UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

MARIANA DE PAULI PAGLIONI

IMPACTO DA CÁRIE DE RADIAÇÃO NA QUALIDADE DE VIDA DE PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO.

IMPACT OF RADIATION CARIES IN THE QUALITY OF LIFE OF HEAD AND NECK CANCER PATIENTS.

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Tese apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Doutora em Estomatopatologia, na Área de Estomatologia.

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Orientador: Prof. Dr. Alan Roger dos Santos Silva
Coorientadora: Profa. Dra. Ana Carolina Prado Ribeiro e Silva

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PROFª DRª LARA MARIA ALENCAR RAMOS INNOCENTINI

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(Eclesiastes 3)

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RESUMO

A cárie de radiação (CR) é uma toxicidade tardia da radioterapia realizada em pacientes com câncer de cabeça e pescoço (CCP) que apesar de ser notoriamente atribuída a grande prejuízo funcional e estético em pacientes oncológicos, não está prevista nos questionários de Qualidade de Vida (QV) desenhados para pacientes com CCP. Tendo em vista esse cenário clínico, esta tese tem como principal objetivo caracterizar o possível impacto negativo da CR em uma série de aspectos relacionados à QV de pacientes submetidos a radioterapia de cabeça e pescoço. Esse estudo coletou dados prospectivos de uma série de 100 pacientes com CCP submetidos à radioterapia, isoladamente ou em combinação com cirurgia e quimioterapia, após o tempo mínimo de 12 meses de conclusão da radioterapia. Os pacientes responderam ao Questionário de Qualidade de Vida da Universidade de Washington (versão 3.0), traduzido e validado para a língua portuguesa, cujos resultados foram interpretados por meio dos domínios físico e socioemocional e, posteriormente, foram avaliados clinicamente para determinação do número de dentes cariados, perdidos e obturados por meio do índice CPOD. Os pacientes foram divididos em dois grupos: (1). pacientes que desenvolveram CR (grupo de estudo) e (2). pacientes que não desenvolveram CR (grupo controle) após conclusão do tratamento oncológico. No grupo de estudo, a média global dos valores de QV foi 878,1 e no grupo controle a média foi 927,2 (p=0,24). A média do índice CPOD no grupo de estudo foi 30,5 e no grupo controle foi 20,7 (p=0,001). Pacientes com CR apresentaram impacto negativo em quase todos os itens dos domínios físico e socioemocional quando comparados aos pacientes do grupo controle, contudo, significância estatística foi identificada apenas para os itens saliva (p=0,047) e recreação (p=0,031). A maioria dos pacientes dos dois grupos identificou que os itens do domínio físico foram o mais afetados em termos de eventos relacionados à QV, principalmente, por meio de queixas relacionadas à saliva. A CR tem potencial para gerar impacto negativo em aspectos físicos e socioemocionais da QV de pacientes oncológicos, sobretudo, por meio de alterações relacionadas à hipossalivação e habilidades de recreação.

Palavras-chave: Câncer de cabeça e pescoço. Cárie de radiação. Questionário de qualidade de vida.

ABSTRACT

Radiation caries (RC) is a late toxicity of radiotherapy performed in patients with head and neck cancer (HNC), which, although it is notoriously attributed to great functional and aesthetic impairment in cancer patients, is not provided for in the quality of Life (QoL) questionnaires designed for patients with HNC. Considering this clinical scenario, this thesis aims to characterize the possible negative impact of RC on a series of aspects related to QoL of patients submitted to head and neck radiotherapy. This study collected prospective data from a series of 100 patients with HNC who underwent radiation therapy alone or in combination with surgery and chemotherapy after a minimum of 12 months of radiotherapy conclusion. The patients responded to the University of Washington Quality of Life Questionnaire (version 3.0), translated and validated to Portuguese language, whose results were interpreted through the physical and socio-emotional domains and were subsequently clinically evaluated for the number of decayed, missing and filled teeth using the DMFT index. The patients were divided into two groups: (1). patients who developed RC (study group) and (2). patients who did not develop RC (control group) after conclusion of cancer treatment. In the study group, the mean overall QoL values were 878.1 and in the control group the mean was 927.2 ($p = 0.24$). The mean DMFT index in the study group was 30.5 and in the control group it was 20.7 ($p = 0.001$). Patients with RC had a negative impact in almost all items in the physical and socioemotional domains when compared to patients in the control group, however, statistical significance was only identified for the items saliva ($p = 0.047$) and recreation ($p = 0.031$). The majority of patients in the two groups identified that items in the physical domain were the most affected in terms of QoL events, mainly through saliva-related complaints. RC has the potential to generate a negative impact on the physical and social-emotional aspects of the QoL of cancer patients, mainly through changes related to hyposalivation and recreational skills.

Key words: Head and neck cancer. Radiation caries. Quality of life questionnaire.

SUMÁRIO

1 INTRODUÇÃO

O câncer de cabeça e pescoço (CCP) representa um grupo de neoplasias que acomete a cavidade oral, a orofaringe, a hipofaringe, a laringe, a nasofaringe e as glândulas salivares, entre outras topografias anatômicas. O CCP está entre as seis neoplasias malignas mais comuns mundialmente, com uma média anual que varia de 400.000 a 700.000 novos casos (Marur et al., 2008; Fitzmaurice et al., 2017), ocasionando grande impacto global em termos de morbimortalidade e políticas em saúde pública e privada (Ferlay et al., 2015; Torre et al., 2015).

Os principais fatores de risco relacionados ao desenvolvimento do CCP são o tabagismo e o consumo de bebidas alcoólicas que, quando associados, apresentam efeito carcinogênico sinérgico (Pelucchi et al., 2008). Mais recentemente, a infecção pelo papiloma vírus humano (HPV - genótipos 16 e 18) foi identificada como fator de risco emergente, especificamente para carcinomas espinocelulares (CECs) não queratinizantes de orofaringe (D'Souza et al., 2007; Sturgis et al., 2007). Adicionalmente, a exposição solar crônica também é considerada fator de risco para os tumores malignos de pele e lábio. Fatores pouco compreendidos inerentes à dieta, eventos genéticos e epigenéticos também foram relacionados com a patogênese desses tumores (Pelucchi et al., 2008; Tarvainen et al., 2008; Hashibe et al., 2009).

