UNIVERSIDADE ESTADUAL DE MONTES CLAROS

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Dedico este trabalho

Aos meus pais amados: Juvenal e Rosa, que dedicam suas vidas com exemplos de determinação, honestidade e amor. Vocês sempre estão presentes em minhas conquistas.

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“O importante é não parar de questionar.”

Albert Einstein

RESUMO

O carcinoma espinocelular é o tipo de câncer mais comum na região de cabeça e pescoço, representando 90% das neoplasias malignas que acometem a cavidade oral. Como principais modalidades de tratamento oncológico, cirurgia, quimioterapia e⁄ou radioterapia, podendo ou não estarem associadas. Qualquer escolha de tratamento, efeitos nocivos poderão provocar danos, reversíveis ou não, em órgãos de risco, como glândulas salivares, que são altamente radiossensíveis. Nos primeiros dias de radiação, células serão afetadas, prejudicando gravemente a produção de água, o que reduz o fluxo salivar,levando a hipossalivação, ou a sensação subjetiva de boca seca, xerostomia. A saliva importante para homeostasia da cavidade oral e, alterações no fluxo salivar interferem nas funções orais básicas, impactando a qualidade de vida do indivíduo. Existem vários tratamentos propostos, entre eles, a fotobiomodulação. Porém, a falta de protocolo preciso dificulta a obtenção de evidências científicas capazes de gerar protocolos terapêuticos eficazes. O presente estudo tem o objetivo avaliar o efeito da fotobiomodulação no tratamento da xerostomia e hipossalivação em pacientes portadores de carcinoma de células escamosas na região de cabeça e pescoço. Como método, um ensaio clínico unicego, paralelo, randomizado, controlado por dois braços, foi realizado seguindo as diretrizes Consort. A pesquisa foi registrada no Registro Brasileiro de Ensaios Clínicos ReBEC com UTN nº. U1111-12599-9624 ⁄ RBR-9bt3cbj, e realizada no Hospital Dilson Godinho de Quadros, no Município de Montes Claros, entre dezembro de 2018 a março de 2021. De 111 participantes, 85 foram incluídos na pesquisa, divididos de forma aleatória e randomizada em grupo intervenção (n = 41) ou sem intervenção (n = 44). Utilizou-se um aparelho de laser DUO portátil, emissor de luz semicondutor (GaAIAs e InGaAIP), potência ótica do laser de 100 mW, área do feixe Laser de saída do bico da caneta de 3 mm^2, área do spot 0,030 cm^2, modo de operação do equipamento contínuo, com combinação de dois comprimentos de onda (660 nm e 808 nm). Foram entregues aos tecidos doses de energia de 9 J por ponto de cada comprimento de onda separadamente, densidade de energia 300 $J⁄cm^2$, densidade de potência 3,33 $W⁄cm^2$, forma de irradiação pontual, com incidência da luz em 90° em relação aos tecidos, em glândulas salivares maiores, duas vezes na semana, durante a radioterapia. Como desfecho primário esperava-se a redução da xerostomia e da hipossalivação e desfecho secundário, diminuição dos escores de ansiedade e depressão. Os resultados demostraram não haver diferenças estatísticas entre os grupos para redução objetiva do fluxo salivar, hipossalivação, no volume, na densidade e no pH da saliva. Em relação ao sintoma auto relatatado pelo paciente, sensação de boca seca, escores obtidos

através do questionário de xerostomia não foram diferentes estatisticamente entre os grupos comparados. Em relação à pontuação dos inventários de ansiedade e depressão, também não foram verificadas diferenças, corroborando com achados anteriores e concluindo que a fotobiomodulação para xerostomia e hipossalivação, com o protocolo proposto por este estudo, não demonstra diferença estatística entre os grupos que receberam ou não intervenção logo após a finalização do tratamento radioterápico.

Palavras-chave: Glândulas salivares. Radioterapia. Terapia com luz de baixa intensidade. Xerostomia.

