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WAGNER GOMES DA SILVA

IMPACTO DA RADIAÇÃO NA SOBREVIDA DENTÁRIA DE PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO: UM ESTUDO RETROSPECTIVO BASEADO EM DOSIMETRIA

IMPACT OF RADIATION ON TEETH SURVIVAL OF HEAD AND NECK CANCER PATIENTS: A DOSIMETRIC-BASED RETROSPECTIVE STUDY

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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 Doutor em Estomatopatologia, na Área de Patologia.

Thesis presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of the requirements for the degree of Doctor in Stomatopathology, in Pathology area.

Orientador: Prof. Dr. Alan Roger dos Santos Silva
Coorientador: Prof. Dr. Mario Fernando de Goes

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PROF. DR. MÁRCIO AJUDARTE LOPES

A Ata da defesa com as respectivas assinaturas dos membros encontra-se no processo de vida acadêmica do aluno.

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RESUMO

Objetivos: Caracterizar eventos dentários adversos (EDA) associados à extração pós-radioterapia (RT) e analisar o impacto da radiação na sobrevida dos dentes de pacientes com carcinomas espinocelulares (CEC) da cabeça e do pescoço. Métodos: Este é um estudo retrospectivo, baseado na distribuição dosimétrica dentária individual de pacientes com CEC da cabeça e do pescoço. O estudo caracterizou os EDA mais relevantes associados a extrações pós-RT, investigou o impacto de 3 gradientes de radiação dentária (<30 Gy, 30-60 Gy e >60 Gy), assim como os grupos dentários anatômicos [anteriores (A), pré-molares (PM) e molares (M); ipsilaterais (i) ou contralaterais (c); maxilares (Max) ou mandibulares (Man)] na sobrevida de dentes pós-RT por meio da análise de sobrevida de Kaplan-Meier e o teste de log-rank. Por fim, o risco de extração dentária pós-RT para cada gradiente de radiação foi calculado por meio do *odds ratio* (OR) com intervalos de confiança (IC) de 95%. Resultados: 1.071 dentes, de 66 pacientes que concluíram a RT para o tratamento de CEC da cabeça e do pescoço, foram incluídos neste estudo. A cárie-relacionada à radioterapia (CRR) foi o EDA mais frequentemente (67.8%) associado a extrações pós-RT. A prevalência de CRR e periodontite apical variou de modo estatisticamente significativo ($p<0.01$ e 0.04, respectivamente) entre os dentes que receberam diferentes gradientes de radiação. Após 41,5 (±17,4) meses de seguimento pós-RT, a taxa de sobrevida dentária global foi de 38.7%, as taxas de sobrevida específicas por gradiente de radiação (<30 Gy, 30-60 Gy e >60 Gy) foram 44.4%, 37.1% e 18.8%, respectivamente, e a sobrevida média dentária específica por gradiente de radiação foi de 38,6 meses (IC: 36.1-41.2), 39,6 meses (IC: 37.7-41.5) e 30,5 meses (IC: 25.0-36.1), respectivamente ($p=0.004$). Considerando-se os grupos dentários anatômicos, os resultados revelaram a seguinte distribuição da sobrevida média dentária: MiMax < McMan < McMax < MiMan < PMiMan < AiMan < AcMan < PMcMan < PMiMax < PMcMax < AiMax < AcMax ($p<0.001$). O OR para extração dentária pós-RT aumentou seguindo a tendência crescente dos gradientes de radiação dentários e alcançou um risco aproximadamente três vezes maior para dentes submetidos a doses >60 Gy (IC: 1.56-5.35; $p<0.001$). Conclusão: A CRR foi o principal EDA em dentes submetidos à extração pós-RT e a análise dosimétrica sugeriu que dentes que receberam doses de radiação >60 Gy apresentaram menor sobrevida pós-RT.

Palavras-chave: Neoplasias de cabeça e pescoço. Radioterapia. Cárie dentária. Doenças periodontais. Dentes.

ABSTRACT

Purpose: To characterize the dental adverse events (DAE) associated with post-head and neck radiotherapy (HNRT) teeth extractions and to investigate the impact of radiation on teeth survival in head and neck squamous cell carcinoma (HNSCC) patients. Methods: A retrospective dosimetric-based analysis of individual post-HNRT tooth from HNSCC patients was conducted. The most prevalent DAE affecting post-HNRT extracted teeth were categorized and the impact of 3 different radiation dose tiers (<30 Gy, 30-60 Gy and >60 Gy) as well as the anatomical teeth groups [anterior teeth (A), premolars (PM), and molars (M); ipsilateral (i) or contralateral (c); maxillary (Max) or mandibular (Man) teeth] on teeth survival was analyzed, using the Kaplan-Meier analysis and the log-rank test. The risk assessment, *odds ratio* (OR), for post-HNRT tooth extraction was further calculated for each studied radiation dose tier with a 95% coincidence level set to test the significance. Results: 1,071 teeth, from 66 patients with HNSCC who underwent HNRT, were included in this study. Radiation-related caries (RRC) was the most frequent (67.8%) DAE associated with post-HNRT teeth extractions. The prevalence of RRC and apical periodontitis significantly differed among teeth subjected to the different studied radiation dose tiers (p<0.01 and 0.04, respectively). After a mean follow-up of 41.5 (±17.4) months, the overall teeth survival rate was 38.7%, and specific teeth survival rates regarding each radiation dose tier (<30 Gy, 30-60 Gy and >60 Gy) were 44.4%, 37.1% and 18.8%, respectively. Following the same radiation dose tiers distribution, mean teeth survival was 38.6 (CI: 36.1-41.2) months, 39.6 (CI: 37.7-41.5) months and 30.5 (CI: 25.0-36.1), respectively (p=0.004). In terms of anatomical teeth groups, the results showed that mean teeth survival was: MiMax < McMan < McMax < MiMan < PMiMan < AiMan < AcMan < PMcMan < PMiMax < PMcMax < AiMax < AcMax (p<0.001). The OR for post-HNRT tooth extraction increased according to the increment of the radiation dose tiers, reaching approximately 3-fold higher risk for teeth subjected to >60 Gy (CI: 1.56-5.35; p<0.001). Conclusions: RCC was the major cause of dental extractions following HNRT and the dosimetric analysis suggested that teeth exposed to radiation doses >60 Gy presented reduced survival.

