Impact of Antineoplastic Treatment on Oral Cavity and Oropharyngeal Microbiota of Head and Neck Cancer Patients: Systematic Review

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Impacto do Tratamento Antineoplásico na Microbiota da Cavidade Oral e Orofaríngea de Pacientes Acometidos pelo Câncer de Cabeça e Pescoço: Revisão Sistemática

Impacto del Tratamiento Antineoplástico en la Microbiota Oral y Orofaríngea de Pacientes Afectados por el Cáncer de Cabeza y Cuello: Revisión Sistemática

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ABSTRACT

Introduction: A great diversity of microorganisms are found in the oral and oropharyngeal cavities, which are normally in homeostasis with other microorganisms and the host itself. Patients with head and neck cancer undergoing cancer treatment may trigger physiological changes in their bodies and impact the resident microbiota. **Objective:** Systematically review studies on the impact of antineoplastic treatment on oral and oropharyngeal microbiota in patients with head and neck cancer. **Method:** Systematic review carried out between April and June 2020. Articles were searched in the Virtual Health Library, Google Scholar, PubMed and ScienceDirect databases in English, utilizing the descriptors "head and neck neoplasms", "mouth neoplasms" and "microbiota" and "*neoplasias de cabeça e pescoço*", "*neoplasias bucais*" and "*microbiota*" in Portuguese. Original articles available in full, published in the last decade (2010 to 2020), in Portuguese and English were selected. **Results:** 8 articles were included in this review. Most of studies have shown quantitative changes in resident microorganisms or invasion of exogenous bacteria in patients in antineoplastic treatment; uncontrolled microbiota homeostasis triggered cariogenic and inflammatory processes in the mucosa. **Conclusion:** Changes in the microbiome of the oral cavity and oropharyngeal resulting from antineoplastic treatment may be predisposing factors for adverse effects as the development of caries and oral mucositis.
Key words: mouth neoplasms; head and neck neoplasms; microbiota; antineoplastic agents.

RESUMO

Introdução: As cavidades oral e orofaríngea apresentam uma grande diversidade de micro-organismos que se encontram normalmente em homeostase com outros micro-organismos e o próprio hospedeiro, contudo, pacientes com câncer de cabeça e pescoço submetidos ao tratamento oncológico podem desencadear modificações fisiológicas nos seus organismos, assim como impactos na sua microbiota residente. **Objetivo:** Revisar sistematicamente os estudos sobre o impacto provocado pelo tratamento antineoplásico sobre a microbiota oral e orofaríngea em pacientes com câncer de cabeça e pescoço. **Método:** Revisão sistemática, realizada entre abril e junho de 2020. Busca nas bases de dados Biblioteca Virtual em Saúde, Google Acadêmico, PubMed e *ScienceDirect.* Utilizaram-se os descritores "head and neck neoplasms", "mouth neoplasms" e "microbiota" em inglês; e "neoplasias de cabeça e pescoço", "neoplasias bucais" e "microbiota" em português. Foram selecionados artigos originais e disponíveis na íntegra, publicados na última década (2010 a 2020), nos idiomas português e inglês. **Resultados:** Foram incluídos oito artigos nesta revisão. Assim, a maioria dos estudos apresentou alterações na quantidade de micro-organismos residentes ou invasão de bactérias exógenas nos pacientes submetidos ao tratamento antineoplásico; o descontrole da homeostase da microbiota desencadeou processos cariogênicos e inflamatórios na mucosa. **Conclusão:** As alterações no microbioma da cavidade oral e orofaríngea advindas do tratamento antineoplásico podem ser fatores de predisposição a efeitos adversos no indivíduo, como desenvolvimento de cárie e mucosite oral.
Palavras-chave: neoplasias bucais; neoplasias de cabeça e pescoço; microbiota; antineoplásicos.

RESUMEN

Introducción: Las cavidades bucal y orofaríngea presentan una gran diversidad de microorganismos que normalmente se encuentran en homeostasis con otros microorganismos y su propio hospedador, sin embargo, los pacientes con cáncer de cabeza y cuello sometidos a tratamiento contra el cáncer pueden desencadenar cambios fisiológicos en tu cuerpo, así como también impactos en su microbiota residente. **Objetivo:** Revisar sistemáticamente los estudios sobre el impacto del tratamiento antineoplásico en la microbiota oral y orofaríngea en pacientes con cáncer de cabeza y cuello. **Método:** Revisión sistemática realizada entre abril y junio de 2020. Se buscaron artículos en las bases de datos de la Biblioteca Virtual en Salud, Google Scholar, PubMed y ScienceDirect. Se utilizaron los descriptores "head and neck neoplasms", "mouth neoplasms" and "microbiota" en inglés y "neoplasias de cabeça e pescoço", "neoplasias bucais" e "microbiota" en portugués. Incluyeron artículos originales y disponibles en su totalidad, publicados en la última década (2010 a 2020), en portugués e inglés. **Resultados:** En esta revisión se incluyeron ocho artículos. Así, la mayoría de los estudios han mostrado cambios en el número de microorganismos residentes o invasión de bacterias exógenas en pacientes sometidos a tratamiento antineoplásico, la homeostasis de la microbiota sin controle desencadena procesos cariogénicos e inflamatorios en la mucoso. **Conclusión**: Los cambios en el microbioma de la cavidad oral y orofaríngea por el tratamiento antineoplásico pueden ser factores predisponentes a los efectos adversos en el individuo, como el desarrollo de caries y mucositis oral.
Palabras clave: neoplasias de la boca; neoplasias de cabeza y cuello; microbiota; antineoplásicos.

