Evaluation of Oral Mucositis and its Risk Factors in Patients with Head and Neck Cancer Undergoing Radiotherapy Treatment

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Avaliação da Mucosite Oral e seus Fatores de Risco em Pacientes com Câncer de Cabeça e Pescoço em Tratamento Radioterápico

Evaluación de la Mucositis oral y sus Factores de Riesgo en Pacientes con Cáncer de Cabeza y Cuello Sometidos a Tratamiento de Radioterapia

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ABSTRACT

Introduction: Oral mucositis is a painful and debilitating condition, often observed as an acute adverse effect of antineoplastic treatment. Patient-related risk factors, as age and gender, as well as treatment variables, as dose and irradiated area, can influence the severity of mucositis, negatively impacting the quality of life of cancer patients and the progress of the treatment. **Objective:** To analyze the prevalence of oral mucositis and identify the main risk factors associated with its occurrence and severity in patients with head and neck cancer undergoing radiotherapy. **Method:** Cross-sectional observational retrospective study, based on the analysis of 209 medical records of patients treated at the "*Hospital do Câncer de Muriaé*" between 2018 and 2022. **Results:** The results showed a significant association between female gender and the occurrence of mucositis (p=0.020), as well as tumors located in the tongue and mouth (p=0.022). The use of nasogastric tubes was also associated with worsening of mucositis (p<0.001), and increased use according to the severity of the lesion. Patients with xerostomia were more likely to develop the condition (p=0.019). Furthermore, mucositis was more prevalent and severe in patients undergoing radiotherapy for curative purposes, compared to palliative (p=0.001 and p=0.013, respectively). **Conclusion**: Factors as gender, tumor location, xerostomia, use of tubes and type of radiotherapy directly influence the occurrence and severity of oral mucositis. These findings reinforce the importance of individualized prevention strategies for more effective management of this condition.

Key words: Mouth Neoplasms; Radiotherapy; Stomatitis; Risk Factors.

RESUMO

Introdução: A mucosite oral é uma condição dolorosa e debilitante, frequentemente observada como efeito adverso agudo do tratamento antineoplásico. Fatores de risco relacionados ao paciente, como idade e gênero, variáveis do tratamento, dose e área irradiada, podem influenciar a gravidade da mucosite, impactando negativamente a qualidade de vida dos pacientes oncológicos e a evolução do tratamento. **Objetivo:** Analisar a prevalência da mucosite oral e identificar os principais fatores de risco associados à sua ocorrência e gravidade em pacientes com câncer de cabeça e pescoço submetidos à radioterapia. **Método:** Estudo observacional transversal de natureza retrospectiva, baseado na análise de 209 prontuários de pacientes atendidos no Hospital do Câncer de Muriaé entre 2018-2022. **Resultados:** Os resultados mostraram associação significativa entre sexo feminino e ocorrência de mucosite (p=0,020), bem como tumores localizados na língua e boca (p=0,022). O uso de sonda nasoenteral também esteve associado ao agravamento da mucosite (p<0,001), com aumento da utilização conforme o grau da lesão. Pacientes com xerostomia apresentaram maior predisposição ao desenvolvimento da condição (p=0,019). Além disso, a mucosite foi mais prevalente e severa em pacientes submetidos à radioterapia com finalidade curativa em comparação à paliativa (p=0,001 e p=0,013, respectivamente). **Conclusão:** Os fatores como sexo, localização tumoral, xerostomia, uso de sonda e tipo de radioterapia influenciam diretamente a ocorrência e gravidade da mucosite oral. Tais achados reforçam a importância de estratégias de prevenção individualizadas para um manejo mais eficaz dessa condição.

Palavras-chave: Neoplasias Bucais; Radioterapia; Estomatite; Fatores de Risco.