ABSTRACT

Squamous cell carcinoma is the most common type of cancer in the head and neck region, representing 90% of malignant neoplasms that affect the oral cavity. As the main modalities of cancer treatment, surgery, chemotherapy and/or radiotherapy, which may or may not be associated. Any choice of treatment, harmful effects may cause damage, reversible or not, in organs at risk, such as salivary glands, which are highly radiosensitive. In the first days of radiation, cells will be affected, severely impairing water production, which reduces salivary flow, leading to hyposalivation, or the subjective sensation of dry mouth, xerostomia. Saliva is important for oral cavity homeostasis and changes in salivary flow interfere with basic oral functions, impacting the individual's quality of life. There are several proposed treatments, including photobiomodulation. However, the lack of a precise protocol makes it difficult to obtain scientific evidence capable of generating effective therapeutic protocols. The present study aims to evaluate the effect of photobiomodulation in the treatment of xerostomia and hyposalivation in patients with squamous cell carcinoma in the head and neck region. As a method, a single-blind, parallel, randomized, two-arm controlled clinical trial was performed following Consort guidelines. The research was registered in the Brazilian Registry of Clinical Trials ReBEC with UTN nº. U1111-12599-9624 / RBR-9bt3cbj, and performed at Hospital Dilson Godinho de Quadros, in the Municipality of Montes Claros, between December 2018 and March 2021. Of 111 participants, 85 were included in the research, randomly and randomly divided in the intervention group (n = 41) or without intervention (n = 44). A portable DUO laser device was used, semiconductor light emitter (GaAIAs and InGaAIP), laser optical power of 100 mW, laser beam area of pen nozzle output of 3 mm2, spot area 0.030 cm2, continuous equipment operation, with a combination of two wavelengths (660 nm and 808 nm). Energy doses of 9 J per point of each wavelength were delivered to the tissues separately, energy density 300 J/ cm2, power density 3.33 W/ cm2, form of punctual irradiation, with light incidence at 90° in tissue, in major salivary glands, twice a week during radiotherapy. As a primary outcome, a reduction in xerostomia and hyposalivation was expected, and a secondary outcome, a decrease in anxiety and depression scores. The results showed no statistical differences between the groups for objective reduction of salivary flow, hyposalivation, volume, density and pH of saliva. Regarding the symptom self-reported by the patient, dry mouth sensation, scores obtained through the xerostomia questionnaire were not statistically different between the groups compared. Regarding the scores on the anxiety

and depression inventories, no differences were found either, corroborating previous findings and concluding that photobiomodulation for xerostomia and hyposalivation, with the protocol proposed by this study, does not show statistical difference between the groups that received or not intervention soon after completion of radiotherapy treatment.

Keywords: Salivary glands. Radiotherapy. Low-intensity light therapy. Xerostomia.

LISTA DE ILUSTRAÇÕES

LISTA DE ABREVIATURAS E SIGLAS

ABEP .....Associação Brasileira de Empresas de Pesquisa
ABNT .....Associação Brasileira de Normas Técnicas
ANVISA .....Agência Nacional de Vigilância Sanitária
BIREME .....Biblioteca Regional de Medicina
CAAE .....Certificado de Apresentação para Apreciação Ética
CCE .....Carcinoma de células escamosas
CEP .....Comitê de Ética em Pesquisa
CID .....Classificação Internacional de Doenças
cGy .....Centigray (dose administrada de radioterapia)
CONSORT .....Padrões Consolidados para Relatar Ensaios
CTC .....Common Toxicity Criteria
EMEDOR .....Escala Multidimensional de Evaluación del Dolor
GaAIAS .....Gallium-aluminum-arsenium
GBq .....Bequerel – unidade de medida
Gy .....Gray – unidade de medida
IBGE .....Instituto Brasileiro de Geografia e Estatística
IGRT .....Image guided radiotherapy
IMRT .....Intensity-modulated radiation therapy
INCA .....Instituto Nacional do Câncer
InGaAIP .....Indium gallium alluminum phosphorus
J .....Joule – unidade usada para medir energia mecânica
MEC .....Ministério da Educação
NCI .....National Cancer Institute
Nm .....Nanômetro – unidade de medida
QT .....Quimioterapia
RTX .....Radioterapia
RTOG .....Radiation therapy oncology group
SAB .....Stereotatic ablative radiotherapy
SBRT .....Stereotatic body radiotherapy
SUS .....Sistema Único de Saúde

PBM ..... Fotobiomodulação

PDT .....Terapia Fotodinâmica

PPGCS .....Programa de Pós-graduação em Ciências da Saúde

pH .....Potencial hidrogeniônico

T .....Tamanho da lesão tumoral

TCLE .....Termo de Consentimento Livre e Esclarecido

TNM .....Classification of Malignant Tumours

UNIMONTES .....Universidade Estadual de Montes Claros

WHO .....World Health Organization Criteria

WHOMQOL-bref .....World Health Organization Quality of Life-briefly

2D .....Duas dimensões

2DRT .....Radioterapia convencional – 2D

3D .....Três dimensões

3D-CRT .....Radioterapia conformacional tridimensional – 3D

SUMÁRIO

1. INTRODUÇÃO

1.1 Epidemiologia do câncer

Doenças malignas, como o câncer, são consideradas como um dos maiores problemas de saúde pública em todo o mundo, o que acarreta problemas em larga escala para a sociedade, diminuíndo os anos de vida ou incapacitando os indivíduos de forma geral, além de consumir grande quantidade de recursos econômicos, públicos e privados. (1, 2) A incidência, a morbidade e a mortalidade por essa neoplasia maligna estão a atingir o mundo de forma cada vez mais crescente. (3) O câncer é uma doença multifatorial, porém, entre os fatores etiológicos diversos encontram-se o envelhecimento da população e a prevalência de fatores de risco, em especial, o desenvolvimento socioeconômico, associado à melhoria do estilo de vida com novas atitudes e formas de viver, como sedentarismo, alimentação inadequada, hábitos nocivos etc. (3)