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INTRODUCTION

Malignant tumors of the lip, oral cavity, pharynx, larynx, nasal cavity and thyroid are grouped as head and neck cancers. Oral cavity (buccal mucosa, gingiva, hard palate, tongue and floor of the tongue), the pharynx (oropharynx and hypopharynx), nasal cavity and paranasal sinuses, the glottic, supraglottic larynx and glands are the main locations affected in this group of neoplasms. Nearly 49% of the lesions occur in the oral cavity, 15% in the pharynx, 25% in the larynx and the remaining 20% are distributed in other locations[1]. The number of new cases of oral cavity cancer anticipated for Brazil for each year of the triennium 2020-2022 is 11,200 in males and 4,010 in females[2].

Typically, head and neck cancer is diagnosed at advanced stages[3]. Delay of diagnosis and modality of treatment eventually lead to more aggressive therapeutic and treatment-associated adverse effects[4]. Radiotherapy is usually the first choice centered to the head and neck and can trigger adverse effects as mucositis, xerostomia, dysgeusia, odynophagia and infections[5].

More than 700 species of microorganisms are found in the regions of oral cavity and oropharynx; it is estimated that several species were not catalogued taxonomically, considering that the similarity of its genetic material with species already registered impedes a complete description of the microbial bioma[6]. The bacterial phyla already identified and more prevalent are *Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria* and *Fusobacteria*, while the genera of bacteria with great predominance are *Streptococcus, Actinomyces, Veillonella, Fusobacterium, Porphyromonas, Prevotella, Treponema, Neisseria, Haemophilis, Lactobacillus, Capnocytophaga, Eikenella, Leptotrichia, Peptostreptococcus, Staphylococcus* and *Propionibacterium*[7,8].

Among the genera quoted, *Streptococcus* is more frequent, a Gram-positive *coccus* bacteria. Even belonging to the resident microbiota, some species as *Streptococcus mutans* in favorable conditions to its proliferation can cause dental caries as they are able to ferment a large variety of sugars[9]. In addition, bacteria as *Enterococcus faecalis, Enterococcus faecium* and *Escherichia coli*, common in the gastrointestinal tract can colonize accidentally the oral cavity through water and contaminated food, infected objects or even contact with contaminated feces and may trigger infectious processes[10,11].

Fungi are found in lower quantity but play a key role in maintaining the balance of the oral microbiota, the genera *Candida, Cladosporium, Aureobasidium, Saccharomyces, Aspergillus, Fusarium* and *Cryptococcus* can be found. The genera *Candida,* basically the species *Candida albicans,* can be a risk factor for infections called candidiasis mainly in immunocompromised patients[12].

It is known that in healthy conditions, the microbiota relates to a status of homeostasis with the host, similar to what occurs with other interactions among microorganisms in different parts of the human body[13]. These microorganisms played a key role for the construction of an ideal environment for its survival, better absorption of nutrients, interaction with other species through microbial communication, regulating the rates of microbial growth and even protecting the host against exogenous microorganisms with pathogenic potential[14]. Among the factors that influence the relation among interactions involved by microorganisms and their *habitat,* stand out the temperature, pH, presence of oxygen (potential oxidation-reduction), nutrients (endogenous and exogenous) and the own defense system of the host[15]. All these factors are indispensable in the microbiota in the process health-disease because they modulate the colonization by certain microorganisms which are able to survive and proliferate in the environment and establish the resident microbiota[16].

Paradigms still exist about the effects of the antineoplastic treatment in relation to the microorganisms living in the oral cavity and oropharynx. Patients in antineoplastic treatment eventually have their immune system compromised in addition to being affected by the reduction of salivary flow and possibly mucositis, which makes the break of the homeostasis of the microbiota more susceptible creating a habitat more prone to infections, either by resident microorganisms that proliferate uncontrollably or invasion and fixation of exogenous pathogenic organisms. This problematic can provoke the worsening of the clinical status of the patient possibly leading to the discontinuation of the antineoplastic treatment[17]. In this context, microorganisms, mainly bacteria, can bring antibiotics multi-resistance and high percentage of virulence, aggravating the infectious process and even sepsis. The "*Instituto Latino-Americano de Sepse* (ILAS)"[18] estimates that 400 thousand cases of sepsis are diagnosed annually in Brazil, provoking approximately 240,000 deaths. The mortality rate in the country is 65% of the cases, 25% higher than the world mean (30%-40%). Still according to ILAS, 25% of beds occupation in Intensive Care Units (ICU) occur by sepsis, the main cause of deaths in these rooms[18].