RESUMEN

Introducción: La mucositis oral es una enfermedad dolorosa y debilitante, que a menudo se observa como un efecto adverso agudo del tratamiento antineoplásico. Los factores de riesgo relacionados con el paciente, como la edad y género, así como las variables del tratamiento, como la dosis y el área irradiada, pueden influir en la gravedad de la mucositis, impactando negativamente en la calidad de vida de los pacientes con cáncer y en el progreso del tratamiento. **Objetivo:** Analizar la prevalencia de la mucositis oral e identificar los principales factores de riesgo asociados a su aparición y severidad en pacientes con cáncer de cabeza y cuello sometidos a radioterapia. **Método:** Estudio observacional transversal de naturaleza retrospectiva, basado en el análisis de 209 historias clínicas de pacientes atendidos en el Hospital del Cáncer de Muriaé entre 2018 y 2022. **Resultados:** Los resultados mostraron una asociación significativa entre el sexo femenino y la aparición de mucositis (p=0,020), así como tumores localizados en la lengua y boca (p=0,022). El uso de sonda nasoenteral también se asoció a un empeoramiento de la mucositis (p<0,001), con el aumento del uso de acuerdo con el grado de lesión. Los pacientes con xerostomía presentaron mayor predisposición a desarrollar la enfermedad (p=0,019). Además, la mucositis fue más prevalente y grave en los pacientes sometidos a radioterapia con fines curativos, en comparación con los paliativos (p=0,001 y p=0,013, respectivamente). **Conclusión:** Factores como sexo, localización del tumor, xerostomía, uso de sonda y tipo de radioterapia influyen directamente en la aparición y gravedad de la mucositis oral. Estos hallazgos refuerzan la importancia de las estrategias de prevención individualizadas para un manejo más efectivo de esta condición.

Palabras clave: Neoplasias de la Boca; Radioterapia; Estomatitis; Factores de Riesgo.

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INTRODUCTION

Head and neck cancer (HNC) is widely known for its aggressiveness and invasiveness, a significant challenge for diagnosis and treatment. In this group, squamous cell carcinoma of head and neck (HNSCC) stands out as the most common and develops from epithelial cells of the affected area[1].

The treatment of HNC can encompass more than one therapeutic modality as surgery, radiotherapy and chemotherapy[2-4]. The preferred modality relies on tumor related factors (histological and molecular features of the tumor) as well as the patient's (smoking, age, clinical condition, comorbidities and sex)[3,5]. Radiotherapy has contributed to increased survival, however, with chemotherapy, they are not recommended for neoplastic cells and their cytotoxic effects also affect healthy cells, potentially causing complications as oral mucositis (OM), xerostomia, candidiasis, palate alteration, dysphagia, radiation caries, trismus and osteoradionecrosis[6].

OM is an acute common and significant complication for patients submitted to radiotherapy of head and neck whose prevalence can range between 40% and 90%. Characterized by inflammation and ulceration of the oral mucosa, it can cause intense pain, difficulty to eat and increased risk of bacterial and fungal infections[7-9].

Its physiopathology is multifactorial and involves complex interaction among chemotherapy agents or ionizing radiation and tissues of the oral mucosa. The direct aggression to keratinocytes and basal cells of the mucosa causes epithelial damages, leading to the activation of inflammatory pathways and release of pro-inflammatory cytokines as the tumor necrosis factor alpha (TNF-α) and epidermal growth factor (EGF) that contribute to the progression of the lesion on the mucosa[9].

OM is classified according to the severity in grades that vary from mild (grade 1) to severe (grade 4); the main symptoms are pain, erythema, ulceration and difficulty to eat. Concomitant radiotherapy and chemotherapy is responsible for higher incidence of OM grade 3 and 4 that can potentially lead to severe complications as temporary suspension or dose reduction of antineoplastic therapy, medical intervention and hospitalization, increasing the cost of treatment and extending recovery time. In extreme situations, enteral or parenteral feeding may be necessary to avoid malnutrition and dehydration[11].

Studies indicate several risk factors for the development of OM, including individual aspects of the patients as age, sex, xerostomia, genetic factors, renal function, smoking, alcohol use and comorbidities in addition to treatment-related variables as irradiated area, dose, type of therapeutic agent and concomitant chemotherapy[12,13].

