

Oral microbiota and mucositis in patients with head and neck cancer undergoing radiotherapy: literature review

Microbiota bucal e mucosite em pacientes com câncer de cabeça e pescoço recebendo radioterapia: um estudo de revisão de literatura

Microbiota bucal y mucositis en pacientes con cáncer de cabeza y cuello que recibe radioterapia: el artículo de revisión

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Abstract

The occurrence and severity of mucositis are the main complaints of patients with head and neck cancer submitted to radiotherapy (RT). This condition appears to be associated with changes in the oral microbiota and other side effects of RT, such as xerostomia and candidiasis. The aim of this study was to evaluate the effect of RT on the oral microbiota and its impact on radioinduced mucositis through literature review. Descriptors were selected for the collection of information in different databases, especially SciELO, BIREME, LILACS and PubMed. It was decided to consider only articles published since 1985. The descriptors radiotherapy, mucositis, dental caries, xerostomia, head and neck neoplasms and health promotion were used. It was selected 91 articles specifically discussing the microbiological aspects of mucositis, dental caries, oral candidiasis and microbial effects on the oral health of cancer patients, and 59 were included in the review. It was observed that microbial contamination is a secondary phenomenon capable of exacerbate the inflammation induced by the interaction of the radiation with the oral tissues, aggravating mucositis mainly in patients who present precarious conditions of oral hygiene, which reinforces the role of preventive dentistry in the follow up of the irradiated patient.

Descriptors: Radiotherapy; Mucositis; Dental Caries; Xerostomia; Head And Neck Neoplasms; Health Promotion.

Resumo

A ocorrência e a severidade da mucosite constituem as principais queixas dos pacientes com câncer de cabeça e pescoço submetidos à radioterapia (RT). Essa condição parece estar associada às modificações da microbiota bucal e aos demais efeitos colaterais da RT, como xerostomia e a candidíase. O presente trabalho de revisão da literatura teve como objetivo avaliar o efeito que a RT exerce sobre a microbiota bucal e seu impacto na mucosite radioinduzida através de revisão de literatura. Foram selecionados os descritores para a coleta de informações em diferentes bancos de dados, destacando-se SciELO, BIREME, LILACS e PubMed. Decidiu-se considerar apenas artigos publicados desde 1985. Utilizou-se como descritores os termos radioterapia, mucosite, cárie dentária, xerostomia, neoplasias de cabeça e pescoço e promoção da saúde. Foram selecionados 91 artigos que discutiam especificamente os aspectos microbiológicos da mucosite, cárie dentária, candidíase oral e efeitos microbianos na saúde bucal de pacientes oncológicos e 59 foram incluídos na revisão. Observou-se que a contaminação microbiana é fenômeno secundário capaz de agravar a inflamação induzida pela interação da radiação com os tecidos bucais, agravando-se, principalmente, em pacientes que apresentam condições precárias de higiene bucal, o que reforça o papel da odontologia preventiva no acompanhamento do paciente irradiado.

Descritores: Radioterapia; Mucosite; Cárie Dentária; Xerostomia; Neoplasias de Cabeça e Pescoço; Promoção da Saúde.

Resumen

La ocurrencia y la gravedad de la mucositis son las principales quejas de los pacientes con cáncer de cabeza y cuello tratados con radioterapia (RT). Esta condición parece estar asociada con cambios en la microbiota bucal y los otros efectos secundarios de la RT como xerostomía y candidiasis. Este estudio bibliográfico fue evaluar el efecto que la RT tiene sobre la microbiota bucal y su impacto sobre la mucositis radio-inducida a través de revisión de la literatura. Se seleccionaron los descriptores para recoger datos de diferentes bases, destacando SciELO, BIREME, lilas y PubMed. Se decidió considerar sólo los artículos publicados desde 1985. Fue utilizado como descriptores radioterapia, mucositis, caries dental, xerostomía, neoplasias de cabeza y cuello y promoción de la salud. Se seleccionaron 91 artículos que analizan específicamente los aspectos microbiológicos de la mucositis, la caries dental, la candidiasis oral y efectos microbianos en la salud oral de los pacientes con cáncer; 59 fueron incluidos en la revisión. Se observó que la contaminación microbiana es fenómeno secundario pero puede agravar la inflamación inducida por la interacción de la radiación con los tejidos orales, empeorando, especialmente en pacientes con mala higiene oral, lo que refuerza el papel de la odontología preventiva en acompañamiento de los pacientes irradiados.

Descriptores: Radioterapia; Mucositis; Caries Dental; Xerostomía; Neoplasias de Cabeza y Cuello; Promoción de la Salud.