Understanding microbiota shifts provoked by head and neck treatment can identify the impacting aspects over the patient survivorship to support better planning and reduction of adverse reactions. The goal of the present systematic review was to comprehend thoroughly the content of the shifts, colonization and prevalence of bacteria and fungi associated with antineoplastic treatment in individuals with head and neck cancer analyzing national and international scientific productions.

METHOD

Evidence-based practice has been ensuring an increase of systematic literature reviews considered secondary studies with primary investigations as their source, which are scientific studies reporting results of observational or experimental researches[19]. It is a systematic review of the literature carried out between April and November 2020 according to the methodology Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[20] and registered at International Prospective Register of Systematic Reviews (PROSPERO) with number CRD42021219974.

During this period, different types of studies were evaluated in the databases Virtual Health Library (BVS), Google Scholar, PubMed and ScienceDirect containing MeSH (Medical Subject Headings) descriptors or its equivalent in DeCS (Health Science Descriptors): "head and neck neoplasms", "mouth neoplasms" and "microbiota" in English and "*neoplasias de cabeça e pescoço*", "*neoplasias bucais*" and "*microbiota*" in Portuguese.

The following combinations were utilized for search strategies: "head and neck neoplasms" OR "mouth neoplasms" AND "*microbiota*", "*neoplasias de cabeça e pescoço*" OR "*neoplasias bucais*" AND "microbiota". The inclusion criteria were articles published between April 2010 and April 2020 (available in English or in Portuguese) addressing studies with human beings evaluating the interaction of oral microbiota and oropharynx in oncologic treatment.

Review articles, studies which failed to enroll patients in use of some antineoplastic treatment and articles in other languages than Portuguese and English were excluded. The Qatar Computing Research Institute (QCRI) software Rayyan was utilized for filing, organization and selection of articles dynamically and safely[21].

After searching the databases and application of search strategies, the articles were exported to Rayyan and the duplicates were identified. Titles and abstracts were reviewed by two investigators to determine the eligibility according to the inclusion criteria and discrepancies were resolved among them. A third investigator was called in if discrepancies still persisted to reach a consensus to minimize potential biases as misinterpretation and design of the studies.

RESULTS

670 articles were found after searching the four databases. After removing 26 duplicate articles, 644 articles remained. At ScienceDirect, 331 articles were found. Of these, 327 were excluded after reading the abstracts for failing to meet the inclusion criteria. 218 articles were found at Google Scholar, 211 were excluded after reading the abstracts. At PubMed, 63 articles were encountered, 58 were excluded after reading the titles and abstracts. Virtual Health Library provided 32 publications, 28 were excluded after reading the abstracts. Ultimately, 8 articles remained after applying eligibility, inclusion and exclusion criteria. Figure 1 summarizes the selection process.

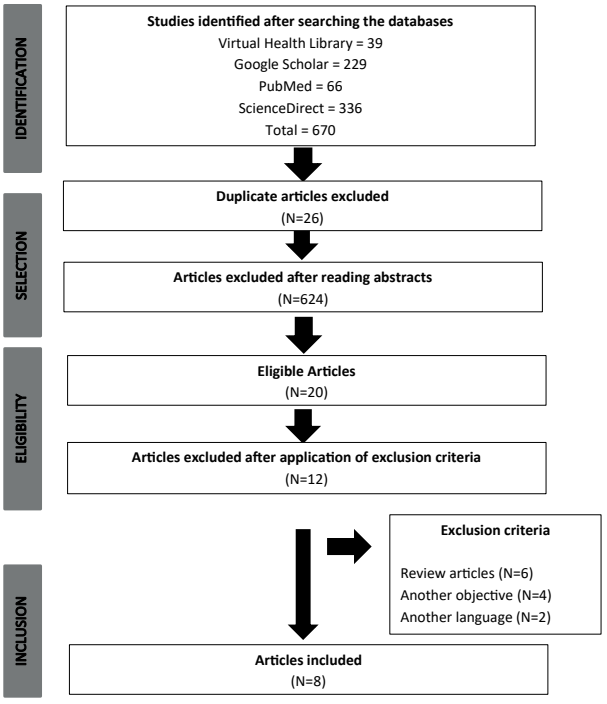

Figure 1. PRISMA flowchart for systematic review with identification of the studies

Table 1 shows the characteristics of the articles included per author, year of publication, local, type of the study, number of samples, gender, age-range and classification of the cancer.