Uma constatação adicional da relevância da problemática do CCP em termos epidemiológicos e populacionais é a estimativa do Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA), válida para o biênio 2018-2019, que aponta o câncer de cavidade oral -subtipo mais comum de CCP (excluindo tumores da pele)- como a quinta neoplasia maligna mais comum entre os homens brasileiros, com aproximadamente 15.000 novos casos entre homens e mulheres, anualmente (INCA et al., 2018). O tipo histológico mais comum nesse contexto é o CEC, que representa aproximadamente 90% de todos casos (Leemans et al., 2011; Ferlay et al., 2015).

Em adição ao cenário supramencionados, estudos clínicos sugerem que aproximadamente 80% dos casos de CCP são diagnosticados tardiamente, cenário que demanda tratamento oncológico de natureza multi-modalidade incluindo geralmente a combinações que envolvem cirurgia, a radioterapia (RT) e a quimioterapia (Rodrigues et al., 2014). Os protocolos de tratamento oncológico dos tumores malignos de cabeça e pescoço são influenciados pelo estadiamento clínico da doença, pelas condições físicas dos doentes (status

performance), pela localização do tumor primário, pela associação do HPV no caso específico dos CECs de orofaringe, pela infraestrutura do centro médico envolvido e pelo treinamento da equipe multidisciplinar envolvida, entre outros. Contudo, de um modo geral, entende-se que a maioria absoluta dos pacientes com CCP será submetida a protocolos de RT (Marur et al., 2008; Pfister et al., 2013; Marta et al., 2015a; Marta et al., 2015b).

A RT é uma modalidade terapêutica que utiliza feixes bem controlados de radiação ionizante com o objetivo de inviabilizar células malignas, diminuindo os índices de proliferação celular e induzir morte celular programada (apoptose) (Sawada et al., 2006). Via de regra, para o tratamento de doença localmente avançada de cabeça e pescoço, a RT é empregada como tratamento adjuvante à cirurgia ou concomitante à quimioterapia em protocolos de preservação de órgão conhecidos como quimiorradioterapia (QRT). A dose de radiação para esse grupo de tumores varia de 60 Gy a 70 Gy (Marur et al., 2008; Pfister et al., 2013). Apesar do grande benefício em termos de taxas de controle locorregional dos tumores e sobrevida global, a RT em cabeça e pescoço está associada a uma série de toxicidades agudas e crônicas com grande potencial de morbidade nos pacientes oncológicos (Palmier et al., 2018).

As toxicidades induzidas pela RT podem gerar complicações orais que afetam a semi-mucosa labial, a mucosa oral, as glândulas salivares, os ossos do complexo maxilomandibular, a musculatura mastigatória e os dentes. Quando a cavidade oral e as glândulas salivares são expostas a altas doses de radiação, sobretudo em pacientes realizando QRT, as consequências clínicas costumam ser mais intensas e incluem toxicidades debilitantes como a hipossalivação, a mucosite, a disgeusia (alteração de paladar), o trismo, a cárie de radiação (CR), a osteorradionecrose, entre outras (Kielbassa et al., 2006).

Nesse desafiador cenário médico e odontológico, a CR afetará aproximadamente 25% dos pacientes (Gonçalves et al., 2014; Gomes-Silva et al., 2017a; Hong et al., 2018). Há um padrão de progressão clínica que se inicia início por meio da alteração da cor da superfície de esmalte para um padrão castanho-enegrecido associada a trincas e fissuras na superfície do esmalte (Madrid et al., 2017; Palmier et al., 2018). Se não tratadas, as lesões de CR afetarão as regiões cervicais e incisais dos dentes de modo generalizado, envolvendo grandes áreas da superfície dental e ocasionando fraturas completas de faces vestibulares do esmalte, fenômeno clínico conhecido como "delaminação" que, por sua vez, acaba por expor dentina ao risco de CR. Uma assinatura clínica dessa toxicidade tardia da RT é o início abrupto e a rápida progressão clínica que geram alto potencial de destruição dental, podendo ocasionar amputação

generalizada de coroas dentais e destruição completa da dentição em poucos meses subsequentes à conclusão da RT em campos bucais (Silva et al., 2009; Palmier et al., 2017). Não obstante ao potencial de destruição dental atrelado à CR, sua progressão também tem potencial para perpetuar focos de infecção crônicos em osso irradiado da maxila e mandíbula, predispondo os pacientes ao risco de osteorradionecrose, toxicidade crônica com grande potencial de morbidade (Hong et al., 2010; Schweyen et al., 2012; Palmier et al., 2017).

A CR é notoriamente reconhecida por se tratar de uma doença de origem multifatorial. Recentemente, existe uma grande dialética acadêmica no que diz respeito à participação de efeitos radiogênicos diretos da RT em cabeça e pescoço sobre a microestrutura do esmalte, da junção amelodentinária, da dentina e da polpa de dentes de pacientes com CCP. Embora a destruição radiogênica desses tecidos e sua participação na patogênese da CR seja controversa, os efeitos indiretos da RT sobre os dentes são universalmente reconhecidos por seu papel no aumento do risco à cárie em populações oncológicas submetidas à RT em campos bucais. Esse conjunto de eventos clínicos relacinados aos efeitos indiretos da RT em CCP é conhecido como "agrupamento de sintomas orais" (Ribeiro et al., 2013; Xiao et al., 2013; Dong et al., 2014; Xiao et al., 2014; Morais-Faria et al., 2015; Santos-Silva et al., 2015; Gomes-Silva et al., 2017a; Gomes- Silva et al., 2017b; Palmier et al., 2017; Xiao et al., 2017; Palmier et., 2018; Ridner et al., 2018).