The identification of specific risk factors and development of preventive interventions are essential to reduce the frequency and severity of OM, contributing for improved clinical outcomes. However, studies about risk factors associated with radiotherapy-induced OM in patients with HNC are scarce yet and present inconsistent results[14].

The objective of this study is to evaluate OM and its risk factors in patients with HNC in radiotherapy treatment. Understand these factors is essential to develop effective preventive and therapeutic strategies, improving clinical outcomes and quality of life.

METHOD

Observational, cross-sectional, retrospective study according to the checklist STROBE (Strengthening the Reporting of Observational Studies in Epidemiology)[15], which is available as Supplementary Material.

Data obtained from the systems MVSOUL[16] and MVPEP[17] from January 1, 2021 to December 31 2022 were utilized. At "*Hospital do Câncer de Muriaé*" 421 individuals diagnosed with HNSCC have been assisted in that period. The sample was calculated utilizing Cochran formula suitable for finite populations, with confidence level of 95%, error margin of 5% and expected proportion (p) of 0.5 to obtain the most conservative size sample as possible, which resulted in a minimum sample of 201 patients. Eventually, 209 charts have been enrolled and analyzed, greater than the required minimum to ensure robustness.

Consecutive sampling was applied to select the 209 charts, including all the patients who met the study inclusion criteria, which reduces the bias of selection. Patients of both sexes, aged 18 years or older, histologically diagnosed with HNSCC who received antineoplastic treatment with radiotherapy, chemotherapy and/or surgery have been enrolled. Incomplete charts were excluded.

Epidemiologic, sociodemographic characteristics (sex, age, color, education and marital status), life habits (smoking, alcohol use) and clinical information as comorbidities, site tumor, staging, type of treatment have been collected from electronic charts of MVPEP and MVSOUL, in addition to buccal condition: OM (grade and frequency), location of the lesion, use of nasogastric probe due to OM and for other reasons and xerostomia.

The descriptive analysis of the categorical variables was performed through absolute and relative (%) frequencies and the numerical variables were expressed as medians. The chi-square test or Fisher's exact test when necessary were utilized to evaluate the association

of categorical variables. The differences of frequency and mucositis grades were analyzed by the Mann-Whitney test[18]. Software R, version 4.3.1[19] (R Core Team, 2023), considering $p < 0.05$ as statistically significant was utilized for the statistical analyzes.

The Ethics Committee of FAMINAS approved the study, report number 6.913.227 (CAAE submission for ethical review 79778124.0.0000.5105), in compliance with Directive number 466/12 of the National Health Council[20]. The informed consent form was waived because only secondary and deidentified data have been utilized. The information was collected according to the current ethical and legal principles in force.

RESULTS

The sample consisted mostly of men (85.65%) and the predominant age range was 60-70 years (37.87%). The majority of the sample claimed they were Brown (55.50%), 52.63% were married, with incomplete elementary school (64.82%) or illiterate (14.07%). 43.7% were ex-alcohol users and 63.16% affirmed they smoked. Most of them had toothed arch (81.35%), 28.2% used some type of prosthesis, 19.4% of which, full prosthesis and 7.18%, removable partial prosthesis. The main comorbidities found at the charts were arterial hypertension (33.50%), diabetes *mellitus* type II (10.29%) and gastritis (11.48%) (Table 1).

The most common site of HNC was the base of the tongue (28.71%). Other common areas were floor of the mouth and palate, both with 11.48%. Less frequent were gingiva (1.91%) and lip (0.96%). Most of the cases were at stage 4 (78.37%), followed by stages 3 (12.50%), 2 (8.17%) and 1 (0.96%) (Table 2).

The majority of the patients (57.89%) received combined radiotherapy and chemotherapy, while 15.79% received radiotherapy alone. 64.82% received curative radiotherapy treatment and 35.18%, palliative. Cisplatin was the most utilized medication (62.20%). Chemotherapy was suspended in 33% of the cases, of which 3.35% due to OM (Table 2).

Half of the patients (50.24%) presented xerostomia, followed by dysphagia in 22.2%, sialorrhea in 13.90%, odynophagia in 9.57%, radiodermatitis in 6.48% and nausea in 6.17% (Table 2).