The publications referenced in the current study were published from 2011 to 2019 in the scientific journals Archives of Health Investigation, EBioMedicine, Journal of Oral Microbiology, *Nutrición Hospitalaria*, PloS One and *Revista Brasileira de Cancerologia*; the types of the studies comprehended cohort studies (n=7; 87.5%) and cohort case-control (n=1; 12.5%). South America and Asia were the origin of most of the studies investigated, both accounting for 37.5% (n=3) with the contributions of Brazil and China (n=3; 37.5%; n=3; 37.5%), followed by North America (USA) (n=1; 12.5%) and Europe (Spain) (n=1; 12.5%). No articles were selected from Africa and Oceania.

Table 1. Characteristics of the studies evaluating the interaction of the microbiota in patients with head and neck cancer in antineoplastic treatment

Author/ year	Local	Type of study	Population (N)	Gender	Age-range	Classification
Gaetti--Jardim Jr et al., 2011	Brazil	Cohort study	50 patients	38 M and 12 F	16 to 80 years (mean 59.5)	44 patients had squamous cell carcinoma, 4, acinic cell carcinoma, 1, basaloid squamous cell carcinoma and another, undifferentiated malignant neoplasm
Simões et al., 2011	Brazil	Cohort study	21 patients	-	32 to 94 years	The most affected was the base of the tongue (6 cases) followed by larynx (5 cases). In 95% of the cases, the histological type encountered was squamous cells carcinoma and the other case diagnosed was metastatic lymphoepithelial carcinoma
Hu et al., 2013	China	Cohort study	8 patients	-	26 to 70 years	-
Souza et al., 2015	Brazil	Cohort study	50 patients	36 M and 14 F	18 to 78 years (mean 51.3)	42 had squamous cells carcinoma, 5, undifferentiated malignant neoplasms, in addition to 3 cases of basosquamous carcinoma
Vidal--Casariego et al., 2015	Spain	Cohort study	35 patients	26 M and 9 F	Mean 63.8	14 had cancer in the larynx region, 9, oral cavity, 4, pharynx and 8, other locations
Zhang et al., 2015	China	Case-control/ cohort	21 patients (12 control group; 9 case group)	-	-	Nasopharynx localized carcinoma
Zhu et al., 2017	China	Cohort study	41 patients	27 M and 14 F	22-75 years (mean 47.2)	Nasopharynx carcinoma
Mougeot et al; 2019	USA	Cohort study	31 patients	26 M and 5 F	24 to 84 years (mean 56.8)	Squamous cells carcinoma

Captions: M = Males; F = Females.

There were 257 participants in the eight studies included, being 153 (59.53%) males, 54 (21.01%), females and 50 (19.45%) unidentified by the authors. Of the total, 12 were the control group who were not diagnosed with cancer and 245 had some type of head and neck cancer in the following anatomic sites: nasopharynx (n=50; 20.4%), larynx (n=19; 7.75%), oral cavity (n=9; 3.7%), tongue (n=6; 2.44%), pharynx (n=4; 1.63%) and (n=157; 64.08%) without information about the site affected.

The histological profile of the tumors reported in the studies was carcinoma (n=196; 80%) and undifferentiated malignant neoplasms (n=6; 2.44%); in 43 individuals (17.55%), there was no histological classification. It was possible to group the types of carcinomas as squamous cell carcinoma (n=137; 69.89%), basosquamous (n=4; 2.04%), acinar cells (n=4; 2.04%) and metastatic lymphoepithelial (n=1; 0.51%). In 25.51% (n=50), there was only the information that it was named as carcinoma.

All the articles (n=8; 100%) reported the predominance of radiotherapy to treat head and neck cancer with or without other therapy; thus, radiotherapy concomitant with chemotherapy or with induction chemotherapy

was reported in five studies (62.5%). Two studies (25%) reported the use of radiotherapy and surgery associated. The findings about the objectives, time of sample collection and conclusion of the studies selected are shown in Table 2. Table 3 presents the dental conditions and microbiological aspects of the studies which evaluated the interaction of the microbiota due to antineoplastic treatment of HNC patients.

Table 2. Characteristics of the studies investigating the interaction of the microbiota in the antineoplastic treatment of patients with head and neck cancer

