

Izabella Henrichs Ribeiro¹
Júlia Lopes Ferigatto²
Dionéia Evangelista Cesar¹
Rodrigo Luiz Fabri¹
Ana Carolina Morais Apolônio^{1,2}

¹Instituto de Ciências Biológicas,
Universidade Federal de Juiz de Fora,
Brasil.

²Faculdade de Odontologia, Universidade
Federal de Juiz de Fora, Brasil.

✉ **Ana Carolina Apolônio**

Campus Universitário, rua José Lourenço
Kelmer, s/n, São Pedro, Juiz de Fora, Minas
Gerais
CEP: 36036-900
✉ carolina.apolonio@ufjf.edu.br

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ABSTRACT

Introduction: Oral microbiota has been implicated on oral mucositis (OM) that occurs during cancer therapy, however without consensus. **Objective:** This study, aimed to establish, through a review, the association between oral microbiota and OM at head and neck cancer therapy (HNCT). **Material and Methods:** The search of PubMed was performed considering 2008-2018 period, and the descriptors "oral mucositis" and "oral microbiota" in subheadings etiology and microbiology into the Medical Subject Heading (MeSH) "Head and Neck Neoplasms". The conducting question was "Is there an oral dysbiosis during HNCT associated with OM?" **Results:** 22 articles were selected under two steps of data extraction: articles that evaluated de oral microbiota during HNCT (n=13), and articles that also focused in OM (n=9). **Conclusion:** The evidence presented in the literature suggests associations of oral microbiota dysbiosis with the progression and worsening of radiation-induced OM. However, to define a microbial core for the disease, future standardized studies are required.

Key-words: Stomatites; Oral Microbiota; Head and Neck Neoplasms.

RESUMO

Introdução: A microbiota bucal tem sido associada à mucosite oral que ocorre durante a terapia para o câncer apesar de não haver consenso. **Objetivo:** Este estudo objetivou estabelecer por meio de uma revisão da literatura a associação entre a microbiota bucal e a mucosite oral durante a Terapia para o Câncer de Cabeça e Pescoço (TCCP). **Material e Métodos:** Foi realizada uma busca na base de dados PubMed no período de 2008-2018 utilizando-se as palavras chave "oral mucositis" e "oral microbiota" nos subtítulos "etiology" e "microbiology" do descritor "Head and Neck Neoplasms" da base Medical Subject Heading (MeSH). A questão norteadora do estudo foi: "Ocorre uma disbiose durante a terapia para o câncer de cabeça e pescoço que esteja associada à mucosite oral?" **Resultados:** 22 artigos foram selecionados em duas etapas de extração dos dados: artigos que avaliaram a microbiota bucal durante TCCP (n=13), e artigos que também focaram na mucosite oral (n=9). **Conclusão:** A evidência apresentada na literatura sugere associação de uma disbiose da microbiota bucal com a progressão e agravamento da mucosite oral induzida pela radiação. Entretanto, novos estudos padronizados são necessários para se definir o core microbiano para a doença.

Palavras-chave: Estomatite; Microbiota Bucal; Neoplasias de Cabeça e Pescoço.



INTRODUCTION

Chemotherapy (CT) and radiotherapy (RT) treatments are commonly used in cancer therapy. However, the agents used in these antitumor treatments do not discern healthy cell from disorderly grown cell. Therefore, the side effects to these therapies are recurrent and worrying to the patient health, being oral mucositis (OM) the most common side effect to the antitumor treatment of the head and neck region.^{1,2}

The establishment of OM is related to a cascade of impactful events for the patient and the community, raising the costs of cancer treatment and the mortality.^{1,3} Its development ranges from increasing number of pro-inflammatory cytokine receptors to damage of affected tissues by cell apoptosis and necrosis.⁴ Its symptoms of pain, difficulty in swallowing, trismus and decreased taste, detract from the nutrition of the patient, therefore, the predisposition to microbial virulence factors is greater, compromising the general state of health.^{1,5} In fact, the oral microbiota has been implicated as an agent of progression and/or aggravation of the OM for years.^{3,6-7}

Despite there are no effective interventions for OM therapy yet,⁸ the knowledge of the oral microbiota of individuals at head and neck cancer therapy could be the first step to comprehend its role in the development and progression of the OM disease. Therefore, the aim of this study was to determine, through a review, the association between oral microbiota and OM at head and neck cancer therapy (HNC).