Nesse contexto, o desenvolvimento da mucosite oral -grave toxicidade aguda da RT- está associado à dor intensa, o que limita a habilidade de higiene bucal dos pacientes e altera padrões de dieta para alimentos mais pastosos e consequentemente mais ricos em carboidratos. A disgeusia, outra toxicidade muito comum de pacientes submetidos à RT em campos orais, afeta a capacidade gustativa fazendo com que os pacientes também modulem dieta e aumentem a ingestão de alimentos ricos em carboidratos devido à satisfação gustativa que esse tipo de alimentos traz (Kilebassa et al., 2006). As alterações qualitativas e quantitativas da saliva de pacientes irradiados talvez sejam os fatores mais importantes no processo de desenvolvimento e progresão da CR tendo em vista seu impacto na redução do fluxo salivar, no aumento da viscosidade (e diminuição do pH) da saliva remanescente, na alteração da microbiota bucal que se tornará mais cariogênica, e na consequente redução da capacidade de regulação dos mecanismos de remineralização do esmalte (Kielbassa et al., 2006). A hipossalivação também costuma modular a dieta dos pacientes oncológicos, demandando consumo de alimentos mais pastosos e ricos em carboidratos, incrementando o desafio cariogênico dessa população em particular. Finalmente, o trismo induzido pela RT em cabeça e pescoço acaba

por limitar a abertura bucal dos pacientes de modo a prejudicar a capacidade de higiene bucal. O agrupamento dos sintomas bucais supramencionados é considerado específico de pacientes irradiados na região de cabeça e pescoço e reconhecido por atuar em sinergia de modo a promover grande desafio cariogênico para os dentes dessa população, por meio do aumento da dieta rica em carboidratos, da indiponibilidade de saliva e da limitação da higiene oral, contribuindo de modo decisivo para a CRR (Ribeiro et al., 2013; Xiao et al., 2013; Dong et al., 2014; Xiao et al., 2014; Santos-Silva et al., 2015; Xiao et al., 2017; Palmier et al., 2017; Palmier et., 2018; Ridner et al., 2018).

O impacto das toxicidades tardias da RT em aspectos de qualidade de vida (QV) de sobreviventes de CCP se tornou grande prioridade para especialistas no suporte médico e odontológico a pacientes oncológicos. A título de exemplo, o Oral Care Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ ISOO) se dedicou a organizar grupos de profissionais que caracterizaram o impacto de uma série de complicações odontológicas do tratamento oncológica na QV de pacientes com CCP. Contudo, até o presente momento, não foram identificados estudos direcionados para a compreensão do impacto da CR na QV de sobreviventes do CCP **(Tabela 1).** Ainda nesse contexto, é relevante mencionar que o aprimoramento técnico e científico, bem como a modernização das modalidades de tratamento oncológico sugerem aumento das taxas de sobrevida livre de doença nesses pacientes, o que colocou as toxicidades do tratamento, tanto as precoces como as tardias, em um cenário ainda mais relevante no que diz respeito à morbidade e à influência na QV (McSweeny et al., 1995; Maguire et al., 1989).

Tendo em vista todo o exposto, a avaliação da QV é considerada uma ferramenta essencial não só para permitir a melhor compreensão do impacto da doença oncológica na vida dos pacientes, mas também dos impactos causados pelo seu tratamento a curto e a longo prazo, permitindo, assim, o delineamento de estratégias efetivas no tratamento e acompanhamento desses pacientes (Deleyiannis et al., 1999; Allal et al., 2003; Hanna et al., 2004; Vartanian et al., 2004). A avaliação de aspectos de QV dos pacientes oncológicos, por meio de questionários específicos e internacionalmente validados foi consagrada na literatura científica médica e odontológica (Rogers et al., 1999; Ringash et al., 2001; Pusic et al., 2007; Rogers et al., 2007). Nesse campo, o *University of Washington Quality of Life Questionnaire* foi um dos primieros questionários publicados para pacientes com CCP (Hassan et al., 1993) e atualmente é um dos mais utilizados no mundo todo (Rogers et al., 2002). Em 2006, o questionário foi traduzido e validado para a língua portuguesa e é considerado, por especialistas, como sendo de fácil

interpretação, conciso e amplamente validado (Vartanian et al., 2006). Interessantemente, apesar de sua notoriedade e reconhecimento universal, ele não comtempla aspectos direcionados aos dentes.

Tendo em vista o exposto, esta tese de doutoramento se propôs a avaliar, por meio de um estudo clínico prospectivo, aspectos relacionados às condições odontológicas de uma grande série de pacientes oncológicos submetidos à RT em cabeça e pescoço, com a finalidade de investigar o impacto da CR em uma miríade de eventos de ordem física e socioemocional relacionados à QV.

Tabela 1. Publicações que correlacionaram toxicidades do tratamento oncológico com aspectos de qualidade de vida.

Toxicidade	**Autores e ano de publicação**
Osteorradionecrose	Jacobson et al., 2013; Rogers et al., 2015
Trismo	Pauli et al., 2013; Johnson et al., 2015; Lee et al., 2015
Hipossalivação/xerostomia	Memtsa et al., 2017; Hawkins et al., 2018; Lastrucci et al., 2018
Disgeusia	Baharvand et al., 2013; Ponticelli et al., 2017
Mucosite oral	Franco et al., 2017; Kanagalingam et al., 2018
Cárie de radiação	-

2 ARTIGO: IMPACT OF RADIATION CARIES IN THE QUALITY OF LIFE OF HEAD AND NECK CANCER PATIENTS

Artigo submetido ao periódico *Supportive Care in Cancer* (Anexo 3).

Authors: Mariana de Pauli Paglioni, DDS, MSc[1], Natalia Rangel Palmier, DDS, MSc[1], Ana Carolina Prado-Ribeiro, DDS, PhD[1,2], Eduardo Rodrigues Fregnani, DDS, PhD[3], Maria Beatriz Duarte Gavião, DDS, PhD[4], Thaís Bianca Brandão, DDS, PhD[2], Marcio Ajudarte Lopes, DDS, PhD[1], Ana Paula Dias Ribeiro, DDS, PhD[5], Cesar Augusto Migliorati, DDS, PhD[5], Alan Roger dos Santos-Silva, DDS, PhD[1]

Affiliation: (1) Oral Diagnosis Department, Semiology and Pathology Areas, Piracicaba Dental School, University of Campinas (UNICAMP), Piracicaba, São Paulo, Brazil; (2) Dental Oncology Service, São Paulo State Cancer Institute (ICESP-FMUSP), Brazil; (3) Department of Oral Medicine, Sírio Libanês Hospital, São Paulo, Brazil; (4) Pediatric Dentistry Department, Piracicaba Dental School, University of Campinas (UNICAMP), Piracicaba, São Paulo, Brazil; (5) College of Dentistry, University of Florida, Gainesville, FL, USA.

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Corresponding Author

Ana Carolina Prado-Ribeiro

1.Dental Oncology Service, Instituto do Câncer do Estado de São Paulo [ICESP], Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil. Av. Dr. Arnaldo, 251, Cerqueira César, São Paulo, Brazil, CEP: 01246-000.