Author/year	Objectives	Timepoint of sample collection	Dental interventions	Conclusion
Gaetti-Jardim Jr et al., 2011	Evaluate the occurrence of yeasts, pseudomonas and enteric bacteria in the oral cavity of patients submitted to RT to treat head and neck cancer	Before the dental treatment and RT (stage 1), immediately after the end of RT (stage 1), immediately after the end of RT (stage 2) and 30 days after the end of RT (stage 3)	Only 38% of the patients sought dental treatment, consisting of dental extractions, periodontal treatment and restorative treatment. In addition, all the patients were guided to use 5 ml of oral suspension containing 100,000 U/ml of aqueous nystatin 3 times a day to prevent oral candidiasis during RT	Modifications of the oral mean due to the RT treatment appear to facilitate the colonization of the oral cavity by members of the family *Enterobacteriaceae*, genera *Enterococcus* and *Candida*
Simões et al., 2011	Identify the presence of species of *Candida* and analyze the possibility of this fungi to act as aggravating factor of mucositis in patients with head and neck cancer undergoing antineoplastic treatment	Minimum period of 2 weeks in RT alone or associated with CT	-	The patients investigated had positive correlation between oral mucositis lesions and fungal colonization by *Candida*
Hu et al., 2013	Explore the dynamic of core microbiome of the oral microbiota in the supragingival plaque in the course of RT of head and neck	All samples collected over 7 sampling time points during 7 weeks. Those collected before the treatment with no dose received were utilized as control group	Evaluation of buccal health before RT. When needed, caries were restored, endodontic treatment carried out and suspicious teeth removed. Patients were guided about oral hygiene, but no fluor therapy was applied	140 genera belonging to 13 phyla were found. 4 phyla (Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria) and 11 genera (*Streptococcus, Actinomyces, Veillonella, Capnocytophaga, Derxia, Neisseria, Rothia, Prevotella, Granulicatella, Luteococcus* and *Gemella*) were found in all subjects, supporting the concept of a core microbiome
Souza et al., 2015	Evaluate the occurrence of opportunistic microorganisms of the family *Enterobacteriaceae* and genera *Enterococcus* and *Staphylococcus* in the buccal microbiota of oncologic patients submitted to RT of head and neck	Before radiotherapy, 15-22 days after the beginning of the treatment, immediately after the end of RT, 30 days after the treatment, 6 and 12 months after the end of the therapy	Only 36% of the patients followed the orientation of RT clinics and sought dental treatment prior to RT, and only 16% of the patients were caries-free in the beginning of RT. All the patients were guided on brushing techniques, flossing and hygiene of prosthetics when samples were collected	The results suggested that buccal colonization by opportunistic microorganisms was frequent and stable along the time but without a clear correlation with buccal health and intensity of the radiotherapy treatment
Vidal-Casariego et al., 2015	Demonstrate whether the modality of the treatment, nutritional status and oropharynx flora contribute for the development of mucositis in head and neck cancer treated with RT	Before RT (enrollment), in the middle and after of RT	-	Isolation of bacterial pathogens in oropharynx can favor the development and aggravation of oral mucositis

to be continued

Table 2. continuation

Author/year	Objectives	Timepoint of sample collection	Dental interventions	Conclusion
Zhang et al., 2015	Investigate the relation between salivary function, oral microbiota and absence of radiation caries	12 to 36 months post RT	-	No clear correlation between the characteristics of the salivary microbiota of the patient and radiation caries one year after RT. These outcomes suggest that the salivary function in patients irradiated does not recover fully after 12 to 36 months but pH values and buffering capacity return to normal after one year or more after RT
Zhu et al., 2017	Investigate dynamic changes in the oral bacterial profile and correlations between the severity of mucositis and bacterial shifts during RT	Before the irradiation, after the 5th, 10th, 15th, 20th, 25th, 30th and 35th irradiation	Before the beginning of the treatment all the patients were examined physically once and instructed about oral hygiene. Surgical procedures were applied in patients with caries, pulpal diseases and gingivitis, including professional dental cleaning, filling, endodontic treatment and extraction of non-restorable teeth	Oral microbiota shifts correlate with the progression and aggravation of RT-induced mucositis in patients with nasopharynx carcinoma
Mougeot et al., 2019	Characterize the oral microbiome of patients with HNC who underwent RT at baseline (T0) and 6 (T6) and 18 (T18) months after RT and determine if there were relationship with increased caries	In three moments: before RT, 6 months after the treatment with RT and 18 months after RT	Oral hygiene included brushing at least twice a day, daily flossing and application of a prescription fluoride toothpaste daily	These data suggest that the baseline microbiome difference is an important factor that can explain dental caries outcome in radiation-treated HNC patients. The data suggest cariogenic role of *P. melaninogenica* and potential protective role of certain bacterial species as *A. defectiva*, however more detailed studies are necessary for confirmation

Captions: RT = radiotherapy; CT = Chemotherapy; HNC = Head and neck cancer.

DISCUSSION

Male patients in this study are more affected by head and neck cancer concurring with world statistics[22]. Among the histopathological profiles, most of the studies indicated squamous cells carcinoma as the most prevalent also in conformity with scientific literature[23,24]. Radiotherapy was the main therapy utilized for head and neck cancers in line with the majority of international protocols of antineoplastic treatment[22].

The microbiota of the oral cavity and oropharynx shift during antineoplastic treatment according to several studies[25-31]. The treatment sequelae as mucositis, xerostomia and depression of immune system directly affect the relation of homeostasis among microorganisms and the health of the host, transforming the already resident microorganisms in potential pathogens[31-33].