INTRODUCTION

In the treatment of head and neck cancer, the use of radiation therapy (RT) plays a central role, leading to a significant improvement in patients' survival, but at the expense of severe side effects, which can interfere with the compliance of patients, deterioration of quality of life, the progress and intensification of the therapeutic regimen¹⁻⁴. Individuals undergoing RT, often report the occurrence of inflammation of mucosa (mucositis), xerostomia, dysphagia, dysgeusia and candidiasis, particularly in patients who have not received previous dental treatment before RT⁵⁻⁸.

The severity of these side effects, specially mucositis, depends on the dose/frequency of RT, volume and anatomical aspects of irradiated tissues, previous dental treatment, age, oral and general conditions of the patients, as well concomitant use of chemotherapy and surgical procedures^{5,9}. These effects may be acute, occurring during the treatment or subsequent weeks, or chronic, detected months or years after RT¹⁰⁻¹¹.

In general, mucositis generally is most frequent complaint¹². The impact of this condition on the patient's

health is significant, and seems to be associated with candidiasis and severe xerostomia, affecting the vast majority of the irradiated subjects^{13,14}, producing extreme discomfort and compromising acceptance, continuity and intensification of the treatment^{6,10,14}. The tissue damage produced by RT on acinar cells of major salivary glands¹⁵ exacerbate the formation and retention of microbial biofilm, creating favorable conditions to secondary microbial colonization of ulcerated lesions on mucosa¹⁶.

Radio-induced mucositis is dose dependent, but the inflammatory process regresses after RT cessation. The severity of the mucositis diminishes more readily after RT than xerostomia¹⁷, which possibly exacerbates the patient's susceptibility to infectious conditions^{1,17}, affecting the intensification or continuity of RT¹⁷. In this sense, the role of the oral microbiota in the development and exacerbation of mucositis still needs clarification, but this oral condition can be exacerbated by the concomitant presence of other local and/or systemic infectious processes^{16,18}.

The development of xerostomia and mucositis is followed by several changes in oral microbiota, but the significance of such phenomenon remains unclear¹⁹. Some evidences suggest that oral environment might act as reservoirs of classical and opportunistic pathogens, facilitating the establishment of opportunistic infections, particularly in patients receiving chemotherapy and undergoing RT simultaneously^{19,20}. In addition, it is evident the deterioration of dental health due to mucositis and radiation caries associated with the aggravation of xerostomia, amplifying the numbers of cariogenic cocci, reducing the pH of biofilm and cooperate, exacerbating the adhesion and proliferation of *Candida* on oral mucosa.

The presence of exogenous Gram-negative bacteria in the biofilm could affect the inflammatory conditions of the mucosa, allowing new pressures to the development of radiation induced mucositis^{20,21}. Thus, the aim of this study was discuss the role played by microorganisms in the development and evolution of mucositis in patients with head and neck cancer undergoing RT.

MATERIAL AND METHOD

This study consists of a literature review and qualitative data analysis. Initially the descriptors for the collection of information in different databases were selected, highlighting the indexed SciELO (Scientific Electronic Library Online), BIREME (Virtual Health Library), LILACS (Latin American and Caribbean Health Sciences), MEDLINE (International Literature on Health Sciences), PubMed (National Library of Medicine) databases. It was decided to consider only articles published since 1985 to prevent further difficulties with the taxonomy of most common genera and oral microbial species, particularly those associated with the etiopathogenesis of orofacial infections.

The following descriptors for research were used: radiotherapy, mucositis, dental caries, xerostomia, head and neck cancer, and health promotion. Out of these publications, studies that do not properly describe the oral conditions of the patients involved, characteristics of RT and/or oncologic treatment, as well theses, dissertations, books and informational texts that were not published in scientific journals were excluded. A total of 399 publications were selected and 91 discussed specifically the microbiological aspects of the mucositis, dental caries, oral candidiasis and microbial effects on oral health of oncologic patients. The 59 most relevant were included in the review.

ORAL MICROBIOTA OF THE PATIENT WITH HEAD AND NECK CANCER

The oral microbiota of patients with head and neck cancer presented several peculiarities, such as a higher frequency of colonization of yeasts of the genus *Candida*^{22,23}, which have been implicated in the production of nitrosamines capable to activate proto-oncogenes responsible for the development of the head and neck cancer²⁴, besides Gram-positive anaerobes of the genus *Actinomyces*, Gram-negative anaerobes of genera *Fusobacterium*, *Prevotella*, and *Porphyromonas*, microaerophilics such as *Capnocytophaga*, and Gram-negative enteric rods of the family *Enterobacteriaceae*²⁵.