MATERIAL AND METHODS

The key question to conduct this review was "Is there an oral dysbiosis during HNC therapy associated with OM?". To answer the key question, a literature search of PubMed was carried out. The Medical Subject Heading (MeSH) "Head and Neck Neoplasms" with the subheadings etiology and microbiology, in combinations with the descriptors "oral mucositis" and "oral microbiota" were used. To restrict the results, the search was limited to studies published from 2008 up to 2018, with full text available and with analysis in humans. Case reports, experimental studies, review articles and letters to the editor were excluded.

RESULTS

The PubMed database is a reference database for the scientific literature including the health field. It contains more than 29 million references from MEDLINE, life science journals, and online books.⁹ Considering only MEDLINE, it comprises scientific journal articles from over 70 countries around the world being every day updated.¹⁰

Regarding the search terms used and their associations, several articles were retrieved, which were selected considering the flow process presented in figure 1. At the end of the process, 22 articles were selected, nine of them specifically worked with oral microbiota analysis during head and neck cancer treatment focusing in OM.

The 22 articles included in this review met the eligibility criteria, were identified to respond to the objective of the study and presented adequate

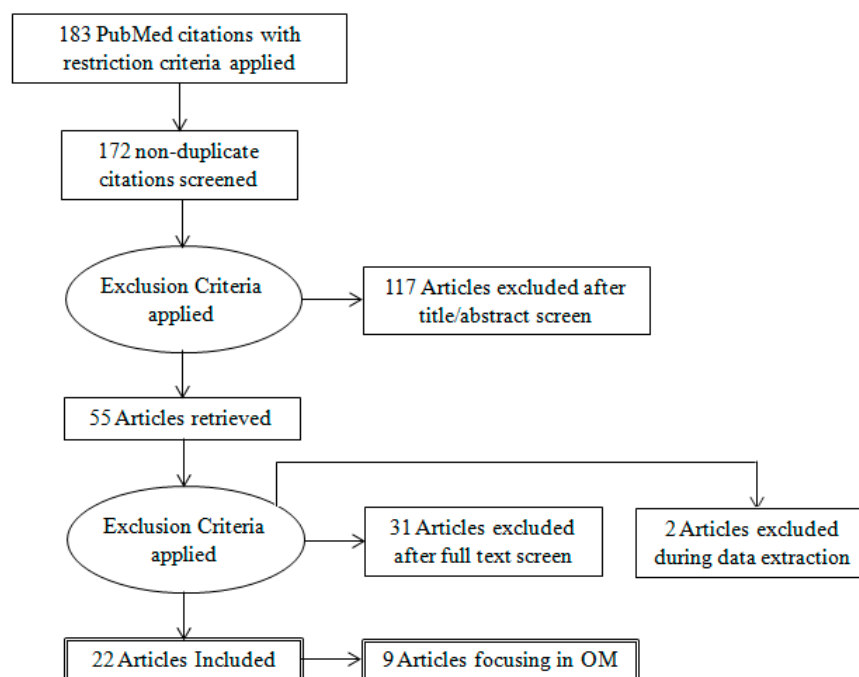


Figure 1: Flow diagram showing the retrieval process of studies included in the review.

methodological relevance and quality. However, the process of data extraction were divided on two steps: first were analyzed the articles that evaluated oral microbiota during the head and neck cancer treatment (n=13), and then the articles that also focused in OM (n=9). These nine articles, named as "OM articles", were studied and a synthesis of the literature was performed with the data extracted summarized in table 1.