Five of these studies reported the oral care adopted for the patients: three of them prepared a protocol of adjustment of buccal environment to restorative, periodontal and surgical procedures, in addition to oral hygiene[26,29,30] and two of them, only oral hygiene instructions[25,27]. Even though, in none of the studies selected oral care was a methodological variable of the study because it was adopted for all the patients. The other studies did not mention any type of dental intervention[28,31,33]. Additionally, one of the studies with adjustment of the buccal mean of the patients concluded that only 38% of the patients sought dental treatment[30], while another study described that only 36% of the patients followed the guidelines of radiotherapy clinics and sought treatment prior to radiotherapy[27].

The genera *Candida* is the most predominant among resident fungi of the oral cavity[32], however, several

Table 3. Characteristics of the dental conditions and microbiological aspects of the studies evaluating the interaction of the microbiota during the antineoplastic treatment of patients with head and neck cancer

Author/year	Dental conditions	Bacteriologic alterations of the microbiota	Mycological alterations of the microbiota
Gaetti-Jardim Jr et al., 2011	Complete dentures or dental status (presence or absence of cavitated caries) held no influence on mucositis (chi-square test, p=0.139). Periodontal status did not influence mucositis (chi-square test 0.779). Mucositis was associated with xerostomia (chi-square test 0.021)	Initially, before RT, enteric macroorganisms were cultivated from oral mucosa samples and identified as *E. faecalis* and *Citrobacter freundii*. In addition, 30 days after RT, enteric bacteria and *Pseudomonas* were cultivated in 77.8% of edentulous patients and in 46.9% of dentate patient. Edentulous patients had more frequency of oral colonization by enteric microorganisms (p=0.038) and RT was associated with significant increase of these microorganisms (p<0.001)	15 patients (30%) were initially colonized by Candida spp, increasing to 78% soon after RT and 84%, 30 days after RT; the increase was not directly associated with the dental or periodontal condition. 30 days after the RT, yeasts were recovered from all the edentulous individuals and 75% of all the dentated. Fungi isolates were identified as *Candida albicans, C. tropicalis, C. krusei, C. glabrata* or *C. parapsilosis*. The presence of *C. albicans* concomitantly with non-albicans *Candida species* was particularly common after RT
Simões et al., 2011	-	-	Most of the patients investigated received irradiation of 2.880cGy and 6.160cGy and in only 3, proliferation of *Candida* fungi was not detected. 19 cases had fungal colonization. The patients investigated had positive correlation between oral mucositis lesions and fungal colonization
Hu et al., 2013	Patients with untreated cavitated caries or oral abscesses and unable to keep oral hygiene during the study were excluded	Only 2 genera (*Streptococcus* and *Actinomyces*) were present in all points during RT from 10 Gy to 60 Gy. The relative abundance of *Streptococcus* varied between 21.33% (20 Gy) and 3.2% (50 Gy), and of *Actinomyces* remained stable (nearly 4.48% to 4.85%) in the initial of time points (10 Gy, 20 Gy, 30 Gy) but raised to 23.32% in the time point of 50 Gy. Several other genera including *Veillonella, Capnocytophaga, Derxia, Neisseria, Rothia, Prevotella, Granulicatella, Luteococcus* and *Gemella* were identified in some moment in the subjects during RT (10 Gy-60 Gy)	
Souza et al., 2015	The patients presented quite variated conditions of buccal hygiene, 18% were satisfactory, 36%, regular and 46% , poor conditions. A significant deterioration was detected during and immediately after RT because of visible biofilm accumulation (chi-square test, p=0.042). All the patients who developed mucositis grades III and IV had poor dental hygiene (chi-square test, p<0.001)	The presence of species of the family *Enterobacteriaceae, Enterococcus* and *Staphylococcus*. It was believed initially that the hypothesis of poor buccal hygiene common in the patients investigated could be the main factor for the transmission of microorganisms found, in addition to mucositis and xerostomia, which would deteriorate the already poor buccal status. The isolated role of these factors would suggest that the presence of microorganisms in the patients could be temporary. However, the target-microorganisms were present in a significant portion of the patients during the evaluation and increased with RT and continued in high levels even 12 months after the conclusion	
Vidal-Casariego et al., 2015	-	Bacterial colonization was found in 28.6% (10/27) of the patients and the isolated species included *Staphylococcus aureus* (3/10), *Escherichia coli* (3/10), *Pseudomonas aeruginosa* (2/10), *Serratia* spp. (2/10), *Enterobacter cloacae* (2/10), *Citrobacter freundii* (2/10), *Klebsiella oxytoca* (1/10) and *Agrobacterium radiobacter* (1/10). In 4 cases, more than one bacterial specie was isolated	Fungi were cultivated in 35.3% (12/35) of the patients: 11 samples matched *Candida albicans* and 1, *Candida tropicalis*