The high prevalence of the species of *Enterobacteriaceae* on the surface of malignant neoplasms in the mouth may have impact on oral and/or systemic infectious diseases and could reflect the microbial adhesion abilities of bacteria and receptors of the neoplastic cells²³. In addition, the presence of enteric Gram-negative rods on the surface of oral soft tissues could exacerbate microbial proteolytic activity on fibronectin and expose receptors for adhesion of other members of the family *Enterobacteriaceae*. In addition, the Gram-negative microorganisms are still able to affect, even secondarily, the oral conditions of the irradiated patients, almost always exacerbating inflammatory processes¹⁸, which follow the direct damage produced by the RT¹⁵, particularly during the development of secondary local or systemic infections²⁶. Gram-negative anaerobes, such as the genera *Fusobacterium*, *Porphyromonas* and *Prevotella*, induce the release of different pro-inflammatory cytokines and, thereby, exacerbate the radio-induced mucositis²⁷.

RADIATION CARIES, ORAL STREPTOCOCCI AND MUCOSITIS

The result of pronounced and sometimes persistent xerostomia is the change of oral microbiota, producing a significant increase of oral acidogenic cocci in supragingival biofilm, and a significant elevation in salivary levels of cariogenic cocci, particularly *Streptococcus mutans*²⁸⁻³⁰. This phenomenon is cumulative, usually established after 2000 cGy of radiation, accompanying the severity and persistence of xerostomia¹⁷. However, the use of sodium fluoride in aqueous solutions or gel minimizes the changes of cariogenic cocci populations, constituting a recognized strategy to prevent the rampant caries associated with RT and xerostomia³⁰⁻³². Then, the elevations of cariogenic microorganisms in RT might be understood as result of the absence or precariousness of the preventive measures and the poor hygiene conditions of the patients and their deterioration along RT^{33,34}.

In radiotherapy centers where preventive dentistry is considered relevant and plays a central role in the prevention of side effects of RT, populations of cariogenic cocci are under partial control^{19,30}, consisting transient phenomenon^{33,35,36}, and hygiene standards evidences relevant improvement during RT and follow-up period, particularly when intensity modulated radiation therapy is used, which produces less pronounced effects on the salivary glands^{19,37}.

Oral streptococci such as *Streptococcus anginosus*, *S. mitis*, *S. mutans*, *S. oralis*, *S. sanguinis*, and *S. sobrinus* present mucolytic capacity by the production of glycosidases and may exacerbate chemotherapy and radiotherapy induced mucositis^{38,39}. According to Vanhoecke et al.¹⁶, it is possible to observe significant changes in the composition and

thickness of the oral muco, which, together with a possible increase in the virulence of these microorganisms in immunocompromised patients⁴⁰ could contribute to the deterioration of the conditions of the mucosa.

RADIO-INDUCED MUCOSITIS AND CANDIDIASIS

Mucositis is associated with ulcerated areas, hinder nutrition and might facilitate the deployment of local or systemic infections⁵, usually caused by opportunistic microorganisms, such as enteric pathogens, anaerobic Gram-negative rods and yeasts^{7, 19, 20, 41, 42} sometimes already present in higher proportions in cancer patients before RT²³.

The presence, severity and persistence of xerostomia seem to be the main factors associated with the presence of candidiasis in irradiated patients, facilitating the colonization of surfaces that previously did not harbor these fungi, allowing the growth of yeast populations^{43, 44}. This phenomenon is also exacerbated by the acidification of the oral biofilm and the reduction of the buffer capacity of the residual saliva. The prevalence and populations of yeasts are directly related to RT^{23, 34, 44}, being involved in the severity of mucositis and secondary infections.

Patients presenting the highest populations of these yeasts prior to RT are also the first to develop clinically detectable infection^{7, 20}, which reinforces the need for antifungal preventive approach for oral candidiasis in irradiated patients^{20, 21}. On the other hand, as opportunistic pathogens, the high prevalence and populations of fungi also reflect the poor conditions of oral hygiene and deterioration along the RT³⁴, as well nutritional deficiencies and loss of weight in irradiated patients. Oral candidiasis in RT patients might also be associated to the exacerbation of virulence of the fungi⁴⁰.

The occurrence of *Candida* sp. varies from 20 to 70% in patients undergoing RT, and some studies suggest that other species besides *C. albicans* are more favored in the irradiated patients^{7, 45}. However, literature has failed to discover any advantage for non-albicans *Candida* during or after RT^{23, 34, 44, 46, 47}.

The prevention/control of oral candidiasis, by improving oral hygiene standards, use of antifungal solutions and nutritional support, could also be a measure with impact on mucositis intensity in irradiated patients^{7, 34}, particularly the systemic use of fluconazole and aqueous solution of nystatin^{20, 21, 34, 47}.

MUCOSITIS, ORAL BACTERIAL MICROBIOTA, ENTEROBACTERIACEAE AND BIOFILM

The occurrence and populations of autochthonous microorganisms of the oral microbiota may be higher among patients with head and neck squamous cell carcinoma²³, but this phenomenon is not universal^{12, 19, 20, 48}. Alcohol and tobacco consumption and poor hygiene might facilitate oral colonization of the patients by exotic microbial species^{12, 20, 48}. Patients with severe xerostomia are generally colonized by some Gram-negative microaerophilic and anaerobic bacteria. Thus, new strategies of RT that reduce tissue damage on salivary glands tend to minimize the impact on oral microbiota and produce a reduction of the prevalence and populations of autochthonous microorganisms^{19, 49}.