2. Piracicaba Dental School, University of Campinas (UNICAMP), Brazil; Adress:

Av. Limeira, 901, Bairro Areão, Piracicaba-SP, Brasil. Postal code: 13414-903

Telephone: +55 11 3893-2341

E-mail: carol_pr@yahoo.com.br ; ana.prado@hc.fm.usp.br

Telephone: +55 19 21065320

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Abstract

Purpose: The objective of this study was to verify the relationship between the scores of Quality of Life (QoL) and the Decayed, Missing and Filled Teeth (DMFT) and radiation caries (RC) in patients treated with radiation therapy (RT) for head and neck cancer and through this determined if RC is capable of causing a significant decrease in the QoL. **Methods:** One hundred patients were divided into 2 groups; Patients with at least one year of RT completion who developed RC (study group, n=50); and patients with at least one year of RT completion who did not develop RC (control group, n=50). All patients answered the Brazilian-Portuguese validation of the University of Washington Quality of Life (UW-QoL) questionnaire, which was divided into 2 domains: physical and social-emotional functions and had the DMFT index score evaluated. **Results:** The mean score of QoL was 878.1 in the control group and 927.2 in the study group (P=0.24). The mean score of DMFT was 30.5 in the study group and 20.7 in the control group (P=0.001). The items recreation and saliva, which belong to the physical function domains, showed a statically significant difference between study and control groups (P=0.031 and P=0.047, respectively). The saliva was the item with the higher number of complaint of patients of both groups. **Conclusion:** RC had a negative impact on the QoL of HNC patients.

Introduction

Radiation caries (RC) is one of the most common toxicities of head and neck radiotherapy (HNRT), affecting approximately 25% of patients irradiated in the head and neck region [1,2]. RC lesions tend to appear about a year after the completion of HNRT and presents specific patterns of progression and clinical features when compared to conventional caries [3]. The mainly affected topographies are the incisal edge and cervical region near the amelocemental junction leading to the amputation of the dental crown in the most severe cases. These regions are unusual locations for caries development when compared to conventional caries lesions that occur mostly in pits, fissures and proximal regions [2-8]. Another serious concerning risk related to RC is the increased risk of infection and development of osteoradionecrosis [9].

During the past few years, QoL evaluation has been recognized as an important outcome measure in medicine, including oncology [10-14]. Many studies have already shown that the side effects related to RT, like oral mucositis, [15,16] dysgeusia [16,17], salivary gland dysfunctions [16,18], osteoradionecrosis [16] can affect negatively the QoL of the cancer patients. However, the impact of RC in the patient's QoL has not yet been evaluated in the context of HNRT.

Based on the stated above, the aim of this study was to test whether or not the RC can cause an impact on the QoL of head and neck cancer (HNC) patients. This was accomplished by using a validated University of Washington Quality of Life Questionnaire (UW-QoL), and by measuring the DMFT index.

Materials and methods

This is a prospective study of HNC patients who received high doses of RT (6070gy).

This study was approved by the Ethics Committee for Human Studies, São Paulo State Cancer Institute (ICESP-FMUSP) (protocol number 53869216.2). All participants in the study agreed to participate in this research by free will. The study included data from August 2015 to December 2016.

Inclusion criteria

We enrolled adult patients diagnosed with head and neck squamous cell carcinoma (SCC) and Salivary gland tumor (SGT) who received RT with curative intent (tumor eradication), with or without concomitant chemotherapy, and who had 1 year of disease-free survival. The patients in the study group had characteristic RC lesions while patients in the control group presented conventional caries features. All patients were submitted to mouth conditioning protocols before the beginning of the RT as part of the institutional protocol.

Exclusion criteria

Totally edentulous patients and patients under 1 year of completion of RT treatment were excluded.

Patients

Clinicopathological data such as gender, age, tumor site, tumor staging, RT dose and time of treatment conclusion were obtained from the medical records.

DMFT index and Questionnaire application

Patients were evaluated by a dental clinician using the DMFT index [19]. Digital intraoral photographs of all patients were taken with a Digital Camera Canon 7D with Canon Lens EF 100mm Macro F2.8 and Ring Light Flash Canon MR-14 EX TTL (figure 1).

All patients answered the validated Portuguese version of the UW-QoL questionnaire [13]. The UW-QoL includes variables that assess aspects of QoL and is composed of 16 objective areas: 12 related to variables of QoL specific areas (pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood, and anxiety). The

questionnaire was divided into two domains: (1). physical function: involving chewing, swallowing, speech, taste, saliva and appearance, and (2). social-emotional function: involving anxiety, mood, pain, activity, recreation, and shoulder function [14]. Patients were asked to choose only one option. They had to answer 1 question about the most important happening during the previous 7 days (chosen from 3 options). There were 3 questions about global issues related to the QoL affecting the mouth prior to the cancer diagnosis, in the previous 7 days of the UW-QoL application, and evaluation of QoL related to factors such as family relationship / friends, spirituality and personal leisure. There was an open question, where the patient could report another matter (medical or non-medical) that was found important to their QoL and that had not been properly addressed in previous contacts. The score was scaled equally, depending on the number of responses for each item, so that a score "0" would represent the worst possible response (greater impact on QoL), whereas "100" would represent the best possible response. The obtained scale allowed the evaluation of each QoL domain through specific scores. It also allowed the integration of all measures in a general synthetic score for each patient, being 1200 the highest possible total score.

Statistical analysis

T-test, Chi-squared, Fisher and Mann-Whitney were performed in order to evaluate the statistical significance of observed differences between subgroups. For all statistical tests, P values below 0.05 were considered statistically significant.

Results

The clinicopathologic features of the study and control groups including gender, age, oncologic diagnoses, treatment, among others, are shown in table 1. A total of 100 (one hundred) patients were included in the study.

The study group was composed of 50 patients from which 39 (78%) were men and 11 (22%) women. The mean age was 59.87 (range 28-85) years. Sixteen (32%) patients were

diagnosed with oral cavity SCC, 23 (46%) with oropharyngeal SCC and 11 (22%) with cancer in other sites of the head and neck. Eight (16%) were treated with surgery and RT, 1 (2%) received only RT was treatment, 29 (58%) received chemoradiotherapy and 12 (24%) surgery and chemoradiotherapy. Eight patients (16%) received 60Gy of RT, 7 patients (14%) received 66Gy and 35 patients (70%) received 70Gy.