OM was diagnosed in 65.37% of the patients and classified according to the World Health Organization (WHO) as grade 3 for 36.56%. Lips were the most affected for 6.70% of the patients, followed by tongue (5.74%) and jugal mucosa (4.78%). The use of nasoenteral probe due to OM was observed in 10.29% of the sample. The mean of the total of radiotherapy fractions up to

Table 1. Sociodemographic, oral and lifestyle of patients with head and neck cancer assisted at "Hospital do Câncer de Muriaé" (2018-2022)

Variable	n (%)
Sex	
Female	30 (14.35%)
Male	179 (85.65%)
Age range	
<50	37 (13.00%)
>70	32 (20.19%)
50 – 59	66 (28.94%)
60 – 70	74 (37.87%)
Race/Color	
Brown	116 (55.50%)
White	60 (28.71%)
Black	33 (15.79%)
Marital status	
Married	110 (52.63%)
Single	69 (33.01%)
Legally separated	19 (9.09%)
Widow/widower	10 (4.78%)
Consensual union	1 (0.48%)
Education	
Incomplete elementary	129 (64.82%)
Illiterate	28 (14.07%)
Complete elementary	19 (9.55%)
High school	13 (6.53%)
Complete university	9 (4.52%)
Incomplete university	1 (0.50%)
Alcohol	
Ex-user	99 (47.37%)
Yes	92 (44.02%)
Never	18 (8.61%)
Tobacco	
Yes	132 (63.16%)
Ex-smoker	57 (27.27%)
Never	20 (9.57%)
Type of arch	
Toothed	170 (81.35%)
Toothless	39 (18.65%)
Prosthesis	
No	150 (71.80%)
Yes	59 (28.20%)
Full prosthesis	
No	169 (80.86%)
Yes	40 (19.14%)
Removable partial prosthesis	
No	194 (92.82%)
Yes	15 (7.18%)
Implant	
No	207 (99.04%)
Yes	2 (0.96%)
Hypertension	
No	135 (66.50%)
Yes	68 (33.50%)
Diabetes	
No	183 (89.71%)
Yes	21 (10.29%)
Gastritis	
No	185 (88.52%)
Yes	24 (11.48%)

Note: Education: "Unknown" n=10, Hypertension: "Unknwon" n=6, Diabetes: "Unknwon" n=5.

the onset of OM was 21.20, based on a mean dose of radiation of 59.36 Gy associated with grades 3 and 4. The mean time for onset of OM after radiotherapy was 40.97 days (Table 3).

Significant association was observed for females and incidence of OM (p = 0.020), although there was no association between sex and OM grade (p = 0.267). No significant correlation between age and OM grade was found (p = 0.111). Also, no associations between smoking and OM (p = 0.702), or tobacco and OM grade (p = 0.093) have been found. Similarly, there was no association between alcohol use and OM grade (p = 0.362) or occurrence (p = 0.702) (Table 4 and Table 5). There was no significant association between the presence of comorbidities and the occurrence or OM grade (p = 0.074 and p = 0.520, respectively) (Table 4 and Table 5).

Significant association between OM and use of probe (p = 0.001) was found, and with OM grade and use of probe (p < 0.001). Significant association between xerostomia and OM (p = 0.019) was detected but no association between xerostomia and OM grade was found (p = 0.991) (Table 4 and Table 5).

There is significant association between the site of the tumor and OM (p = 0.022) and between OM and type of radiotherapy (p = 0.001), with high prevalence of OM in patients treated with curative radiotherapy. In addition, the OM grade was also higher in patients who received curative radiotherapy (p = 0.013) (Table 4 and Table 5).

DISCUSSION

OM affected 65.37% of the study patients, severity grade 1 to 4, corroborating the literature that reports OM as the most frequent adverse event in patients with HNC, and may reach 80% to 90% of these patients, especially with concomitant chemotherapy and radiotherapy[21,22].