After the emergence of ulcerations and lesions near the gingival sulcus in irradiated patients with mucositis, creating a more irregular surface and exposing new receptors for microbial adhesion, new possibilities for microbial

colonization opens, allowing adhesion high populations of the pathogens present in the biofilm of oncologic patients with oropharyngeal carcinoma²⁵. Most of these pathogens are Gram-negative and with a wide spectrum of virulence, exacerbating the production and release of cytokines and chemokines¹⁶.

Among Gram-negative bacteria, enteric rods of the family *Enterobacteriaceae* have been implicated in severe mucositis^{20, 21, 50} and the oral carriage of these microorganisms is resilient to antimicrobials commonly used, what needs combined strategies involving improvement of oral hygiene to reduce the presence of enteric rods in the mouth of mucositis patients, particularly in patients presenting severe xerostomia^{32, 51}. Their presence on the surface of the oral soft tissues could exacerbate the microbial proteolytic activity on the fibronectin and connective tissues, intensifying the mucositis by the induction of inflammation by direct action of LPS and release of interleukins II-1 and II-6²³.

The occurrence and populations of the main periodontopathogens are not usually affected by RT, but this aspect is deeply dependent on oral hygiene of the patients⁴⁹. RT has been associated with the reduction of the blood supply to the irradiated areas, leading to a significant reduction of local immunity, redox potential of the tissues and delay of the wound repair, creating favorable conditions for the proliferation obligate anaerobes, such as genera *Fusobacterium*, *Prevotella*, *Porphyromonas*, and *Treponema*²³, most of them considered putative periodontopathogens. In addition, radiation-induced xerostomia appears to affect the populations of anaerobic bacteria in oral cavity and exacerbate the prevalence and proportions of non-oral opportunistic pathogens, particularly staphylococci, enteric rods and cocci, as well pseudomonads in the oral biofilm from irradiated patients with adequate oral hygiene conditions^{19, 32, 51, 52}. However, only Gram-negative anaerobes producing black pigment (*Porphyromonas* spp. and *Prevotella* spp.) have been implicated in RT subgingival microbiota²³.

These anaerobes frequently associated with periodontitis present a metabolism based on the fermentation of amino acids, end up upregulating the release of cytokines and pro-inflammatory chemokines^{16, 18}, which could exacerbate the initial acute effects of mucositis.

The effects of RT are relevant and have a deep impact on the quality of life of irradiated patients, mainly due to mucositis, radiation caries, xerostomia, dysphagia and dysgeusia^{1, 17}. Thus, preventive dental care should be used to minimize these conditions and must be implemented before, during and after RT^{8, 19, 21, 51}. The importance of preventive dental care and oral hygiene are aspects that constitute a common place^{13, 17, 19, 53, 54}, but many radiotherapy centers in Brazil do not offer this support, which remains without adequate follow-up.

Moreover, since most of patients undergoing RT in Brazil for cancer treatment present low socioeconomic conditions and inadequate oral hygiene standards^{20, 48, 55}, the relevance of protocols capable to restore the equilibrium between patients' immune response and microbial biofilm should be considered priority in the prevention of side effects of RT. Moreover, ameliorate xerostomia by using sialogogues and artificial saliva is considered relevant to reduce the impact of RT on oral ecology and, as consequence on severity of mucositis. However, literature emphasize the needs of dental and periodontal examinations, as well as the elimination local infections by mean of

restorative dentistry, endodontic and periodontal treatments and surgery^{7,9,20}. The use of chemical control of biofilm must be considered for patients with poor oral hygiene and for those ones evidencing significant deterioration of oral health⁵⁶. Surgical procedures should be avoided during or soon after end of oncologic treatment due to vascular and immunological changes induced RT, particularly when associated with chemotherapy, preventing osteoradionecrosis.

Some studies have proposed the selective elimination of the enteric rods in the oral microbiota in irradiated patients with mucositis^{57,58}, but the benefits of such approach are uncertain⁵⁹. In general, microbial suppression in biofilm is transient and must be followed by improvement of oral hygiene.

CONCLUSION

Mucositis is primarily the result of direct damage of oral tissues by RT, but microorganisms are capable to exacerbate inflammation by mean of enzymatic destruction of mucosa and up-regulation of the production and release of pro-inflammatory cytokines. The most commonly found species belong to genus *Candida*, family *Enterobacteriaceae* and black-pigmented oral anaerobes.

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CONFLICTS OF INTERESTS

The authors declare no conflicts of interests.

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