Key Words: Head and neck neoplasms. Radiotherapy. Dental caries. Periodontal diseases. Teeth.

SUMÁRIO

1 INTRODUÇÃO

O câncer de cabeça e pescoço (CCP) envolve um amplo grupo de neoplasias malignas, que inclui os tumores do trato aero-digestivo superior, como aqueles que afetam a cavidade oral, a faringe e a laringe. Devido à maneira com a qual os dados epidemiológicos do CCP são reportados, os números referentes à exata prevalência das neoplasias afetando essa região anatômica são difíceis de serem conhecidos. No entanto, de maneira geral, o CCP ocupa a sexta colocação dentre os tumores malignos mais frequentes na população mundial (Huber e Terezhalmy, 2003; Duvvuri e Myers, 2009). O câncer de cavidade oral e dos lábios encontra-se na 15ª colocação mundial de neoplasias malignas mais prevalentes, com mais de 300.000 novos casos diagnosticados em 2012 (2% do total). E os tumores malignos da faringe são estimados em mais de 140.000 neste mesmo levantamento, representando, aproximadamente, 1% do total de casos de câncer no mundo (Ferlay et al., 2013). Além disso, estimam-se mais de 670.000 novos casos de CCP em todo o mundo anualmente, totalizando aproximadamente 6% de todas as neoplasias malignas; assim como aproximadamente 350.000 mortes a cada ano (Parkin et al., 2002; Argiris et al., 2008; Matzinger et al., 2009; INCA, 2016). Cerca de 90% destes casos são classificados como carcinomas espinocelulares (CECs), sendo este, portanto, o tipo histológico mais comumente encontrado (Duvvuri e Myers, 2009).

Os principais fatores de risco para os CECs da cabeça e do pescoço são o tabagismo e o consumo de bebidas alcoólicas, os quais, quando associados, apresentam efeitos carcinogênicos sinérgicos (Pelucchi et al., 2008). Outros fatores de risco como a infecção pelo papiloma vírus humano (HPV - genótipos 16 e 18) – principalmente para os tumores não-queratinizantes de orofaringe (D’Souza et al., 2007; Sturgis et al., 2007) –, a exposição solar (no caso dos tumores de lábio), a dieta, fatores genéticos e epigenéticos, dentre outros, também estão relacionados com a patogênese desses tumores (Pelucchi et al., 2008; Tarvainen et al., 2008; Hashibe et al., 2009).

Três modalidades principais são usadas no tratamento dos CECs da cabeça e do pescoço: ressecção cirúrgica, radioterapia (RT) e terapias sistêmicas, incluindo drogas quimioterápicas. Dependendo, principalmente, do tipo de tumor e do estágio clínico da doença, as estratégias de tratamento podem incluir uma, duas, ou até mesmo as três modalidades supramencionadas em associação. A escolha da combinação dos tratamentos adequados dependerá, adicionalmente, das condições físicas do paciente, das morbidades esperadas, da qualificação da equipe médica, da infraestrutura disponível em cada serviço e da decisão individual de cada paciente (Scully et al., 2006; Huang e O'sullivan, 2013; Marta et al., 2015).

O estadiamento clínico dos CECs de cabeça e pescoço considera, principalmente, o tamanho do tumor primário, o tamanho e a quantidade dos linfonodos cervicais envolvidos, e a presença de metástases à distância, como os principais fatores clínicos prognósticos, cujas características influenciam diretamente na escolha do tipo de abordagem terapêutica indicada (Wittekind et al., 2001; Kowalski et al., 2005). Diversos estudos têm mostrado que a maior parte desses tumores é diagnosticada tardiamente, ou seja, no momento do diagnóstico o paciente apresenta estadiamento clínico avançado, o que costuma ocasionar, por consequência, um pior prognóstico e a necessidade de tratamentos mais agressivos (Scully e Felix, 2006; Warnakulasuriya et al., 2007).

A cirurgia ainda é considerada o tratamento primário para grande parte dos casos de CEC de cabeça e pescoço. Contudo, esta técnica muitas vezes é limitada por sua morbidade nos casos de tumores avançados ou quando há o envolvimento de estruturas anatômicas importantes ou vitais para o paciente (Brener et al., 2007). Nestas circunstâncias, a RT é central no tratamento oncológico e pode ser utilizada de modo isolado ou combinado a terapia sistêmicas, de maneira adjuvante, ou até mesmo como alternativa para tratamentos com intuito paliativo e hemostático (Lefebvre, 2006). Um aprimoramento nas taxas de sucesso terapêutico de casos avançados e um aumento nas taxas de sobrevida foi obtido com a introdução da radioquimioterapia concomitante, que combina o efeito dessas duas modalidades, ao aumentar a sensibilidade das células malignas aos efeitos da radiação ionizante e melhorar a capacidade de controle de possíveis metástases (Leibel et al., 1991; Adelstein et al., 1997; Bucheler et al., 2012).

No princípio da prática da RT, utilizava-se a técnica bidimensional (2D) baseada em exames de radiografias convencionais tomadas dos pacientes. Posteriormente, a radioterapia conformacional tridimensional (3DRT) foi introduzida na prática clínica, o que permitiu a avaliação da distribuição da dose de radiação nos tecidos alvos a partir de cortes axiais obtidos de exames de tomografia computadorizada. Mais recentemente, a radioterapia de intensidade modulada (IMRT) permitiu gradientes maiores entre a dose entregue no volume alvo e a dose no volume dos órgãos adjacentes em risco (não-alvo), possibilitando, portanto, uma maior eficiência em entregar a dose de tratamento ao tumor, sem, contudo, aumentar as toxicidades decorrentes da radiação (Huber e Terezhalmy, 2003; Vissink et al., 2003; Lee e Terezakis, 2008).

A despeito dos seus efeitos terapêuticos anti-neoplásicos e da evolução tecnológica mencionada, a radiação ionizante é responsável pelo desenvolvimento de diversos efeitos adversos nos tecidos incluídos no interior do campo de radiação, no qual estão inseridos o tumor primário, cadeias linfáticas acometidas ou potencialmente acometidas, e a área delineada ao seu redor; podendo resultar em considerável morbidade física e psíquica (Huber e Terezhalmy, 2003; Vissink et al., 2003; Sciubba e Goldenberg, 2006). Na região da cabeça e do pescoço, encontram-se estruturas que desempenham papéis importantes como a pele, músculos, mucosas, glândulas salivares, ossos e dentes, entre outros, os quais são potencialmente afetados quando envolvidos nos campos de radiação. Consequentemente, desenvolvem-se toxicidades bucais e maxilofaciais que incluem, principalmente, a radiodermite, o trismo, a mucosite oral, a disgeusia, a disfagia, a disfunção das glândulas salivares (hipossalivação), a osteorradionecrose (ORN) e a cárie relacionada à radioterapia (CRR), entre outras (Vissink et al., 2003; Kielbassa et al., 2006; Sciubba e Goldenberg, 2006; Tolentino et al., 2011).