to be continued

Table 3. continuation

Author/year	Dental conditions	Bacteriologic alterations of the microbiota	Mycological alterations of the microbiota
Zhang et al., 2015	Individuals with recent post-RT dental caries and those with periodontitis were excluded	11 genera were found (*Streptococcus, Neisseria, Scardovia, Porphyromonas, Fusobacteria, Lautropia, Veillonella, Capnocytophaga, Rithia, Leptotrichia* and *Prevotella*), being *Streptococcus* spp. and Neisseria spp. present in more than 80% of the samples	-
Zhu et al., 2017	Patients with poor buccal hygiene and/or severe periodontal diseases were excluded	Significantly higher relative abundance of *Streptococcus* was found in cases of mucositis grades III and IV. In addition, comparing with healthy individuals, oncologic patients enrolled harbored significant higher abundance of *Pseudomonas*, *Pediococcus* and *Oscillibacter* in oropharynx all of them associated with human infections	-
Mougeot et al., 2019	Two groups were investigated, one with patients who developed caries and the other who did not develop dental caries	Species *Streptococcus* mutans increased in 6 months post-treatment in patients with and without increase of dental caries. Species *Prevotella melaninogenica* diminished in 6 months after antineoplastic treatment without increase of dental caries. The health-related species *Abiotrophia defeituosa* diminished in the group of patients with increase of dental caries	-

Caption: RT = Radiotherapy.

alterations its host is submitted to during antineoplastic therapy can modify its harmonic position in the microbial balance. Vidal-Casariego et al.[28] cultivated yeasts in 35.3% of the patients with cancer in treatment having 11 (97.7%) samples corresponding to species *Candida albicans* and one (8.3%) to *Candida tropicalis*[28] with lower number than the variety of isolate species in the study of Gaetti-Jardim Jr et al.[30] who identified in 84% of the patients after 30 days of radiotherapy sessions the following fungi species: *Candida albicans, C. tropicalis, C. krusei, C. glabrata* and *C. parapsilosis*. Even with the orientation to suspend nystatin during radiotherapy, the proliferation of fungi *Candida* spp. occurred, which is related to low adherence of the patient, therefore, dental follow-up is important for an effective therapeutic[30].

In addition, the study of Gaetti-Jardim Jr et al.[30] identified a raise of 78% of the fungi *Candida* spp. immediately after the end of the radiotherapy treatment and of 84%, 30 days after the last session and are associated with the manifestation of mucositis grades III and IV[30]. This data is compatible with the study of Simões et al.[31] which showed the development of candidiasis in association with oral mucositis grades III and IV, proving the positive correlation between the lesions and fungal colonization by *Candida*[31].

In the isolates of Gaetti-Jardim Jr et al.[30], prior to radiotherapy, the enteric microorganisms were cultivated from oral mucosa samples of four edentulous patients (22.5%) and subgingival biofilms of three dentate patients (9.4%), being identified exogenous bacteria with pathogenic potential as *E. faecalis* in six samples of edentulous or dentate patients and *Citrobacter freundii* in a sample of one edentulous patient. Besides, 30 days after the end of the radiotherapy treatment, enteric bacteria and pseudomonas were cultivated in 77.8% of edentulous patients and in 46.9% of dentate patients, determining *Citrobacter, Enterobacter, Enterococcus, Klebsiella, Morganella, Proteus* and *Pseudomonas* as the genera most frequent detected. Edentulous patients had more frequency of oral colonization by enteric microorganisms and radiotherapy was associated with a significant raise of the occurrence of these microorganisms, which was not associated with gingivitis or periodontitis, but were seen more frequently in tobacco users and patients with oral mucositis level III or IV[30].

In the study of Souza et al.[27] it was possible to find, after the therapy began, that the first microbial group, whose prevalence raised, was of members of the family *Enterobacteriaceae* in the first two to three weeks of treatment and in the end of the radiotherapy, lasting in the sub and supragingival biofilm, saliva and mucosa of the irradiated 12 months after radiotherapy. The occurrence of Gram-positive *coccus* did not rise in the beginning of the radiotherapy, but *E. faecalis* was more prevalent

in the end, keeping high occurrence one year after the conclusion of the radiotherapy treatment. Similar results were obtained for genera *Enterococcus* and *Staphylococcus,* while *E. faecium* did not present significantly modified occurrence by radiotherapy. The presence of members of the family *Enterobacteriaceae* and *E. faecalis* was related to the conditions of oral hygiene, predominating in patients with poor hygiene. After 12 months of evaluation only in the patients who developed oral mucositis grades II and III there was colonization by *Enterococcus spp*. and/or Gram-negative rods of the family *Enterobacteriaceae*[27].