The sample size of the OM articles was quite similar, having the sample ranging from 19 to 49 patients. However, the age of the study group was very different, with some of them working with age up to 18 years,¹¹ and other from 18 years.³ Furthermore, five studies are from countries of the European continent, among them Sweden,^{11,12} Croatia,¹³ Spain and Italy.^{3,14} Three studies are from Asian countries, among them India,¹⁵ China and Japan.^{1,2,16} In addition, one study is from the American continent, more specifically Brazil.⁵

The microbial analysis of OM articles

The studies selected had used different methodologies, both those of conventional culture with the microorganisms being analyzed by cultures in selective media,^{3,5,12-15} as microbial analysis by 16S sequencing.^{1,2,11} Six studies have analyzed bacteria and two studies analyzed mainly fungi.^{1-3,11-15} One study analyzed both microbiological groups.⁵

The kind of sample of OM articles

From the nine manuscript selected, three studies collected the sample with oropharyngeal swab before and after RT.^{2,13,15} One study collected the supragingival plaque before and after CT.¹⁴ One study collected the supra and subgingival plaque before and after RT.⁵ One study performed the injury swab before and during RT.¹ One study performed mucosal smear before, during and after RT.³ One study used strips of paper placed on the mucosa or OM if occurred.¹¹ And one study used the mucosal swab and scraped the dorsum tongue during the treatment.¹²

Considering the above, some distinct shifts were expected when comparing the manuscripts studied, because the sample region was distinct. However, the divergence of the manuscript goes beyond of the local of sample. It includes the RT and/or CT protocol, age of the cases studied, sampling time and microbial analysis type, which varied very much as described above in the results section and summarized in table 1.

DISCUSSION

In the mouth region the representativeness of the different microorganisms varies according to their different sites. This depends on specific characteristics such as nutrient availability, oxidation reduction

potential, pH, contact with saliva, access to host defense molecules, and others.¹⁶ In the oral microbiota of healthy individuals the predominant groups in the mucosa are *Streptococcus* and *Haemophilus*, in supra and subgingival biofilms are *Actinomyces* and *Prevotella*, respectively.^{3,18} In the gingival sulcus, there is predominant colonization of obligate anaerobes, besides *Prevotella*, also stand out *Veillonella*, *Corynebacterium*, *Fusobacterium* and *Rothia*.⁴ In the lips we can find facultative anaerobes like *Streptococcus* and in smaller quantity *Veillonella*, *Neisseria* and *Candida*. In the cheeks and tongue, we find *Streptococcus*, *Actinomyces* and *Haemophilus*.⁴ The microorganisms found in saliva come from other sites of the mouth region, not being considered as having a resident microbiota.¹⁶ Other microorganisms besides bacteria can also be found frequently in the oral cavity, such as yeasts of the genus *Candida*.¹⁹

The microbiota has important functions for the host. Among these functions can be mentioned: auxiliary of human being to synthesis compounds that degrade toxic products, immune system modulating and serving as a barrier against pathogens colonization by inhibitory substances production.⁵ However, when in disequilibrium with the host, this same microbiota, due to its great diversity and virulence potential, can become pathogenic by its amphibiotic character.^{2,5} Therefore, resident microorganisms have the ability to live in harmony with the host, but eventually, due to some imbalance factor, are able to change the virulence factors expression presenting the aggression capacity. Furthermore, this change in the microbiota, called dysbiosis, is correlated with a higher risk of developing several diseases, including OM, since it may deregulate the immune system responses.^{5,20}

Neoplasm, as well as their cytotoxic therapies, leads to a myelosuppression in which bone marrow activity is decreased. Thus, the defense system cells production of the individual being treated for cancer is reduced.⁴ The myelosuppression state may influence the diversity of the microbiome,²¹⁻²³ and distinct antitumor treatments result in different oral microbiome changes but in a specific manner in each host.²⁴⁻²⁵ In the surgical treatment, the prevalence of *T. forsythia* tended to decrease.²⁴ The RT induces changes in the oral microbiota and this is significantly different when associated with the mutational changes of the cancer,^{1,5,22,23,26} changing progressively with tumor progression.^{23,27} In the treatments of RT with or without adjuvant CT, there is an increase of bacteria from some groups including Proteobacteria, Spirochaetes,^{2,28} *Treponema*, *Granulicatella*, *Capnocytophaga*,² *Pseudomonas*,^{1,2} *Pediococcus*, *Oscillibacter*,¹ *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Fusobacteria*, *TM7*,²⁸ *C. albicans*, *C. tropicalis* and *C. Parapsilosis*,^{15,29} and a decrease of *Fusobacteria*, *Prevotella*, *Leptotrichia* and *Campylobacter* with increased radiation.^{1,2} Schuurhuis et al²⁴ related that *A. actinomycetemcomitans*, *P. gingivalis*,