The control group was composed of 36 (72%) men and 14 (28%) women. The mean age was 52.80 (range 21-69) years. Fifteen (30%) patients were diagnosed with oral cavity cancer, 20 (40%) with oropharyngeal cancer, 4 (8%) with salivary gland tumors and 11 (22%) with other location. Eight (16%) received surgery and RT as treatment, 2 (4%) received only RT as treatment, 17 (34%) received chemoradiotherapy and 23 patients (46%) surgery and chemoradiotherapy. Eight patients (16%) received 60Gy of RT, 11 patients (22%) received 66Gy and 31 patients (62%) received 70Gy.(Table 1).

Quality of Life results

Patients who developed RC presented worse QoL scores in almost all items when compared to patients who did not develop RC. However, there was no statistically significant differences. For the study group, the mean QoL score was 878.1 while for the control group the mean QoL score was 927.2 (P=0.24). When comparing the physical function and the socialemotional function domains, the study group had lower scores, but not significant differences were observed. The mean score of the physical function domains in the study group was 390.2 and mean score in the control group was 411.9 (P=0.41). The mean score of socialemotional function was 487.9 in the study group and 515.3 in the control group (P=0.19).

In regard to the DMFT analysis, the mean DMFT score for the study group was 30.5 and for the control group was 20.7 (P=0.001). The mean score of decayed teeth was 6.2 for the study group and 1.7 for the control group (P=0.0001), for missing teeth was 17.9 for the study group and 11.8 for the control group (P=0.0002), for filled teeth the mean score was 6.1 for the

study group and 7.0 for the control group (P=0.21), finally the mean score of sound teeth for the study group was 1.6 while for the control group was 11.3 (P=0.001) (results are shown in table 2).

When comparing the questionnaire items separately, in the study group the mean scores of appearance, swallowing, chewing, speech, taste, saliva, pain, activity, recreation, shoulder, mood, and anxiety were 77.00; 67.44; 65.00; 70.80; 68.68; 41.30; 82.50; 78.50; 74.50; 87.38; 83.00 and 82.04, respectively. In the control group these mean scores were 76.00; 72.10; 69.34; 76.30; 64.00; 54.66; 90.50; 81.00; 84.84; 91.86; 84.00 and 82.90 respectively. The only physical domain that showed significant differences between the groups was saliva (P=0.047). When comparing the social-emotional domains, recreation was the only domain that showed significant differences between the groups (P=0.031) (table 3).

In the study group, the domain with the greatest number of complaints was saliva with 29 patients (58%), followed by speech with 17 patients (34%), and chewing with 14 patients (28%) (Table 3). In the control group, the domain with the greatest number of complaints was also saliva with 26 patients (52%), followed by swallowing with 18 patients (36%), and speech with 12 patients (24%) (table 4).

When correlated physical functions and social-emotional functions with the DMFT index in the study group was possible observed a negative (-0.280) and significant correlation (P=0.049) between the missing and a positive (+0.368) and significant correlation (P=0.009) between filled teeth and the physical function domain. When correlated the DMFT index the control group with both domains was possible observed a negative (-0.345) and significant correlation (P=0.014) between the filled teeth and the social-emotional domain (table 5).

Discussion

RC is a well-known chronic side effect of the RT for HNC patients and is

responsible for generating a negative impact on the aesthetics and function of patients. The present study represents the first attempt to evaluate the impact of this condition in the QoL and in the oral health of these patients.

The clinicopathological findings of the present study are consistent with the literature regarding the epidemiological profile of HNC patients, with a higher prevalence of HNC occurring in middle-aged men diagnosed in an advanced stage of the disease requiring aggressive multimodal treatments that are usually associated with poor survival rates [20, 21]. The age was the only feature that showed a statistically significant difference between groups. The study group had a higher mean age and lower mean quality of life scores compared with the control group. This is consistent with the study which demonstrated that with aging and its consequences such as declining muscle mass, strength, power, and physical performance, there is also a deterioration of QoL [22].

Previously published studies showed that pain is the most significative, debilitating, and feared symptom of cancer and has a significant impact on the QoL of cancer patients [2326]. This could be a good explanation for the absence of statistically significant differences in the QoL total score between the study and control groups (P=0.084). Curiously, the RC, even when aggressive is not associated with pain [27]. Patients under RT may present with teeth reacting negatively to standard sensitivity testing and do not feel pain even with the absence of periapical lesion indicating a pulp vitality.

In table 2, the DMFT index was higher in the RC group, showing a worse oral health condition of patients in this group. The number of decayed and missing teeth showed statistically significant difference when comparing study and control groups. This aggressive type of caries has a faster progression with a high potential for tooth destruction, which can lead to complete loss of dentition within short periods of time. [3]. The rapid decay progression associated with poor oral health status observed in this patient population [28] makes it difficult to control and maintain a good oral health status in the post-RT period. This could explain the

increased number of decayed and missing teeth found in the study group [29]. For the same reason, the mean scores of sound teeth are statistically higher in the control group. Regarding filled teeth, the control group showed a higher number compared to the study group, but without a statistically significant difference. The causes for the early failure of RC lesions restorations is still controversial. There are increased evidences that residual and secondary RC lesions could facilitate restoration failure when compared to conventional caries [30-33]. This could explain the higher number of filled teeth on the control group even with a smaller number of decayed teeth.

There was a statistically significant difference between study and control group in the saliva and recreation items. The observed hyposalivation in the study groups could be correlated with the development and progression of RC. This could be considered a significant side effect of the RT influencing negatively the QoL [34-36]. In almost all tested variables the patients in the study group had lower mean scores with the exception of appearance and taste. This lowest score in the control group can be explained by the fact that a large number of patients in the control group (62%) underwent major surgical procedures as part of treatment, compared to 40% of the study group. This procedures often are related to extension tumor size and requiring flap, which often generates a considerable change in the appearance and the taste capacity of these patients, as well as the studies by Roger et al., 2010 that show a decrease in these items when related to large tumor size and the presence of flaps [14].