Apesar de alguns autores atribuírem à radiação efeitos diretos na microestrutura do esmalte, da dentina e da polpa dentária, bem como em seus tecidos de suporte; os efeitos indiretos relacionados ao aglomerado de complicações bucais (Brennan et al., 2010; Ribeiro et al., 2013) que incluem a hipossalivação, as alterações na composição da microbiota bucal, o incremento de uma dieta rica em carboidratos (mais cariogênica) e a higiene bucal deficiente, são apontados como os principais fatores para o início e o desenvolvimento de eventos dentários adversos (EDA) relacionados à RT como a CRR e a doença periodontal (DP), que costumam apresentar um padrão mais agressivo nesses pacientes (Silva et al., 2009; Gomes-Silva et al., 2017a). É relevante mencionar, nesse contexto, que a controvérsia impera no que diz respeito ao potencial da RT causar dano direto aos dentes e aos tecidos do ligamento periodontal incluídos nos campos de radiação de pacientes oncológicos (Lieshout e Bots, 2014).

A CRR, considerada um dos maiores desafios no tratamento odontológico dos pacientes irradiados na região de cabeça e pescoço, pode tornar-se evidente pouco tempo (6 a 12 meses) após a conclusão da RT (Kielbassa, 2006; Palmier et al., 2017). Clinicamente, a

CRR inicia-se nas áreas cervicais dentárias, nas superfícies incisais dos dentes anteriores e pontas das cúspides dos dentes posteriores, afetando inclusive faces dentárias menos frequentemente afetados por cárie em pacientes não irradiados, como as superfícies vestibulares e linguais dos incisivos inferiores (Silva et al., 2009). As lesões de cárie evoluem de forma progressiva, circundando a região cervical dos dentes, gerando mudanças no padrão de translucidez e coloração na forma de uma pigmentação amarronzada nas superfícies lisas do esmalte e da dentina que já podem apresentar desmineralizações sub-superficiais (não-cavitadas) (Silva et al., 2009). Adicionalmente, um aumento da friabilidade dentária, com consequente perda do esmalte em um padrão conhecido como "delaminação", pode ser notado, nos casos de CRR não tratados; e este é considerado fenômeno clínico basilar na progressão da CRR (Kielbassa et al., 2006; McGuire et al., 2014a; McGuire et al., 2014b). O insidioso início e a rápida progressão das lesões de CRR podem levar à amputação das coroas dentárias e, em estágios avançados, perda completa da dentição em um curto período de tempo (Kielbassa et al., 2006; Silva et al., 2009; Madrid et al., 2017; Palmier et al., 2017).

Em uma revisão sistemática, Hong et al. (2010) revelaram que a prevalência de cáries em pacientes pós-RT, e pós-radioquimioterapia foi de 24% e 21,4%, respectivamente. Nestes mesmo estudo, os autores sugeriram que o índice CPOD (dentes cariados, perdidos e obturados) pode chegar a 17,01 nos pacientes tratados com RT na região de cabeça e pescoço. Estima-se, contudo, que esses números podem variar consideravelmente dependendo da população estudada e, principalmente, do nível socioeconômico e cultural dos pacientes.

Ainda no contexto dos EDA atribuídos à RT, estudos prévios já apontaram aumento nos índices de perdas dentárias, por perda de inserção clínica e perda óssea alveolar, além de retrações gengivais em pacientes submetidos à RT em cabeça e pescoço (Yusof e Bakri, 1993; Epstein et al., 1998; Ammajan et al., 2013). Um estudo em particular concluiu que a inclusão da maxila no campo de radiação do tumor aumenta os índices de perda de inserção óssea, presumindo que os efeitos diretos da radiação induzem DP (Marques et al., 2004). Contudo, ainda não estão disponíveis resultados de estudos clínicos com base dosimétrica que avaliem o impacto da RT no início e na progressão da DP.

Uma etapa crucial na prevenção das toxidades bucais e dos EDA relacionados à RT é a adequação bucal prévia ao início do tratamento oncológico (Lockhart et al., 1994). Nesta etapa pontos importantes devem ser considerados, como o prognóstico oncológico do paciente e sua condição médica geral, o estado geral dos dentes, a capacidade de higiene bucal, a presença, ou não, das glândulas salivares maiores no campo de radiação, a capacitação e a infraestrutura da equipe odontológica (Sonis et al., 1990; Ben-David et a., 2007). Infelizmente, a atenção odontológica pré-RT para pacientes com CCP não é acessível e protocolar em todos os serviços de Oncologia. Outro agravante é o fato das diretrizes clínicas de atendimento odontológico variarem consideravelmente entre equipes e diferentes centros de tratamento; sendo baseados, em grande parte, na experiência empírica dos profissionais das equipes odontológicas (Lalla et al., 2017). Neste campo, existe uma tendência contemporânea a considerar os gradientes e os padrões dosimétricos que serão entregues aos tecidos inseridos no campo de radiação para o planejamento da adequação bucal com o objetivo de prever riscos relativos para o desenvolvimento de toxicidades bucais e EDA (Reuther et al., 2003; Deasy et al., 2010; Walker et al., 2011).

A título de exemplo, estudos recomendam que a hipossalivação severa pode ser prevenida ou reduzida se uma das glândulas parótidas receber dose de radiação <20 Gy ou se as duas glândulas receberem doses <25 Gy (Deasy et al., 2010). Também é bem aceito o fato do risco da ORN ser maior nos segmentos dos ossos maxilo-mandibulares que receberam >60 Gy; e este risco é considerado moderado para áreas que receberam doses de radiação entre 40 e 60 Gy e baixo para doses <40 Gy (Reuther et al., 2003). Nesse mesmo cenário, existe uma tendência atual pela busca de parâmetros dosimétricos que possam prever o risco de desenvolvimento de EDA relacionados à RT. Entre os poucos estudos clínicos disponíveis até o momento está o trabalho de Walker et al. (2011) que mostrou que dentes que receberam doses de radiação >60 Gy apresentaram risco aumentado (até 10 vezes superior ao dos dentes que receberam doses menores) de colapso da estrutura dentária (*dentition breakdown*) relacionado à CRR. O mesmo estudo apontou que até mesmo os dentes que receberam doses entre 30 e 60 Gy apresentaram risco aumentado de dano radiogênico direto.