Table 1: Characteristics of oral mucositis articles.

Author (year)	Samplepopulation	Study design	Main results	Conclusion
Ognjenović M, Milatić K, Parat K, Kovacic I, Buselić Ma, Bozić J ¹²	Cases: 25 patients with head and neck cancer treated with surgery and RT. The irradiation dose was 6000 cGy in 30 separate doses of 200 cGy each. Study type: longitudinal Age: 47 to 84 years.	Sample: oral swabs Sampling time: before, during the second week and after 3 weeks after the end of irradiation. Microbial Analysis: Fungal culture in selective medium	<ul style="list-style-type: none"> • Before irradiation: 80% negative and 20% positive patients (16% <i>C. albicans</i>, 4%<i>C. krusei</i>). • Second week of irradiation: 64% negative and 36% positive patients (5 species: <i>C. albicans</i>, <i>C. glabrata</i>, <i>C. parapsilosis</i>, <i>Saccharomyces cerevisiae</i> and <i>C. guilliermondii</i>). • 3 weeks after irradiation: 80% negative and 20% positive patients (2 species: 16% <i>C. albicans</i> and 4% <i>C. Krusei</i>). • Oral mucositis degree increased simultaneously with increasing numbers of oral yeast species in positive patients. 	<ul style="list-style-type: none"> • The <i>Candida</i> occurrence is statistically associated with mucositis. • Mucositis appeared more frequently during RT, with increased positive isolation of yeast species.
Ye Y, Carlsson G, Agholme MB, Wilson JA, Roos A, Henriques-Normark B et al ¹⁰	Cases: 37 patients with recent diagnosis of malignancies Control group: n=38 Study type: longitudinal cohort Age: 4 and 18 years.	Sample: paper strips of oral mucosa Sampling time: first at the time of diagnosis and during the CT prior to any sign of OM. Patients in whom MO occurred, samples of mucositis were collected using strips of paper placed on the top of the lesion Microbial analysis: 16S sequencing	<ul style="list-style-type: none"> • Microbial diversity during CT did not change significantly compared to before CT, both for patients who developed OM (p0.11) and those who did not (p0,67). • The patients who later development of OM are more heterogeneous among one another and showed higher microbial diversity at the time of diagnosis of malignancy. • A more pronounced modification of the bacterial community by CT was detected with subsequently development of OM 	<ul style="list-style-type: none"> • Mucosal oral microbial stability may be beneficial in the OM course.
Vidal-Casariego A, Fernández-Natal I, Calleja-Fernández A, Parras-Padilla T, Cano-Rodríguez I, Prieto-Alonso B et al ³	Cases: 35 patients with head and neck cancer treated under RT. Study type: cohort Age: >18 years.	Sample: Mucosa smear Sampling time: before RT, in the middle of the RT period, and after RT termination. Microbial analysis: bacterial and fungal culture research in selective media aerobic incubated.	<ul style="list-style-type: none"> • OM was more frequent in patients undergoing RT. Bacteria and yeast were found in the study. • A positive correlation between severe mucositis and bacterial cultures before RT was detected. 	<ul style="list-style-type: none"> • The oropharyngeal isolation of bacterial pathogens may favor the development of severe OM during radiation therapy.