Analyzing the domains most voted, it was observed that the most cited complaints reported by both groups of patients as the main complaint regarding QoL were item related to physical function (saliva, speech and chewing in the study group and saliva, swallowing and speech in the control group) as well as results observed in other studies, which showed that there is a trend for patients to have a more significant physical deficit after treatment and persisting into the longer-term, whereas the social-emotional scores recover faster than the physical domains [14]. In both groups (study and control), the saliva was the domain that received the largest number

of complaints (58% and 52% in the study and control group, respectively), supporting the idea that the xerostomia and hyposalivation is one of the most important toxicities of the HNRT, and is responsible for a large decline in the QoL of the patients [34-36].

And finally, making a correlation between the DMFT index and the physical and social-emotional domains in the study group, it was possible to observe a negative and significant correlation among the number of missing teeth in relation to physical domains. Since this group has a type of caries with a rapid progression pattern, the control of caries becomes difficult and the loss of teeth ends up happening quickly [3], which makes almost impossible prevent a negative impact in the physical factors related to the quality of life, such as chewing, speech and of course, appearance, like the result presented in previous studies which show that specific physical symptoms in the head and neck area present the most difficulties to patients who underwent a head and neck cancer treatment, the absence of teeth became the physical function problems even worse [37,38]. It was also possible to observe a positive and significant correlation among filled teeth and the physical domain. The higher the number of teeth that can be filled, the less the number of teeth which need to be extracted, and thus the maintenance of the function and esthetics, which is an important factor in the patients' QoL [37-38].

In the control group, it was possible to observe a negative and significant correlation among the number of filled teeth in relation to the social-emotional domain, it means that the higher the number of filled teeth, lower the quality of life related to the social-emotional domain. How this group of patients did not develop RC , the number of missing teeth is not so high [3] and the restoration in this group has a long duration and doesn’t present the great number of failure compared to patients with RC [31] what helps in the maintenance of the physical functions like chewing, speech, and appearance compared to the study group. So, the mean problem of this group is related to social-emotional domains and influence how they enjoy life and socialize. It also affects their self-esteem, self-image, and feelings of social well-being [39].

Nevertheless, the findings of the present study contribute to the advancement of scientific knowledge for two main reasons. First, it evaluated general and oral-related QoL (through the QOL questionnaire and DMFT index, respectively) in patients with HNC underwent antineoplastic treatment. Second, it allowed for the identification of the determinants of QoL related to the development of RC in the HNC patients.

Conclusion

RC is related to higher scores of DMFT index, which represent a poor oral health, and lower scores of QoL in patients subjected to RT. Among all the possible items which can alter the QoL, the hyposalivation has the strongest relationship to poor QoL.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflict of interest.

Control of the Data: The authors have full control of all primary data and agree to allow the journal to review our data if requested.

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TABLES

Table 1. Clinicopathological features of patients of study and control groups.

Clinical Features	No. Patients (%)	No. Patients (%)	
	Study group (n=50)	Control group (n=50)	*P* value
Gender			
Male	39 (78)	36 (72)	0.488*
Female	11 (22)	14 (28)	
Age (years)			
Mean (SD)	59.87 (11.12)	52.80 (10.5)	p<0.05**
Range	28-85	21-69	
Location			
Oral cavity	16 (32)	15 (30)	
Oropharynx	23 (46)	20 (40)	0.28***
Salivary glands	0 (0)	4 (8)	
Others	11 (22)	11 (22)	
Stage			
I	0 (0)	1 (2)	
II	5 (10)	3 (6)	0.287†
III	19 (38)	13 (26)	
IV	26 (52)	33 (66)	
Dose (Gy)			
60	8 (16)	8 (16)	0.57*
66	7 (14)	11 (22)	
70	35 (70)	31 (62)	
Treatment			
Sur+RT	8 (16)	8 (16)	
RT	1 (2)	2 (4)	0.057†
CRT	29 (58)	17 (34)	
Sur+CRT	12 (24)	23 (46)	

Sur=surgery; RT= radiotherapy; CRT= chemoradiotherapy; *=Chi2; **=T-test; ***= Mann-Whitney; †=Fisher.

Table 2. Mean score of total QoL questionnaire, physical function, social-emotional functional, and DMFT index for study and control groups.

Groups	QoL total	Physical function	Social-emotional function	DMFT	D	M	F	S
Study	878.1 (182.5) *	390.2 (109.1)*	487.9 (96.9) *	30.5 (2.6) *	6.2 (6.2) *	17.9 (7.3) *	6.1(6.6) *	1.6 (2.6) *
Control	927.2 (131.5) *	411.9 (100.2)*	515.3 (76.9) *	20.7 (8.3)*	1.7 (4.3)*	11.8 (8.1) *	7.0 (5.6) *	11.3 (8.2) *
***P*- value**	0.24	0.41	0.19	< 0.001	< 0.001	< 0.001	0.21	< 0.001

*= Standard deviation; QoL= quality of life; D=decay; M=missing; F=filled; S=sound

Table 3. Mean score of each questionnaire item in study and control groups.

	Study group	Control group	
Domain	**Mean (SD)**	**Mean (SD)**	***P*-value***
Appearance	77.00 (21.33)	76.00 (20.18)	0.810
Swallowing	67.44 (24.82)	72.10 (23.74)	0.340
Chewing	65.00 (35.36)	69.34 (34.73)	0.537
Speech	70.80 (25.80)	76.30 (21.29)	0.250
Taste	68.68 (35.95)	64.00 (32.98)	0.499
Saliva	41.30 (32.79)	54.66 (33.62)	0.047
Pain	82.50 (23.28)	90.50 (20.76)	0.073
Activity	78.50 (22.02)	81.00 (21.17)	0.564
Recreation	74.50 (27.89)	84.84 (18.34)	0.031
Shoulder	87.38 (21.18)	91.86 (19.07)	0.269
Mood	83.00 (24.97)	84.00 (24.62)	0.841
Anxiety	82.04 (26.29)	82.90(22.49)	0.861

*= T-test.

Table 4. Most voted domains in study and control groups.

	Stud / group		Control ;roup	
Rank order	**Domain**	**No. Patients (%)**	**Domain**	**No. Patients (%)**
1	Saliva	29 (58)	Saliva	26 (52)
2	Speech	17 (34)	Swallowing	18 (36)
3	Chewing	14 (28)	Speech	12 (24)

Table 5. Correlation between DMFT index and physical function and social-emotional function in study and control groups.