The most common sites of OM in the sample investigated were the lips (6.70%) and tongue (5.74%). Chemotherapy-induced OM usually occurs in non-keratinized surfaces as laterals and ventral region of the tongue, buccal mucosa and soft palate[23]. On the other hand, radiotherapy-induced OM is restricted to areas within the radiation field with high impact on non-keratinized tissues[24,25]. Therefore, the combination of concomitant radiotherapy and chemotherapy significantly increases the risk of OM grades 3 and 4, being four times more frequent[26], corroborating the findings that identified this therapeutic regimen as the most associated with OM.

OM is a common radiotherapy complication characterized by inflammation and ulceration of oral mucosa which directly affects the patients quality of life. The increased severity of OM, intense pain and dysphagia

Table 2. Disease, treatment characteristics and adverse events observed during the treatment of patients with head and neck cancer assisted at *Hospital do Câncer de Muriaé* (2018-2022)

Variable	n (%)
Modality of treatment	
Single radiotherapy	33 (15.79%)
Radiotherapy and chemotherapy	121 (57.89%)
Radiotherapy and surgery	21 (10.05%)
Radiotherapy, chemotherapy and surgery	34 (16.27%)
Type of radiotherapy	
Curative radiotherapy	129 (64.82%)
Palliative radiotherapy	70 (35.18%)
Suspended radiotherapy	
No	183 (93.37%)
Yes	13 (6.63%)
Suspended radiotherapy by mucositis	
No	7 (53.85%)
Yes	6 (46.15%)
Cisplatin	
Yes	130 (62.20%)
No	79 (37.80%)
Carboplatin	
No	185 (88.52%)
Yes	24 (11.48%)
Paclitaxel	
No	183 (87.56%)
Yes	26 (12.44%)
Fluorouracil	
No	193 (92.34%)
Yes	16 (7.66%)
Suspended chemotherapy by mucositis	
No	202 (96.65%)
Yes	7 (3.35%)
Site of the tumor	
Base of the tongue	60 (28.71%)
Other parts and unspecified parts of the tongue	29 (13.88%)
Amygdala	25 (11.96%)
Floor of the mouth	24 (11.48%)
Palate	24 (11.48%)
Other parts and unspecified parts of the mouth	21 (10.05%)
Oropharynx	19 (9.09%)
Gingiva	4 (1.91%)
Lip	2 (0.96%)
Staging	
4	163 (78.37%)
3	26 (12.50%)
2	17 (8.17%)
1	2 (0.96%)
Xerostomia	
Present	103 (50.24%)
Absent	102 (49.76%)
Other adverse events	
Dysphagia	144 (22.20%)
Sialorrhea	90 (13.90%)
Odinodysphagia	62 (9.57%)
Radiodermatitis	42 (6.48%)
Nausea	40 (6.17%)
Others (n=58)	270 (41.70%)

Note: Xerostomia: "Unknown" n=4; Suspended radiotherapy: "Unknown" n=13, "Not applicable" n=5; Suspended chemotherapy: "Unknown" n=9; Site of the tumor: "Unknown" n=1; Staging: "Unknown" n=1.

Table 3. Clinical characteristics of OM of patients with head and neck cancer assisted at *Hospital do Câncer de Muriaé* (2018-2022)

Variable	n (%)
OM	
Present	134 (65.37%)
Absent	71 (34.63%)
Higher score of OM	
Grade 1	17 (18.28%)
Grade 2	29 (31.18%)
Grade 3	34 (36.56%)
Grade 4	13 (13.98%)
OM in lip	
No	195 (93.30%)
Yes	14 (6.70%)
OM in tongue	
No	197 (94.26%)
Yes	12 (5.74%)
OM in jugal mucosa	
No	199 (95.22%)
Yes	10 (4.78%)
OM in floor of the mouth	
No	205 (98.09%)
Yes	4 (1.91%)
OM in gingiva	
No	207 (99.04%)
Yes	2 (0.96%)
OM in palate	
No	203 (97.13%)
Yes	6 (2.87%)
OM in oropharynx	
No	205 (98.09%)
Yes	4 (1.91%)
OM in the back of the vestibule	
No	208 (99;52%)
Yes	1 (0.48%)
Nasoenteral probe due to mucositis	
No	183 (89.71%)
Yes	21 (10.29%)
Fractions of RT up to the onset of oral mucositis	
0 – 10	19 (17.60%)
11 – 15	28 (25.90%)
16 – 29	40 (37.00%)
≥30	21 (19.40%)
Dose of radiation associated with OM grades 3 and 4	
<32 Gy	4 (9.10%)
32 – <60 Gy	13 (29.50%)
60 – 72 Gy	25 (56.80%)
>72 Gy	2 (4.50)
Mean time to onset of OM after RT	
≤14 days	2 (2.80%)
15 – 30 days	18 (25.00%)
31 – 60 days	32 (44.44%)
>60 days	20 (27.80%)