<p>Vozza, Caldarazzo, Ottolengh¹⁵</p>	<p>Cases: 30 patients with solid malignancy, divided into 2 groups, which received CT (docetaxel or 5-fluorouracil and oxaliplatin) or not. Study type: cohort Age: 32 to 59 years.</p>	<p>Sample: supragingival plaque of the right lower premolars Sampling time: before CT, 1 day after CT and 7 days after CT. Control subjects were sampled on equivalent dates. Microbial analysis: bacterial culture research in selective media anaerobically and microaerobically incubated.</p>	<ul style="list-style-type: none"> • OM developed in 66.6% patients in CT group and 0% in the control group. • No significant differences were found in bacterial alterations between three times of sampling in CT group. • In the control group, the bacterial count remained unchanged during the observation period. 	<ul style="list-style-type: none"> • There are no microbial changes in dental plaque in patients within 7 days of the first CT cycle. • The correlation between OM and specific microorganisms was not evaluated.
<p>Singh GK, Capoor MR, Nair D, Bhowmik KT¹⁴</p>	<p>Cases: 49 patients with squamous cell carcinoma treated with RT and CT (cisplatin) Study type: cohort Age: 23 to 65 years.</p>	<p>Sample: Throat swab Sampling time: before RT, during (2nd and 6th week) and post-radiotherapy (10th week). Microbial analysis: Fungal culture in selective medium.</p>	<ul style="list-style-type: none"> • 27 samples was positive for <i>Candida</i> species: <i>Non-albicans</i> (36.73%) and <i>Candida albicans</i> (18.36%). • Higher rate of oral fungal colonization and infection was found in patients with grade III and IV OM. 	<ul style="list-style-type: none"> • Emergence of <i>Non-albicans Candida</i> warrants an early diagnosis and appropriate management.
<p>Zhu XX, Yang XJ, Chao YL, Zheng HM, Sheng HF, Liu HY et al¹</p>	<p>Cases: 41 patients with nasopharyngeal cancer undergoing three-dimensional conformal RT, associated or not with CT compared to the control group. Control group: n=49 Study type: cohort Age: 34 to 60 years.</p>	<p>Sample: Mucosal swab of the mucositis lesion region or the retropharyngeal region when they did not present lesions Sampling time: prior to irradiation, after the 5th, 10th, 15th, 20th, 25th, 30th and 35th radiation. Microbial analysis: 16S sequencing</p>	<ul style="list-style-type: none"> • Individuals with nasopharyngeal carcinoma harbor significantly more <i>Pseudomonas</i>, <i>Pedococcus</i>, <i>Oscillibacter</i> than healthy individuals. Relative abundances of nine genera: <i>Phenylobacterium</i>, <i>Acinetobacter</i>, <i>Burkholderia</i>, <i>Sphingomonas</i>, <i>Azospirillum</i>, <i>Rhizobium</i>, <i>Hydrogenophaga</i>, <i>Paracoccus</i> and <i>Nocardioides</i> were significantly positively associated with an increase in RTOG (Radiation Oncology Group Criteria), while two genera <i>Leptotrichia</i> and <i>Peptostreptococcus</i> were significantly negatively associated with it 	<ul style="list-style-type: none"> • Changes in oral microbiota correlate with the progression and aggravation of OM induced by RT.
<p>Almståhl A, Finizia C, Carlen A, Fagerberg-Mohlin B, Alstad T¹¹</p>	<p>Cases: 33 Patients with head and neck cancer received bilateral curative RT. CT was generally given as 2 cycles of cisplatin and 5-fluorouracil. Study type: cohort Age: 51 to 67 years.</p>	<p>Sample: Scraped dorsum tongue and bilateral mucosal swab. Sampling time: During treatment, 6 months, 1 year and 2 years post-treatment Microbial analysis: bacterial culture research in selective media anaerobically, microaerobically and aerobically incubated.</p>	<ul style="list-style-type: none"> • On the tongue: streptococci and <i>Neisseria</i> was decrease, whereas lactobacilli and <i>C. albicans</i> increased during treatment. Two years post-treatment, <i>Neisseria</i> and <i>Prevotella</i> still low and <i>Candida</i> remain high. • On the mucosa: lactobacilli and <i>Staphylococcus aureus</i> increased during treatment. Two years post treatment the total count as well as streptococci, <i>Neisseria</i> and <i>Fusobacterium nucleatum</i> were decreased and lactobacilli increased. • 70% showed severe OM during treatment. 	<p>The RT in the head and neck region changes the oral microbiota, increasing the risk of mucosal infections.</p>

