical-pathological, demographic and bio-behavioral characteristics shows different behaviors depending on the stage of OM. Thus, in-depth knowledge about the relationship between OM and clinical-pathological, demographic and bio-behavioral characteristics is essential to reduce severe toxicity and increase the quality of life of individuals with head and neck cancer.

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