O câncer encontra-se em segundo lugar nas principais causas mundiais de morte (8,97 milhões de mortes), ficando atrás apenas da doença isquêmica do coração.(1) Porém, de acordo com a tendência mundial para 2060, a mortalidade por esta enfermidade alcançará a primeira colocação com estimativa de 18,63 milhões de mortes. (1, 3)

Para o Brasil, de acordo com o Instituto Nacional do Câncer José Alencar Gomes da Silva (INCA), estima-se para o ano de 2022, 625 mil novos casos. Para o câncer de laringe é esperado, para o mesmo ano no Brasil, 6.470 novos casos em homens e 1.180, em mulheres. (4, 5) Sabe-se que com a idade e o envelhecimento da população, a incidência para câncer de lábio e cavidade oral aumenta e a estimativa, também para 2022 segundo o INCA, é de 15.190 novos casos, distribuídos entre homens (11.180 casos) e mulheres (4.010 casos). (4-6)

O risco de desenvolvimento do câncer entre 0 a 74 anos equivale a 20,2% sendo 22,4% em homens e 18,2% em mulheres. (1) As idades que possuem maior risco para desenvolver o câncer de laringe estão acima dos 40 anos de idade. (3, 5) Porém, com o aumento significativo do consumo dos cachimbos de água ou water pipe entre os mais jovens, 30 a 50 anos, o risco para câncer de cabeça e pescoço, incluindo câncer oral, aumentou consideravelmente nesta população. (6, 7) De acordo com o Global Cancer Observatory (GLOBOCAN), em todo o

mundo por ano, são atribuídos 690.000 casos de carcinoma de células escamosas à infecção por alguns dos tipos de Papiloma Vírus Humano (HPV), particularmente o tipo 16, sendo 42.000 localizados na orofaringe, 5.900 na cavidade oral e 4.100 na laringe.(8)

1.2 Carcinoma de células escamosas

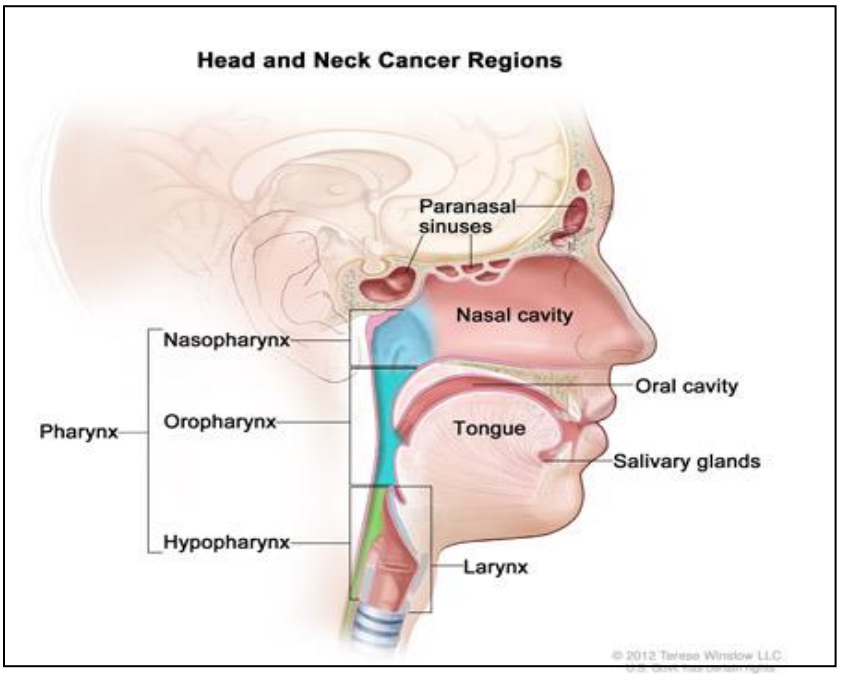
Entre todos os tipos de câncer, o carcinoma de células escamosas é o mais prevalente na região de cabeça e pescoço, correspondendo a 90% dos casos, especialmente na região de cavidade oral. (6, 9) Os fatores etiológicos mais comuns são o tabaco e o álcool, sendo atribuído uma probabilidade 7 vezes maior para a ocorrência do câncer quando se compara com aqueles que não possuem esses hábitos. (4-6, 10) Portanto, quando o uso do tabaco é combinado a bebidas alcóolicas, ocorre um efeito sinérgico e exponencial e o desenvolvimento da doença é potencializado. (6, 10-12) Outros fatores estão associados ao risco de carcinoma de células escamosas como exemplo, a exposição ao sol sem uso do filtro solar, responsável pela maioria dos cânceres de lábio, aumento excessivo de gordura corporal, desnutrição, fatores genéticos e fatores ligados à exposição ocupacional, além dos já citados acima. (4, 5)