<p>Gaetti-Jardim Jr. E, Jardim ECG, Schweitzer CM, Silva JCF, Oliveira MM, Masocatto DC et al⁵</p>	<p>Cases: 28 patients with head and neck cancer of primary lesion under treatment of RT. Control group: n=28 Study type: case-control Age: 18 to 68 years.</p>	<p>Sample: Supra and subgingival plaque. Sampling time: before RT, 15-22 days after RT initiation, immediately after and 6 months after RT. Microbial analysis: bacterial culture research in selective media anaerobically and aerobically incubated.</p>	<ul style="list-style-type: none"> • The severity of OM is related to the presence of xerostomia, candidiasis, precarious oral hygiene, absence of previous dental treatment and predominance of supra and subgingival colonization by representatives of the family Enterobacteriaceae and genus <i>Candida</i>. 	<ul style="list-style-type: none"> • Positive correlation of enteric bacilli with severe OM. • RT induces significant changes in the oral microbiota, with predominance of <i>Enterobacteriaceae</i> and <i>Candida</i> species.
<p>Hou J, Zheng H, Li P, Liu H, Zhou H, Yang X²</p>	<p>Cases: 19 patients with nasopharyngeal cancer (all received RT and 16 of them also received CT) Study type: cohort Age: 35 to 57 years.</p>	<p>Sample: Oropharynx swabbing Sampling time: before irradiation and after 10, 20, 30, 40, 50, 60 and 70 Gy sections of RT. Microbial analysis: 16S sequencing</p>	<ul style="list-style-type: none"> • The phyla Proteobacteria and Spirochaetes showed a tendency to increase, while Fusobacteria showed a decrease. • An increase of <i>Fusobacterium</i>, <i>Treponema</i>, <i>Porphyromonas</i>, and <i>Prevotella</i> are associated with aggravation of OM. 	<ul style="list-style-type: none"> • A dysbiosis in the oral microbiota exacerbates the severity of OM. • Periodontal pathogens are associated with OM. • Gram-negative rods are associated with higher degrees of OM.

P. intermedia, *T. forsythia*, *P. micra*, *F. nucleatum*, *C. rectus* and *S. mutans* decreases after RT initiation, while opportunistic pathogens such as *Staphylococci*, Enteric rods and *Candida sp.* tend to increase in prevalence. However, in general, oral microecological diversity decreases as the dose of radiation increases, but it rises again over time after RT treatment.²⁸

Other factors also contribute to microbial dysbiosis during the head and neck cancer treatment. Xerostomia, for example, another oral manifestation resulting from damage caused to the salivary glands by treatments with CT and RT, also contributes to microbial dysbiosis and development of opportunistic pathogens. The damage to salivary glands leads to reduction of salivary flow, and saliva in turn, has enzymes and antibodies important for the control of the oral microbiota.⁵ These damages may be irreversible³⁰, definitively altering the resident microbiota. Small doses of radiation are able to alter the volume and composition of saliva. Moreover, the severity of the xerostomia is correlated with the radiation dose used.³¹ Saliva contains antimicrobial substances such as lysozyme and immunoglobulin. Changes in saliva due to CT and RT can influence the health/integrity of the mucosa making it more susceptible to microorganisms.⁵

Although the researchers looked for the microorganisms involved in the occurrence of OM, the correlation between specific microorganism and OM severity degree began only recently.^{1,2,5} During RT treatment, bacterial colonization of the oropharynx may favor the development of severe OM being the Gram-negative bacteria and enteric bacilli associated with higher degrees of MO.^{3,2,5} The increase in the number of species of oral yeasts, is also related to the OM aggravation which during the RT is associated with low lymphocytes.^{13,16}