Estudos dosimétricos recentes também demonstraram que a dose de radiação acumulada nos dentes pode chegar a 99% da dose total prescrita para o tumor primário. Nesse sentido, trabalhos recentes de nosso grupo sugeriram que mesmo que a técnica IMRT gere, quando comparada com a técnica 3DRT, gradientes de doses menores para alguns grupos dentários, a dose total de radiação recebida pela maior parte dos dentes de pacientes irradiados em cabeça e pescoço ainda se encontra nos patamares definidos por outros autores como de risco aumentado para alguns EDA (Hansen et al., 2012; Morais-Faria et al., 2015; Bak et al., 2016; Fregnani et al., 2016). É oportuno esclarecer que apesar de existir lastro de literatura sugerindo que pacientes submetidos à IMRT apresentem menores índices de extrações dentárias pós-RT (em relação a pacientes tratados pela técnica convencional ou 3DRT), os resultados não foram significantes do ponto de vista estatístico (Duarte et al, 2014). As bases do conhecimento atual apontam para a definição de protocolos de planejamento radioterápico que busquem a diminuição da dose de radiação entregue aos dentes e seus tecidos de suporte adjacentes, com o intuito de minimizar os potenciais efeitos diretos da radiação no desenvolvimento de EDA (Thariat et al., 2012; Thompson et al., 2013; Rouers et al., 2016).

Apesar da dificuldade de manejo das complicações bucais da RT, sobretudo da CRR, procedimentos mutiladores como exodontias totais ou extrações profiláticas de dentes hígidos devem ser evitadas devido ao impacto negativo que esses procedimentos geram na qualidade de vida dos pacientes (Rankow e Weissman, 1971; Solomon et al., 1968; Main, 1983; Vissink et al. 2003). Somam-se a esse conceito, evidências clínicas de que extrações dentais pré-RDT não são capazes, por si sós, de reduzir o risco de ORN (Wahl, 2006). A despeito do tempo e dos recursos investidos na adequação bucal pré-RT, uma miríade de fatores clínicos, muitos deles ainda pouco caracterizados cientificamente, pode diminuir a sobrevida pós-RT dos dentes e gerar indicação para extrações dentárias após a conclusão da RT, não obstante o risco de ORN (Sulaiman et al., 2003; Koga et al., 2008a; Koga et al., 2008b).

Tendo em vista o exposto, o objetivo deste estudo foi avaliar a frequência dos EDA em dentes extraídos após a RT e o impacto de diferentes gradientes dosimétricos de radiação entregue aos dentes de pacientes com CCP na sobrevida dentária. Foi testada a hipótese de que dentes submetidos a altas doses de radiação, durante o tratamento do CCP, apresentam redução no tempo de sobrevida pós-RT.

2 ARTIGO: Impact of Radiation on Teeth Survival of Head and Neck Cancer Patients: A Retrospective Dosimetric-based Study

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Conflict of interest statement

The authors declare that they have no conflicts of interest.

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Abstract

Purpose: To characterize the dental adverse events (DAE) associated with post-head and neck radiotherapy (HNRT) teeth extractions and to investigate the impact of radiation on teeth survival in head and neck squamous cell carcinoma (HNSCC) patients. Methods: A retrospective dosimetric-based analysis of individual post-HNRT tooth from HNSCC patients was conducted. The most prevalent DAE affecting post-HNRT extracted teeth were categorized and the impact of 3 different radiation dose tiers (<30 Gy, 30-60 Gy and >60 Gy), as well as the impact of anatomical teeth groups [anterior teeth (A), premolars (PM), and molars (M); ipsilateral (i) or contralateral (c); maxillary (Max) or mandibular (Man) teeth], on teeth survival, were analyzed using the Kaplan-Meier analysis and the log-rank test. The risk assessment, *odds ratio* (OR), for post-HNRT tooth extraction was further calculated for each studied radiation dose tier with a 95% coincidence level set to test the significance. Results: 1,071 teeth, from 66 patients with HNSCC who underwent HNRT, were included in this study. Radiation-related caries (RRC) was the most frequent (67.8%) DAE associated with post-HNRT teeth extractions. The prevalence of RRC and apical periodontitis significantly differed among teeth subjected to the different studied radiation dose tiers (p<0.01 and 0.04, respectively). After a mean follow-up of 41.5 (±17.4) months, the overall teeth survival rate was 38.7%, and specific teeth survival rates regarding each radiation dose tier (<30 Gy, 30-60 Gy and >60 Gy) were 44.4%, 37.1% and 18.8%, respectively. Following the same radiation dose tiers distribution, mean teeth survival was 38.6 (CI: 36.1-41.2) months, 39.6 (CI: 37.7-41.5) months and 30.5 (CI: 25.0-36.1), respectively (p=0.004). The impact of anatomical teeth groups on mean teeth survival times was: MiMax < McMan < McMax < MiMan < PMiMan < AiMan < AcMan < PMcMan < PMiMax < PMcMax < AiMax < AcMax (p<0.001). The OR for post-HNRT tooth extraction increased according to the increment of the radiation dose tiers, reaching approximately 3-fold higher risk for teeth subjected to >60 Gy (CI: 1.56-5.35; p<0.001). Conclusions: RCC was the major cause of dental extractions following HNRT and the dosimetric analysis suggested that teeth exposed to radiation doses >60 Gy presented reduced survival.

Key words: Head and neck cancer, Radiotherapy, Dental caries, Periodontal disease, Teeth, Survival.

Introduction

Head and neck radiotherapy (HNRT) has been widely used for treating head and neck cancer (HNC) (1). In spite of its antineoplastic effects, HNRT can generate damage to sound tissues within the radiation fields, such as skin, muscles, oral mucosa, salivary glands, teeth and jawbones, which are the most affected non-targeted organs and structures in the head and neck region. This scenario gives rise to a myriad of oral toxicities that includes mucositis, dysgeusia, dysphagia, hyposalivation, trismus, radiation-related caries (RRC) and osteoradionecrosis (ORN) (2,3).