		Physical function score*		**Social emotional function score***	
		r(s)	*P*-value	r(s)	*P*-value
Study group	DMFT	-0.265	0.063	-0.044	0.762
	Decay	-0.089	0.537	0.049	0.736
	Missing	-0.280	0.049	-0.126	0.385
	Filled	0.368	0.009	0.069	0.635
	Sound	0.275	0.053	0.055	0.707
Control group	DMFT	0.082	0.570	-0.104	0.472
	Decay	0.015	0.920	0.073	0.613
	Missing	-0.016	0.914	0.119	0.409
	Filled	-0.057	0.693	-0.345	0.014
	Sound	-0.087	0.549	0.096	0.506

*Rogers SN, Lowe D, Yueh B, Weymuller EA Jr (2010). The physical function and social-emotional function subscales of the University of Washington Quality of Life Questionnaire. Arch Otolaryngol Head Neck Surg.136(4):352-7. doi: 10.1001/archoto.2010.32

FIGURES

Figure 1. Images of patients underwent HNRT for at least one year. A. Control group patient showing some areas of restoration due to conventional caries, with preservation of the cervical and incisal areas. B. Control group patient showing some areas of conventional caries and incisal wear caused by bruxism. C. Study group patient showing a brown/blackish color alteration affecting the cervical and incisal areas and causing crow amputation of some teeth. D. Study group patient with generalized crown amputation due to RC.

3 CONCLUSÃO

A cárie de radiação é uma toxicidade crônica do tratamento do câncer de cabeça e pescoço com grande potencial de destruição dos dentes, cuja expressividade clínica é capaz de impactar negativamente uma série de aspectos físicos e socioemocionais relacionados à qualidade de vida de pacientes oncológicos. Entretanto, esse prejuízo foi relevante apenas para contextos que envolveram a saliva e as habilidades de recreação dos pacientes.

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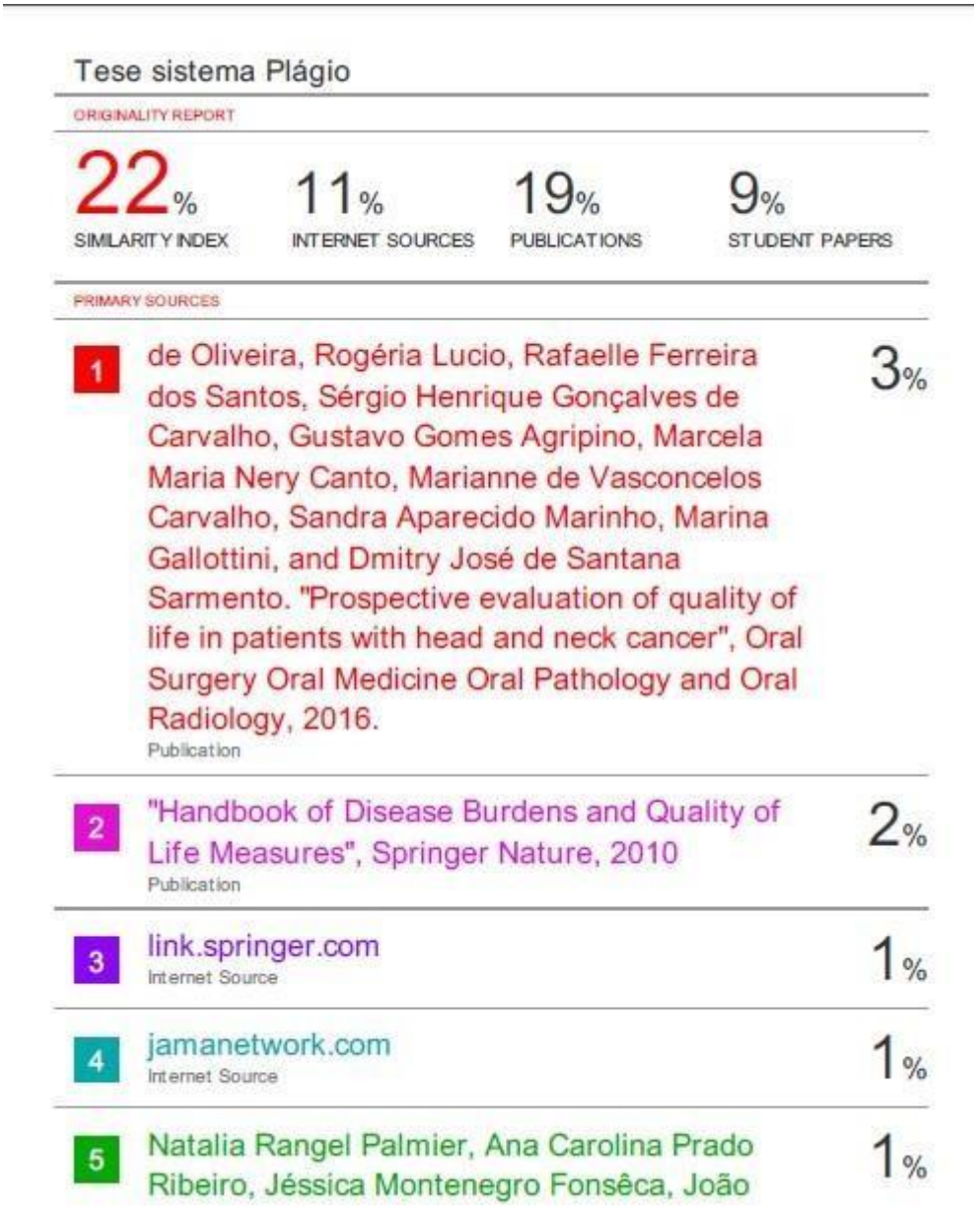
ANEXO 1- Verificação de originalidade e prevenção de plágio



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ANEXO 2. Aprovação do comitê de ética em pesquisa.

USP - FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO - FMUSP

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Impacto da Cárie relacionada à radiação na qualidade de vida de pacientes submetidos à radioterapia de cabeça e pescoço.