OM affects patients commonly few days after initiation of CT or RT therapy. However, no significant microbiological changes occur in the first 7 days of CT.¹⁴ The signs of OM are due to an inflammatory process in the mucosa, which may lead to ulceration, and consequently to odynophagia, dysgeusia, dysphagia or discomfort,⁵ symptoms very impacting to the individual general health that can lead to cancer treatment interruption. The inflammatory characteristics of OM and the immune defense suppression are important for the microbial ecosystem imbalance of the mouth and this dysbiosis may exacerbate the severity of this inflammation.^{5,1,2,11,15} These factors, together with the ulcerations generated in OM, serve as gateways for a greater number of pathogenic microorganisms,¹² as the periodontopathogens that are strongly found in the mouth cancer and are associated with OM.^{27,2}

Considering fungal colonization, it begins to increase during the second week of CT and its apogee takes place during the sixth week.²⁹ When systemic opportunistic infections are detected, the identification

of the causative agents and their susceptibility will allow the early identification of the treatment options.¹⁹ According to Singh et al¹⁴, the use of prophylactic Fluconazole in patients under treatment with RT and CT has the potential to reduce the morbidity associated with OM. Considering RT, after the end of this therapy, there was a decrease in the number of patients presenting any type of *Candida*,²⁹ but the degree of OM increases simultaneously with the increase of oral yeasts species during RT.¹³ The most prevalent yeasts are *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. subliniensis* and *S. cerevisiae*.¹⁹ In addition, the total RT dose, the RT method, the OM and the minimal lymphocyte count during RT are significantly associated with the incidence of oral candidiasis.¹⁶

A variation of the bacterial composition during the CT is more evident in patients who develop the MO,¹¹ while OM is more present in patients who undergo radical RT treatment.³ The bacterial colonization of patients who have mouth cancer, are predominant in phyla Firmicutes, Bacteroidetes, Actinobacterias,^{23,27} Proteobacteria,^{22,23,27} and Actinobacteria.²⁷ According to Schmidt et al²¹ occurs a significant reduction of Firmicutes and Actinobacteria in cancerous regions when compared to anatomically normal regions. The most prevalent genera are *Streptococcus*, *Prevotella*,^{23,26,27} *Neisseria*,^{23,25,27} *Veitonella*,^{23,26} *Fusobacteria*, *Haemophilus* and *Porphyromonas*.^{27,26} The Actinobacteria, besides being related to CA is also related to potentially malignant lesions (PML).^{22-23,27} On the other hand, the genera of bacteria most associated with OM aggravation are *Fusobacteria*, *Treponema*, *Porphyromonas*, *Prevotella*,² *Phenyllobacterium*, *Acinetobacter*, *Bukholderia*, *Sphingomonas*, *Azospirillum*, *Rhizobium*, *Hydrogenophaga*, *Paracoccus* and *Nocardioides*, while the genera *Leptotrichia* and *Peptostreptococcus* are negatively related to the increase in severity of OM.¹ The most severe cases of OM have a tendency of a greater growth of *Neisseria* in the tongue and a decrease of growth of *Prevotella*, *S. Aureus*, *Candida* and Gram-negative.¹² Furthermore OM severity is related to xerostomia, candidiasis, poor hygiene, absence of previous dental treatment,⁵ sub- and supragingival colonization of Enterobacteriaceae and *Candida*.^{5,12}

It is known that RT and/or CT treatment leads to alteration in the oral microbiota, favoring the development of MO. Studies that correlate microbiota and OM are important to consider treatment possibilities since changes in the oral microbiota are significant and may impair the patient's health status. However, for the complete understanding of the processes involved in the development and progression of OM, other aspects such as the differences between the chemotherapeutics and doses of radiotherapy used, among others, should be considered. Therefore, it is extremely relevant to take care of the patient oral health prior to the start of antineoplastic therapy.

CONCLUSIONS

From the reviewed literature, it has been scientifically proven that changes in the oral microbiota are correlated with the progression and worsening of radiation-induced OM. However the microbial core for the disease has not yet been defined, since there is no consensus on sample type methodologies, time of therapy, patient characteristics, among others.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

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