Many questions remain unclear whether radiation, by its direct effects, can increase the risks for dental adverse events (DAE), such as RRC and periodontal disease (PD) (4-7). These are currently considered multifactorial oral diseases in which the indirect effects of radiotherapy (RT); including salivary dysfunction, oral microbiota shift, dietary changes and deficient oral hygiene; seem to have an impact on its onset and clinical patterns (8-10). This sequence of clinical events, known as 'clustering of oral complications', seems to be more important than direct effects of radiation on dental tissues and periodontium, and may be regarded in the context of the patients submitted to HNRT (9,11,12).

Several DAE are able to reduce teeth survival rates following HNRT, leading to the need of dental extractions following the conclusion of HNRT and a consequent increased risk for ORN (13-15). Although a recent study (6) has identified a radiation threshold (>60 Gy) that would induce direct teeth damage and increase the risk of dentition breakdown 10-fold (>60 Gy), there have been few dosimetric studies examining the impact of different radiation doses on DAE (5,16). To our knowledge, there is no available study analyzing the impact of radiation on teeth survival rates.

It is worth mentioning that, in the recent past, full-mouth dental extractions were advocated before HNRT for most of the patients with advanced head and neck squamous cell carcinoma (HNSCC), prophylactically for ORN (3,17-19). However, recent advances in the field of dental treatment for cancer patients allowed more conservative pre-HNRT dental treatment planning (20). In spite of the advances in the knowledge of the impact of HNRT on teeth and teeth-bearing areas, there's still need for the development of dosimetric-based guidelines aiming to improve clinical decisions and dental treatment protocols (21).

Therefore, the aim of this study was to assess the most prevalent DAE leading to post-HNRT extraction and to investigate the impact of different radiation dose tiers on DAE patterns and teeth survival rates in HNSCC patients.

Methods

Study protocol

This study was approved by the Ethics Committee of the Hospital das Clínicas de São Paulo (737157/2016), Faculdade de Medicina da Universidade de São Paulo, Brazil, and was conducted in accordance with the Declaration of Helsinki to human studies. A retrospective analysis reviewed patients in the period from 2008 to 2013 at *Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina da Universidade de São Paulo, São Paulo*, Brazil. Following the dosimetric protocol of a previous study of our group (22), the current study was based on patients treated for HNSCC of the following primary sites, oral cavity (except tongue), lateral border of the tongue, oropharynx (base of tongue, tonsils and soft palate), nasopharynx and larynx.

Inclusion criteria

Teeth from selected patients were included in this study when comprehensive dental treatment was performed before the beginning of HNRT and complete dental treatment records following HNRT were available in their medical charts. Patients had to be submitted to at least one dental extraction following HNRT and had to be subjected to curative HNRT protocols based on tridimensional conformal radiotherapy (3DRT) in 6 MV linear accelerator on Synergy Platform (Elekta AB, Stockholm, Sweden) or Intensity-Modulated Radiation Therapy (IMRT) in linear accelerator and photons energy ranging from 6 to 15 MV on Linear Accelerator Elekta Axesse (Elekta AB, Stockholm, Sweden) with cumulative radiation doses that ranged from 60 to 70 Gy (2 Gy/day; 5 days/week from Monday to Friday).

Exclusion criteria

Teeth from patients with non-HNSCC, patients subjected to non-curative, unconventional RT protocols (e.g. hypo or hyperfractioned) or re-irradiation, patients with less than one year of follow-up after the conclusion HNRT, and patients lacking complete radiation plan data were exclude from the study.

Patient's and treatment information

Medical and dental treatment records were retrieved from the electronic medical record system Tasy (Philips Clinical informatics, Blumenau, Brazil) and reviewed for gender, age, alcohol and tobacco consumption, primary tumor location, stage of the malignant disease according to the TNM classification system (Union for International Cancer Control – UICC 7th Edition) and the cancer staging from the American Joint Committee on Cancer (AJJC Cancer Stage Manual, 6th Edition). Patient's overall survival rate (OS), disease-free survival rate (DFS) and the incidence of recurrences (local-regional and distant relapse rates) and second primary tumors were also recorded. Data regarding HNRT intention, RT technics employed and mean total volume doses of radiation prescribe to tumor volumes were recorded from the software MOSAIQ Radiation Oncology (Elekta, Stockholm, Sweden).

Dosimetric analysis and DAE characterization

In order to potentially analyze direct effects of radiation on tooth structure, the present study was based on the mean radiation doses delivered to individual tooth, which was calculated following the criteria of previous publications of our research group (22,23). In brief, teeth included in this study were categorized into 3 groups, according to anatomic origin, including anterior teeth, premolars, and molars. These groups were further classified into maxillary and mandibular teeth both ipsilateral and contralateral sides of the primary tumor location. Patient's computerized treatment plans were reviewed to calculate the cumulative doses of radiation delivered to each individual tooth using calculation algorithms that incorporate 3D beam modeling on CMS XiO (Elekta CMS Software, St. Louis, Missouri) version 4.60. Individual radiation tooth doses were calculated by the mean doses delivered for each teeth group as previously described (22). Teeth were further divided into 3 categorical radiation dose tiers (<30 Gy, 30-60 Gy and >60 Gy), following the criteria of Walker et al., 2011 (6), to determine if there was a threshold of exposure at which there would be an impact on DAE patterns or teeth survival rates.

A dentist examiner, blinded to the amount of radiation exposure, retrospectively assessed DAE [RRC, periodontal disease (PD) and apical periodontitis (AP)] associated with post-HNRT teeth extraction. DAE patterns were registered following specific criteria: RRC diagnosis was performed using a combined clinical and radiographic model analysis from dental treatment records and patient's digital panoramic radiographs. PD was diagnosed considering the marginal bone loss (MBL) assessment from patient's digital panoramic radiographs and categorized according the criteria of Panezai et al. (2017) (24). AP diagnosis was conducted according to the modified protocol described by Hommez et al. (2012) (25). DAE other than RRC, PD and AP were not characterized and were pooled together. Non-extracted post-HNRT teeth were only included for teeth survival analysis.