Pesquisador: Mariana de Pauli Paglioni

Área Temática:

Versão: 1

CAAE: 87062518.0.0000.0065

Instituição Proponente:

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.647.209

Apresentação do Projeto:

A maioria dos pacientes com câncer de cabeça e pescoço(CCP) recebem altas doses de radiação (RT), muitas vezes em combinação com outras modalidades, como cirurgia e / ou quimioterapia. Altas doses de RT têm efeitos colaterais graves e crônicos significativos nos tecidos oral e maxilofacial. Um dos efeitos colaterais mais impactantes é a cárie relacionada à radiação(CRR), que é agressiva e com evolução rápida e impacta negativamente sobre a função e a estética desses pacientes e afeta a qualidade de vida (QoL) do paciente.

O objetivo deste estudo multicêntrico é correlacionar os escores de QoL dos pacientes submetidos à RT de cabeça e pescoço através de um questionário específico

(Questionário de Qualidade de Vida da Universidade de Washington (UW-QoL)) com os dentes cariados, perdidos e obturados(CPOD) em patientes que desenvolvem e não desenvolvem a CRR e, por meio disso, determinar se a CRR é capaz de causar uma diminuição significativa na QoL.

Cem (100) pacientes tratados no Instituto do Câncer do Estado de São Paulo (ICESP-FMUSP) para CCP por RDT, isolados ou em combinação com outra modalidade, participarão desse estudo. Os pacientes serão separados em grupos teste (n = 50) e controle (n = 50). O grupo de teste será composto de pacientes que foram submetidos a RDT para tratamento de câncer de cabeça e pescoço há mais de 1 ano e desenvolveram CRR. O

grupo de controle será composto de pacientes submetidos à RDT para o tratamento de câncer de

Endereço: DOUTOR ARNALDO 251 21º andar sala 36
Bairro: PACAEMBU **CEP:** 01.246-903
UF: SP **Município:** SAO PAULO
Telefone: (11)3893-4401 **E-mail:** cep.fm@usp.br

cabeça e pescoço há mais de 1 ano e não desenvolveram CRR.
Os dados clinicopatológicos, como gênero, idade, local do tumor, estadiamento do tumor, dose de RDT e tempo de conclusão do tratamento, serão obtidos dos registros médicos. Todos os pacientes responderão ao questionário UW-QoL. Os pacientes serão avaliados para uma classificação de dentes cariados, perdidos e obturados (CPOD).

Objetivo da Pesquisa:
O objetivo deste estudo é avaliar a aplicação de um questionário específico (UWQoL)
o impacto dessa complicação da RDT na QoL dos pacientes com câncer e através do índice, o CPOD correlacionou a QoL com a saúde bucal do paciente.

Avaliação dos Riscos e Benefícios:
Não existem riscos, uma vez que os pacientes apenas responderam a questionários sobre a qualidade de vida e passarão por uma consulta clínica para avaliação do índice CPOD. Nenhum paciente terá sua identidade revelada. A radioterapia foi utilizada como forma de tratamento nesses pacientes de maneira totalmente independente a realização desse estudo.
Quanto aos benefícios, através dos resultados obtidos poderemos avaliar as principais queixas relacionadas á toxicidades pós - radioterapia dos pacientes, buscando estratégias para melhorar a qualidade de vida desses pacientes no período pós- radioterapia.

Comentários e Considerações sobre a Pesquisa:
Trata-se de um estudo com a finalidade de doutorado. A pesquisa encontra-se bem elaborada e organizada, com objetivo claro e bem definido e metodologia adequada para atingir o objetivo proposto.

Considerações sobre os Termos de apresentação obrigatória:
Os termos de apresentação obrigatória encontram-se adequados.

Recomendações:
Nada a declarar.

Conclusões ou Pendências e Lista de Inadequações:
Sugiro aprovação do projeto.

Considerações Finais a critério do CEP:

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Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_991831.pdf	02/04/2018 14:49:10		Aceito
Outros	faculdademedicina.pdf	02/04/2018 14:48:56	Mariana de Pauli Paglioni	Aceito
Folha de Rosto	1folhaderosto.pdf	02/04/2018 14:48:32	Mariana de Pauli Paglioni	Aceito
Outros	NP.pdf	27/02/2018 14:20:25	Mariana de Pauli Paglioni	Aceito
Outros	4comentarios.pdf	27/02/2018 14:18:50	Mariana de Pauli Paglioni	Aceito
Declaração de Instituição e Infraestrutura	62DecInst.pdf	27/02/2018 14:18:07	Mariana de Pauli Paglioni	Aceito
Declaração de Pesquisadores	61DecPesq.pdf	27/02/2018 14:17:54	Mariana de Pauli Paglioni	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	5TCLE.pdf	27/02/2018 14:17:36	Mariana de Pauli Paglioni	Aceito
Projeto Detalhado / Brochura Investigador	3projeto.pdf	27/02/2018 14:16:42	Mariana de Pauli Paglioni	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 10 de Maio de 2018

Assinado por:
Maria Aparecida Azevedo Koike Folgueira
(Coordenador)

Endereço: DOUTOR ARNALDO 251 21º andar sala 36
Bairro: PACAEMBU **CEP:** 01.246-903
UF: SP **Município:** SAO PAULO
Telefone: (11)3893-4401 **E-mail:** cep.fm@usp.br

ANEXO 3. Comprovante de submissão do artigo.

Dear Dr Prado-Ribeiro,

Your submission entitled "Impact of radiation caries in the quality of life of head and neck cancer patients" has been received by journal Supportive Care in Cancer.

You will be able to check on the progress of your paper by logging on to Editorial Manager as an author. The URL is https://www.editorialmanager.com/jscc/.

Circumstances may vary, but the review process can usually take 6-8 weeks to be completed after reviewers have agreed to evaluate a manuscript. You can follow the progress of your paper through our online system. If you have not received a decision from the Editor-in-Chief by 8 weeks from the date you submitted your paper, you may also inquire regarding its status by clicking on the CONTACT US link in Editorial Manager.

The submission id is: JSCC-D-19-00257
Please refer to this number in any future correspondence.

Thank you for submitting your work to this journal.
Kind regards,

Lori Fleming
Editorial Office
Supportive Care in Cancer

Now that your article will undergo the editorial and peer review process, it is the right time to think about publishing your article as open access. With open access your article will become freely available to anyone worldwide and you will easily comply with open access mandates. Springer's open access offering for this journal is called Open Choice (find more information on www.springer.com/openchoice). Once your article is accepted, you will be offered the option to publish through open access. So you might want to talk to your institution and funder now to see how payment could be organized; for an overview of available open access funding please go to www.springer.com/oafunding.
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