The results of Vidal-Casariego et al.[28] revealed the isolation of pathogens in the oropharynx in 28.6% of the patients who developed oral mucositis; the isolated strains included S*taphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Serratia spp, Enterobacter cloacae, Citrobacter freundii, Klebsiella oxytoca,* and *Agrobacterium radiobacter*. There was no significant difference in the microbial colonization regarding sex, local and cancer stage[28].

In the study of Hu et al.[29], samples of the supragingival plaque collected from the buccal gingival surfaces of the first upper molar in patients in radiotherapy during six weeks of treatment identified 11 microbial genera (*Streptococcus, Actinomyces, Veillonella, Capnocytophaga, Derxia, Neisseria, Rothia, Prevotella, Granulicatella, Luteococcus* and *Gemella*) which were designated as nuclear microbiome in the present study, alternating its relative abundance during the course of radiotherapy. The genera *Streptococcus* was more prevalent in all the subjects during the six sessions and consisted in a great number of cariogenic and non-cariogenic species including *S. sobrinus*, *S. mutans*, *S. oralis*, *S. mitis* and *S. pneumonia*. The genera *Actinomyce* was the second more prevalent[29]. In concurrence, the studies of Zhu et al.[26] have also identified significantly greater relative abundance of *Streptococcus* in patients who had mucositis grades III and IV also related to the progression and worsening of radiotherapy-induced mucositis in patients with nasopharyngeal carcinoma. In the same study, for some patients, significantly greater abundances of *Pseudomonas*, *Pediococcus* and *Oscillibacter* were detected in oropharynx, all of them associated with human infections. These results showed that the shifts in the oral microbial community correlated with the progression and worsening of radiotherapy-induced mucositis in oncologic patients and the search for dental strategies for early treatment and prevention of the incident of severe mucositis during radiotherapy are essential[26].

Patients submitted to radiotherapy have high risk of radiation caries, it is one of the late complications of the treatment. Mougeot et al.[25] conducted a study with two groups of patients, one with increase of dental caries and the other, where no increase was detected. Reduction of the species *Prevotella melaninogenica* was found, frequently associated with caries in small children, in six months after the radiotherapy in the group of individuals with no increase of caries, while the species associated with the health of the host, *Abiotrophia defectiva*, diminished in the group of patients with increase of dental caries. Still, it was noticed that the predominance of the species *Streptococcus mutans* increased in six months after the radiotherapy in patients of the two groups, a microorganism closely associated with caries. Consequently, it is critical to verify how radiotherapy can cause shifts in the profiles of the microbiota of oncologic patients and result in weaknesses of the defense of the host that can be augmented for non-conformity with good practices of oral hygiene[25].

However, Zhang et al.[33] conducted a case-control cohort study where they analyzed the saliva of patients 12 to 36 months from the treatment end, finding 80% of the total bacteria of the species *Streptococcus* spp. and *Neisseria* spp. and similar distributions were detected in the control-group. No clear correlation was found between the characteristics of the salivary microbiota of the patient and caries by radiation one year after the treatment. They suggested still that the salivary function in irradiated patients do not fully recover after 12 to 36 months, but the value of pH and the saliva buffering capacity return to normal conditions after one year, which ensures better control of the homeostasis of the microbiota[33].

Basically, Zhang et al.[33] found lower levels of the plaque index in the caries-free radiation patients than in radiation caries (p=0.038) patients. As the plaque index is a direct evaluation of the level of oral hygiene, a significant difference in the plaque index indicates that the group of radiation caries-free patients have better oral hygiene than the other group. However, more longitudinal studies with larger samples should be conducted to relate poor oral hygiene as a causal factor for the development of radiation caries[33].

This review attempted to present a different scenario found in the literature in the last ten years about the impact of antineoplastic treatment over the microbiota of the oral cavity and oropharyngeal in patients affected by head and neck cancer following PRISMA methodology, but because of the heterogeneity of the studies selected, a meta-analysis is unfeasible.

CONCLUSION

After reviewing the articles selected, the authors reported pathological processes as mucositis and dental caries in great part of the patients caused by microorganisms of the oral

microbiota and oropharynx and the most frequent reported were: bacteria of the species *Streptococcus* spp. and fungi of the species *Candida spp*. In addition, the treatment with radiation influences the behavior of this microbiome through the functional compromise of the organism, changing its immune system, salivary function among others. These factors contributed for the growth of the microbiological proliferation, raising the odds for the patients in treatment or post-treatment to develop pathological processes of the oral cavity and oropharyngeal by microorganisms. Based in this, the understanding of oral microbiome shifts provoked by the treatment against head and neck cancer and an active participation of the hospital odontology team allow a better planning to meet the patients' necessities ensuring improved buccal heath and reducing the impact provoked by the antineoplastic treatment.

CONTRIBUTIONS

All the authors contributed substantially for the study design/conception, acquisition, analysis and/or interpretation of the data, wording and/or critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is conflict of interests to declare.

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