Captions: OM: Oral mucositis; RT = Radiotherapy.
Note: "Unknwon" n=4; High score of OM: "Unknown" n=48, "Not applicable" n=68; Nasoenteral probe "Unknown" n=6; Nasoenteral probe by mucositis: "Unknown" n=5.

Table 4. Relation between oral mucositis and risk factors in patients with head and neck cancer in treatment at *Hospital do Câncer de Muriaé*

Variable	Oral mucositis		*p*
	Present	Absent	
Sex			
Male	109 (61.9%)	67 (38.10%)	0.020*
Female	25 (86.2%)	4 (13.8%)	
Age range			
Youngsters	11 (57.90%)	8 (42.10%)	0.472
Non-youngsters	123 (66.10%)	63 (33.90%)	
Smoking			
Yes	84 (65.10%)	45 (34.90%)	
Ex-smoker	36 (63.2%)	21 (36.80%)	0.702
Never	14 (73.7%)	5 (26.3%)	
Alcohol use			
Ex-user	63 (63.60%)	36 (36.40%)	
Yes	58 (64.40%)	32 (35.60%)	0.702
No	13 (81.30%)	3 (18.80%)	
Site of the tumor			
Oropharynx	9 (50.0%)	9 (50.0%)	
Tongue	64 (71.1%)	26 (28.9%)	0.022*
Palate	10 (43.5%)	13 (56.5%)	
Mouth	15 (71.5%)	6 (28.5%)	
Floor	19 (82.6%)	4 (17.4%)	
Parotid gland	0 (0.00%)	1 (100.0%)	
Amygdala	15 (62.5%)	9 (37.5%)	
Gingiva	1 (25.0%)	3 (75.0%)	
Lip	1 (100.0%)	0 (0.00%)	
Staging			
3	20 (80.0%)	5 (20.0%)	
4	102 (63.4%)	59 (36.6%)	0.377
2	11 (64.7%)	6 (35.3%)	
1	1 (50.0%)	1 (50.0%)	
Treatment			
RT	15 (50.0%)	15 (50.0%)	
CT RT	83 (69.75%)	36 (30.25%)	
CIR RT	18 (81.82%)	4 (18.18%)	0.068
CIR RT CT	18 (62.07%)	11 (37.93%)	
Dose of radiation			
<60 Gy	36 (52.2%)	33 (47.8%)	0.001*
≥60 Gy	97 (75.8%)	31 (24.2%)	
Xerostomia			
Absent	58 (56.9%)	44 (43.1%)	
Present	75 (73.5%)	27 (26.5%)	0.019*
Motive for feeding probe			
Mucositis	21 (100.00%)	0 (0.00%)	<0.001*
Other factors	51 (54.80%)	42 (45.20%)	
No-probe	61 (70.90%)	25 (29.10%)	
Comorbidities (hypertension, diabetes, gastritis)			
No	69 (60.5%)	45 (39.5%)	
Yes	64 (73.6%)	23 (26.4%)	0.074

Captions: * = Statistically significant; RT = Radiotherapy; CT = Chemotherapy; SUR = Surgery.