Statistical analysis and teeth survival

Descriptive statistics was recorded for patient's clinicopathologic data and treatment information; these results were expressed as mean values, standard deviation (SD), and percentages. Mean teeth survival rates were calculated from the date of the conclusion of HNRT to the date of extractions. The log-rank test was used with Kaplan-Meier analysis to evaluate the impact of the 3 radiation dose tiers (<30 Gy, 30-60 Gy and >60 Gy) as well as the impact of anatomical teeth groups [anterior teeth (A), premolars (PM), and molars (M); ipsilateral (i) or contralateral (c); maxillary (Max) or mandibular (Man) teeth] on teeth survival. The risk assessment [*odds ratio* (OR)] for tooth extraction was also calculated for the studied radiation dose tiers with a 95% coincidence level set to test the significance. All data were analyzed using SPSS 17 (SPSS Inc, Chicago, IL, USA).

Results

A total of 1,071 teeth from 66 HNSSC patients met the inclusion criteria and were included in this study; 656 teeth were extracted following HNRT and 415 teeth were still in the oral cavity until this study's endpoint. Patient's clinicopathologic characteristics are summarized in table I. The majority of the patients were male (87.9%), with a mean age of 54.7 years (range 27-77 years). Most patients presented oropharyngeal (36.4%) tumors, followed by tumors of the larynx (28.8%), lateral border of the tongue (15.1%), oral cavity (9.1%) and nasopharynx (10.6%). Six (9.1%) patients presented tumors at I/II stages and 57 (86.4%) patients had advanced-stage disease (III/IV stages). After a mean follow-up of 41.5 (± 17.4) months, after the conclusion of cancer treatment, the OS and DFS rates were 83.3% and 51.8%, respectively. Seven (10.6%) patients developed local-regional recurrence, 3 (4.5%) patients developed distant relapse, and 6 (9.1%) patients developed second primary tumors.

Sixteen (24.2%) patients were primarily treated with surgery and adjuvant chemoradiotherapy (CRT), 10 (15.2%) patients treated by surgery and adjuvant HNRT, 23 (34.9%) patients were submitted to induction chemotherapy (CT) followed by CRT, 2 (3.0%) patients were treated with induction CT and isolated HNRT, 12 (18.2%) patients underwent isolated CRT, and 3 (4.5%) patients to isolated HNRT. Sixty and three (95.5%) patients were treated with 3DRT and 3 (4.5%) with IMRT. Radiation volumes encompassed the primary site and areas of lymph nodes with metastatic disease or at risk, and received a mean of 67.9 Gy (SD ±3.7) cumulative doses. Patient's treatment information is summarized in table II.

A mean of 11 (median of 6; SD ±10.9) dental appointments were performed, per patient, from the conclusion of HNRT to the date of the teeth extractions. The mean time for teeth extraction was of 24 (SD ±16.1) months following HNRT conclusion. After a mean follow-up time of 41.5 (SD ±17.4) months following the conclusion of HNRT, 656 teeth were extracted with a mean of 9.9 teeth extracted per patient. From the total extracted teeth, 445 (67.8%) were extracted due to advanced RRC, 85 (13.0%3) due to PD, 58 (8.8%) due to AP and 48 (7.3%) due to synchronous PD and AP. Twenty (3.1%) teeth were extracted for other reasons. Comparisons of the radiation dose tiers (<30 Gy, 30-60 Gy and >60 Gy) delivered to post-HNRT extracted teeth and the DAE profile are presented in table III.

After the mean follow-up time of 41.5 (SD ±17.4) months following the conclusion of HNRT, the overall teeth survival rate was 38.7%. Specific teeth survival rates regarding each radiation dose tier (<30 Gy, 30-60 Gy and >60 Gy) were 44.4%, 37.1% and 18.8%, respectively. The mean radiation dose for post-HNRT extracted teeth was 31.8 Gy (SD ±21.6); and specific mean radiation doses regarding each studied radiation dose tier were 5.4 Gy (SD ±6.2), 45.5 Gy (SD ±8.0) and 64.7 Gy (SD ±2.7) respectively. For non-extracted post-HNRT teeth included in this study, the mean radiation dose was 27.6 Gy (SD± 18.2); and specific mean radiation doses regarding each radiation dose tier studied were 9.8 Gy (SD ±9.9), 40.7 Gy (SD ±6.8) and 64.3 Gy (SD ±2.2) respectively.

The Kaplan-Meier survival analysis (Figure 1) showed that teeth receiving >60 Gy presented reduced mean survival time [30.5 (CI: 25.0-36.1) months] when compared to teeth exposed to the other two radiation dose tiers [39.6 (CI: 37.7-41.5) months for 30-60Gy and 38.6 (CI: 36.1-41.2) months for <30 Gy; (p=0.004)]. MiMax presented the lowest survival outcome and AcMax teeth the highest survival outcome. Post-HNRT teeth survival increased according with the following distribution: MiMax [29.1 (CI: 23.1-35.0) months] <

McMan [29.2 (CI: 23.0-35.3) months] < McMax [32.8 (CI: 27.2-38.6) months] < MiMan [32.9 (CI: 25.8-40.0) months] < PMiMan [36.2 (CI: 30.9-41.6) months] < AiMan [37.0 (CI: 34.3-41.7) months] < AcMan [39.0 (CI: 35.3-42.7) months] < PMcMan [39.8 (CI:34.4-45.2) months] < PMiMax [41.5 (CI: 35.3-47.7) months] < PMcMax [43.0 (CI: 36.5-49.6) months] < AiMax [43.2 (CI: 38.7-47.6) months] < AcMax [44.5 (CI: 39.9-49.0) months]; (p<0.001). The OR for dental extraction after HNRT increased following the increment of teeth radiation doses and reached 2.9-fold (CI: 1.56-5.35; p<0.001) higher risk for teeth receiving >60 Gy (Table IV).

Discussion

There is increasing concern about the lifespan of teeth following HNRT and the maintenance of adequate dentition function in head and neck cancer survivors. In this context, teeth that cannot be reliably maintained in the oral cavity during or after cancer treatment should be extracted prior to HNRT (26,27). However, as the result of several DAE, a considerable amount of patients may require dental extractions after the conclusion of HNRT (14,28). Notwithstanding, as far as we know, few studies have focused in this matter and no available studies were found to address the radiation impact on teeth survival.

Following the trends of a previous study (6), that found that radiation doses >60 Gy were associated to a higher risk of dentition breakdown of more than 10-times compared to lower doses, our study originally analyzed the patterns of DAE and teeth survival in relation to 3 dental radiation dose tiers (<30 Gy, 30-60 Gy and >60 Gy). The current study accepted the hypothesis that teeth exposed to high radiation doses (>60 Gy) may present reduced survival.

Although a previous systematic review (4) demonstrated that approximately 24% of the patients subjected to HNRT could be affected by RRC, it seems that this prevalence can be evidently higher, especially for advanced HNSCC patients of low socioeconomic surveys, as those included in the current study, which was based in a Brazilian population. Our results showed that approximately 68% of extracted teeth were due to advanced RRC, which is similar to the results of a previous study based on a post-HNRT Belgian population (25). This finding originally demonstrated that RRC might be a DAE of major clinical relevance for HNSCC survivors.

The potential direct impact of radiation on dental tissue has gained special attention in recent studies that aimed to investigate whether radiation can directly impact RRC onset and clinical progression as well as affect microstructural components (9,29-32), mechanical properties (29,33-37) and biochemical/molecular content (31-33,37-39) of teeth. It is still controversial if these potential radiogenic effects on teeth could work in synergy with well-accepted indirect effects of HNRT (reduced salivary flow, microbiota dysbiosis, poor oral hygiene and dietary changes, among others) on dentition that often lead to RRC and dentition breakdown (3,8,9).

Even though high radiation doses (>60 Gy) were previously attributed to an increased damage to the dental tissues (6), radiation's impact on teeth seems to depend on multiple factors, since the prevalence of teeth extractions due to RRC did not appear to follow a predictable and increasing pattern of radiation doses in our analysis. In addition, the current study demonstrated that RRC affected irradiated teeth in a generalized way regardless of radiation dose tiers delivered to teeth, which may reinforce the theory of 'clustering of oral complications' (12).

PD has also been regarded as a relevant DAE in HNSCC, which could be worsened by HNRT. Increased tooth loss rates, periodontal loss of attachment, gingival recession and clinical bone attachment loss have been previously documented in post-HNRT populations (40-42). Additionally, periodontal sites receiving high doses of radiation or the inclusion of maxilla in the primary radiation fields were linked to increased attachment loss indexes (40,43). PD was not the main cause of dental extractions in the present study and did not seem to correlate with the different radiation dose tiers investigated, which suggests that PD may not be regarded a major radiation-related DAE in individuals that appear to be more susceptible to RRC, which progress more rapidly and leads to tissue breakdown. PD should be considered as a multifactorial disease in which indirect effects of RT, such as oral microbiota changes and deficient oral hygiene can impact more on its pathogenesis than genuine direct radiation effects.

AP increased rates were also previously associated with teeth receiving high radiation doses and it was regarded as a relevant DAE in the context of HNRT (25). We found prevalence for AP that is similar to a previous publication based on post-HNRT patients (25). In the present study, AP was most likely detected in extracted teeth that received radiation doses >60 Gy. Nonetheless, it is difficult to infer, within the limits of this study, that AP was a direct consequence of high radiation doses as previously assumed by another group of researchers (25). Although a series of jawbone changes, such as widening of the periodontal ligament space have been recently linked to HNRT (44), it seems more reasonable to suggest that the high rates of RRC affecting the studied population may predispose to AP. Interestingly, a recent publication originally demonstrated a series of ORN cases developing from AP, which should raise awareness about the importance of this DAE in HNSCC survivors (45).

Previous studies analyzed the patterns of radiation distribution to teeth (and tooth-bearing areas), and the impact of radiation doses reduction on oral toxicities from HNRT (5,16,46-50). Although one of these studies (16) showed lower percentages of dental extractions following IMRT protocols, this was not statistically significant when compared to 3DRT. A recent collaborative study (23) that included our group showed that even though IMRT would permit delivering lower doses of radiation for some specific groups of teeth, when compared to 3DRT, it could not significantly reduce individual radiation doses to levels under 30 Gy, which is still considered high enough to cause mild direct damage to the dentition (6). Almost all of the patients included in the present study were treated with 3DRT protocols, which may explain the number of teeth receiving high doses of radiation (22). Inasmuch, contemporary HNRT planning should consider, whenever possible, sparing teeth from high radiation doses, which may be helpful to allow a lower impact of radiation on teeth and a longer maintenance of the irradiated teeth (23,51,52). However, prospective studies using dental maps will be necessary to clarify whether delineating and sparing teeth during RT planning can be less harmful to dental tissues, as well as to confirm the potential advantages of IMRT or other modern planning (e.g. proton beam RT) in reducing the impact of radiation on DAE patterns and teeth survival following HNRT. Likewise, it is difficult to predict if modern HNRT modalities that are capable of sparing major salivary glands would indirectly diminish DAE rates. Hence, studies addressing the impact of salivary glands function maintenance, and the impact of reducing radiation doses to individual tooth, will be necessary to estimate the weight of each factor that might harm teeth following the conclusion of HNRT.

In conclusion, the current results showed that teeth exposed to radiation doses >60 Gy, and molars in general, that usually receives higher radiation doses during HNRT, may present reduced mean survival time due to the higher risk of post-HNRT extraction, and that dental extractions following HNRT were more frequently associated with RRC. Therefore, the current results suggest that high radiation doses delivered to teeth could negatively impact the dentition of HNC patients. Limitations that could impair the interpretation of these results include the large spectrum of primary HNSCC locations evaluated and, most importantly, the retrospective nature of the study, which limited access to complete clinical information regarding patient's compliance with dental treatment protocols (53), salivary flow rates, dosimetry of parotid gland, and post-HNRT oral hygiene levels. Prospective studies will be necessary for more conclusive results about the direct impact of radiation on the dentition of HNC survivors.

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Tables

Table I. Patient's clinicopathologic characteristics.

Characteristics	Patients	
	No.	%
Gender		
Male	58	87.9
Female	8	12.1
Age, years		
Mean (range)	54.7 (27-77)	
Smoking habit		
Current or former	57	86.4
Never	8	12.1
Unknown	3	4.5
Alcohol abuse		
Current or former	58	87.9
Never	8	12.1
Tumor sites		
Oral cavity*	6	9.1
Tongue	10	15.1
Oropharynx	24	36.4
Nasopharynx	7	10.6
Larynx	19	28.8
T status		
1	6	9.1
2	8	12.1
3	19	28.8
4	30	45.5
Unknown	3	4.5

Continuation of table I.