Table 5. Risk factors associated with the grade of oral mucositis in patients with head and neck cancer assisted at *Hospital do Câncer de Muriaé* (2018-2022)

Variable	Grade of oral mucositis				*p*
	1	2	3	4	
Sex					
Male	16 (21.10%)	29 (38.20%)	22 (28.90%)	9 (11.80%)	0.267
Female	1 (5.90%)	5 (29.40%)	7 (41.20%)	4 (23.50%)	
Age range					
Youngsters	3 (33.30%)	0 (0.00%)	5 (55.60%)	1 (11.10%)	
Non youngsters	14 (16.70%)	34 (40.50%)	24 (28.60%)	12 (14.30%)	0.111
Smoking					
Yes	7 (13.00%)	22 (40.70%)	19 (35.20%)	6 (11.10%)	
Ex-smoker	10 (34.50%)	9 (31.00%)	6 (20.70%)	4 (13.80%)	0.093
Never	0 (0.00%)	3 (30.00%)	4 (40.00%)	3 (30.00%)	
Alcohol use					
Ex-user	11 (25.00%)	15 (34.10%)	12 (27.30%)	6 (13.60%)	0.362
Yes	6 (15.00%)	15 (37.50%)	15 (37.50%)	4 (10.00%)	
Never	0 (0.00%)	4 (44.40%)	2 (22.20%)	3 (33.3%)	
Site of the tumor					
Oropharynx	3 (75.0%)	0 (0.00%)	1 (25.0%)	0 (0.00%)	
Tongue	4 (9.1%)	18 (40.9%)	13 (29.5%)	9 (20.5%)	
Palate	1 (16.7%)	3 (50.0%)	2 (33.3%)	0 (0.00%)	
Mouth	3 (27.3%)	2 (18.2%)	4 (36.3%)	2 (18.2%)	
Floor	1 (7.7%)	6 (46.2%)	5 (38.5%)	1 (7.7%)	0.467
Parotid gland	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Amygdala	5 (37.5%)	4 (28.6%)	4 (28.6%)	1 (7.1%)	
Gingiva	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Lip	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	
Staging					
3	2 (16.7%)	4 (33.3%)	5 (41.7%)	1 (8.3%)	
4	14 (18.4%)	27 (35.5%)	24 (31.6%)	11 (14.5%)	0.868
2	1 (20.0%)	3 (60.0%)	0 (0.0%)	1 (20.0%)	
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Treatment					
RT	0 (0.0%)	5 (62.5%)	2 (25.0%)	1 (12.5%)	
CT RT	12 (20.69%)	19 (32.76%)	19 (32.76%)	8 (13.79%)	
SUR RT	3 (23.43%)	6 (42.86%)	4 (28.57%)	1 (7.14%)	
SUR RT CT	2 (15.38%)	4 (30.77%)	4 (30.77%)	3 (23.08%)	
Modality of RT					
Palliative (<60 Gy)	0 (0.0%)	10 (43.5%)	7 (30.4%)	6 (26.1%)	0.013*
Curative (≥60 Gy)	17 (24.6%)	24 (34.8%)	21 (30.4%)	7 (10.1%)	
Xerostomia					
Absent	14	13	7	5	0.991
Present	20	16	10	7	
Motive for feeding probe					
Mucositis	0 (0.00%)	8 (44.44%)	1 (5.56%)	9 (50.00%)	*p<0.001**
Other factors	6 (20.00%)	14 (46.67%)	10 (33.33%)	0 (0.00%)	
Non-probe	11 (24.44%)	12 (26.67%)	18 (40.00%)	4 (8.89%)	
Comorbidities (hypertension, diabetes, gastritis)					
No	21 (42.8%)	15 (30.6%)	7 (14.3%)	6 (12.3%)	0.520
Yes	13 (29.5%)	14 (31.8%)	10 (22.8%)	7 (15.9%)	

Captions: * = Statistical significance $p < 0.05$; RT = Radiotherapy; CT = Chemotherapy; SUR = Surgery.

can hamper food intake, requiring nutritional support through enteral probes[21].