N status		
0	17	25.8
1	10	15.2
2	22	33.3
3	13	19.7
Unknown	4	6.1
M status		
x	14	21.2
0	49	74.2
Unknown	3	4.5
Stage		
I-II	6	9.1
III-IV	57	86.4
Unknown	3	4.5

*Corresponds to tumors of the alveolar bridge/palate (2), floor of the mouth (2) and retromolar area (2).

Table II. Patient's treatment information.

Characteristics	Patients No.	%
Treatment modality		
Primary surgery	26	
Surgery + CRT	16	61.5
Surgery + HNRT	10	38.5
Primary HNRT	40	
Induction CT + CRT	23	57.5
Induction CT + HNRT	2	5.0
Isolated CRT	12	30.0
Isolated HNRT	3	7.5
Radiotherapy technique		
3DRT	63	95.5
IMRT	3	4.5
Radiation dose (Gy)		
Mean (±SD)	67.9 (±3,7)	

Abbreviations: CRT, chemoradiotherapy; HNRT, head and neck radiation therapy; CT, chemotherapy; 3DRT, tridimensional radiation therapy; IMRT, intensity-modulated radiation therapy; Gy, Gray; SD, standard deviation.

Table III. DAE profile of the post-HNRT extracted teeth.

Characteristics	<30 Gy No. (%)	30 - 60 Gy No. (%)	>60 Gy No. (%)
RRC	215 (96.8%)	329 (90.9%)	54 (96.4%)
PD (MBL ≥5 mm)	121 (54.5%)	204 (56.4%)	26 (46.4%)
AP	20 (9.0%)	73 (20.2%)	19 (33.9%)

Abbreviations: DAE, dental adverse events; HNRT, head and neck radiation therapy; Gy, Gray; RRC, radiation-related caries; PD, periodontal disease; MBL, marginal bone loss; AP, apical periodontitis.

Table IV. *Odds ratio* (OR) for post-HNRT teeth extraction.

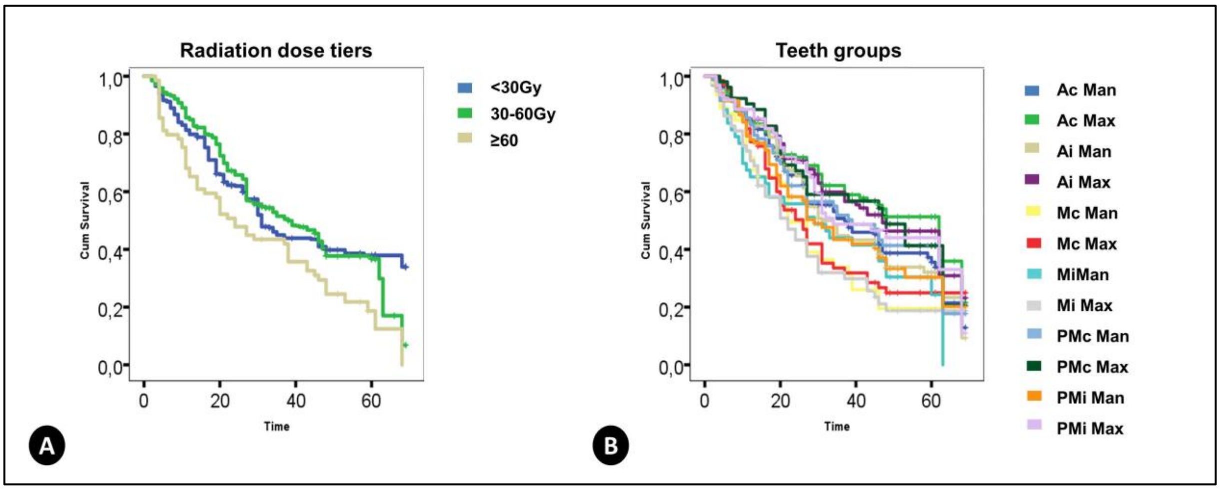
Radiation doses tiers	OR	CI	*p* value
<30 Gy	0.68	0.53-0.87	0.003*
30 - 60 Gy	1.35	1.04-1.74	0.023*
>60 Gy	2.89	1.56-5.35	<0.001*

Abbreviation: HNRT, head and neck radiation therapy; CI, Confidence interval.

*$p<0.05$, $\chi 2$ test.

Figures

Figure 1. Kaplan-Meier teeth survival curves in months for the 3 different radiation dose tiers (A; p=0.004) and the anatomical teeth groups (B; p<0.001).



3 CONCLUSÃO

Dentes expostos a doses de radiação >60 Gy, e molares em geral, apresentaram sobrevida reduzida. Adicionalmente, dentes que receberam >60 Gy mostraram um risco de extração pós-RT aproximadamente 3 vezes superior ao de dentes que receberam doses menores de radiação.

O principal fator de risco para extrações pós-RT foi a CRR e diferentes doses de radiação influenciaram na frequência relativa dos EDA relacionados às extrações pós-RT.

A hipótese teste deste estudo foi aceita por meio da identificação da redução da sobrevida de dentes que receberam altas doses de radiação durante o tratamento do CCP.

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ANEXO 1 - Aprovação do Comitê de Ética em pesquisa

FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO - FMUSP

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação do perfil de extrações dentárias em pacientes submetidos à radioterapia na região da cabeça e do pescoço. Um estudo retrospectivo.

Pesquisador: Wagner Gomes da Silva

Área Temática:

Versão: 1

CAAE: 58937716.8.0000.0065

Instituição Proponente: FUNDACAO FACULDADE DE MEDICINA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.700.729

Apresentação do Projeto:

Estudo retrospectivo, para avaliação do perfil de pacientes submetidos a extração dentária em cenário de tratamento radioterápico para Ca cabeça e pescoço

Objetivo da Pesquisa:

investigar as causas mais frequentes de extrações dentárias após a RDT, assim como a correlação entre as diferentes variáveis clínicas relevantes nas decisões clínicas, a relação da dose de radiação recebida por cada dente, a adesão do paciente ao acompanhamento odontológico e a taxa de sobrevida global e livre de progressão da doença.

Avaliação dos Riscos e Benefícios:

benefícios superam riscos

Comentários e Considerações sobre a Pesquisa:

estudo para obtenção de título

Considerações sobre os Termos de apresentação obrigatória:

apresentados de maneira correta

Recomendações:

Aprovação