In the present study, there was significant association between OM and use of probe (p = 0.001), in addition to correlation between the grade of the lesion and the use of the probe (p < 0.001). These findings are aligned with a prospective study[27] which has also identified a relation between the severity of OM and high rate of feeding probes with the frequency of probes increasing as the lesion severity rises.

The data have also revealed that women tend to present OM more frequently than men, suggesting possible differences of susceptibility or response to the treatment among men and women. A retrospective study[28] corroborates this observation, suggesting that female sexual hormones as estrogen and progesterone can negatively impact the oral immunity, contributing to the etiopathogenesis of OM.

Another relevant factor is xerostomia, a frequent radiotherapy complication for patients with HNC that can indirectly contribute to the development and aggravation of OM. The reduction of the salivary flow compromises the protective feature of the saliva in the oral cavity, making the mucosa more susceptible to lesions and inflammations, which can intensify the severity of OM[29]. Furthermore, hyposalivation changes the balance of the oral microbiota, favoring the growth of opportunist pathogens as fungi, which can lead to secondary infections and increase the risk of recurrence of OM during the treatment[30]. These alterations of the oral microbiome are associated with the development of severe OM. This finding is consistent with the literature, which demonstrates that xerostomia can be associated with modifications of the oral microbiota and proliferation of pathogenic microorganisms exacerbating the inflammatory setting[31]. Consistently, the findings of another study[32] indicate that hyposalivation results in increase of acidogenic coccus in the supragingival biofilm and elevation of the salivary levels of cariogenic coccus, especially *Streptococcus* of the group *mutans*, favoring the development of OM.

Finally, the results demonstrate a significant association between curative radiotherapy (≥60 Gy) and OM, and progression to severer grades (p = 0.013). This finding can be attributed to the cumulative effect of radiotherapy since the severity of OM is influenced by factors as total dose administered, technique adopted and presence of concomitant systemic therapy[21].

Curative therapy tends to cause more damages to the oral mucosa because it involves a more prolonged time of treatment and total doses higher than palliative. Evidences suggest that the dose of radiation received is one of the main predictors of OM with cumulative doses higher than 50 Gy associated with elevated risk of severe forms of the complication[33]. The study of Mazzola et al.[34] indicated that a mean dose of 50 Gy and a maximum dose of 65 Gy on oral mucosa are strongly related to grade 2 OM or higher. These findings reinforce the necessity of effective strategies to minimize the adverse effects of radiotherapy, especially in high-dose curative regimens.

CONCLUSION

OM is a significant complication of oncologic treatment, its occurrence and severity are influenced by demographic, anatomic and therapeutic factors. High predisposition in women and patients with tumors in the tongue and mouth suggests possible biological and anatomic variations that increase the risk of OM.

The association between severe OM and nasoenteral probe indicates that the severe form of the disease damages food intake, requiring nutritional support. In addition, xerostomia was identified as risk factors, reinforcing the importance of measures to maintain the saliva during the treatment. Patients submitted to curative radiotherapy presented high prevalence and severity of OM, standing out the influence of the dose in the evolution of the disease. These findings emphasize the necessity of customized approaches to prevent and treat OM in patients with HNC submitted to antineoplastic treatment.

However, a limitation of the retrospective study based on medical charts is the quality and accuracy of information registered in medical records. Charts are filled according to criteria and clinical practice of each professional and some discrepancies can exist while documenting important data as symptoms, treatments and complications. In addition, the retrospective design hampers the strict control of the variables that could be better observed in a prospective study, which can result in bias of selection or loss of relevant data.

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CONTRIBUTIONS

Laila Thainara André de Souza contributed to the study design, acquisition, analysis and interpretation of the data, writing and critical review. Juliana Chagas Pereira Costa contributed to the conception and design of the study. Cristiane Ferreira Alfenas contributed to

the critical review. Ana Carolina Ribeiro de Oliveira contributed to the analysis and interpretation of the data. Adriele de Freitas Neiva Lessa contributed to the conception and design of the study, writing and critical review. All the authors approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

DATA AVAILABILITY STATEMENT

All content underlying the text of the article is contained in the manuscript.

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