A taxa de sobrevida, relativamente baixa, encontra-se em média de 5 anos e a chance de cura diminui em pacientes com recidiva. (9) Quanto mais tarde for realizado o diagnóstico, pior o prognóstico e maiores as complicações decorrentes do tratamento, desencadeando sequelas importantes e deformidades estéticas, funcionais e psicológicas, que impactam negativamente na qualidade de vida do paciente (13, 14). Com isso, pode ser instalado quadros de ansiedade e depressão, com ato ou ideação suicida entre os pacientes. (15, 16)

Para o carcinoma de células escamosas que acomete a região de cabeça e pescoço, as localizações mais comuns são cavidade oral (40%), representadas pelas mucosas jugais, palato e dorso central da língua em menor porcentagem e com maior prevalência em regiões como lábios, principalmente o inferior, gengiva, borda lateral de língua e assoalho bucal (6). O câncer nestas regiões podem se estender em sentido à orofaringe e, apesar de representar apenas 20% de toda a área da cavidade oral, representa 70% dos sítios acometidos pelos cânceres na boca. (6)

Além dos sítios acometidos pelo carcinoma de células escamosas citados acima, de acordo com o INCA, a laringe (25%) e faringe (15%) são áreas comuns para a região de cabeça e pescoço. (4, 5) (Figura 1).

Figura1 - Regiões da cabeça e pescoço acometidas pelo Carcinoma de células escamosas



Fonte: http://www.scielo.br/img/revistas/bjmbr/

A condição clínica do paciente, associado ao tamanho do tumor e a possibilidade de metástase nos linfonodos próximos ou à distância resultam em uma classificação de estadiamento da doença que possibilita a identificação real da situação em que se encontra o paciente e a padronização e escolha do tratamento pelos profissionais. (17, 18) O Sistema TNM avalia a classificação dos tumores malignos e descreve a sua extensão, utilizando três componentes como, T – extensão do tumor primário, N – extensão da metástase em linfonodos próximos ao tumor e M – metástase à distância. São adicionados números ao TNM indicando a extensão da doença, como T0, T1, T2, T3 e T4 de acordo com o agravamento, o qual avalia também, a "profundidade de invasão" e "extensão extranodal" do câncer. (17, 18) O estadiamento clínico visa obter, através de parâmetros clínicos e laboratoriais, a condição atual do paciente em relação à gravidade, à complexidade da doença e ao prognóstico, facilitando a escolha do protocolo de tratamento para cada caso individualmente. (17, 18)

1.3 Tratamento do câncer e efeitos colaterais

Para o paciente diagnosticado com câncer existem modalidades de tratamento como a cirurgia, a quimioterapia e a radioterapia, (19) que podem ser realizadas de forma isolada ou em concomitância, adjuvância ou neoadjuvância, em busca não somente da cura da doença, mas, em alguns casos, da remissão ou da paliação. (19) A decisão e escolha da modalidade mais adequada estará de acordo com o estadiamento clínico do paciente. (19-21)
Com a descoberta do raio-X, efeitos biológicos foram detectados, e muitas doenças, inclusive o câncer, passaram a ser submetidas à exposição da radiação ionizante em busca da cura.(19) Como primeiro tratamento não cirúrgico de tumores malignos, foi utilizada a radioterapia, que se apresenta como um dos tratamentos mais antigos da oncologia. (19) Estima-se para países desenvolvidos que cerca de 60% dos indivíduos com neoplasia maligna poderão ser submetidos a esta modalidade de tratamento em algum momento, (22) enquanto países em desenvolvimento, devido às características epidemiológicas e de avanço da doença, a necessidade de tratamento radioterápico possui uma demanda ainda maior. (19)

A radioterapia é uma especialidade médica multiprofissional e multidisciplinar que utiliza radiação ionizante, acarretando intenso estresse oxidativo, o que provoca danos diretos e indiretos ao DNA, com consequente morte celular por apoptose ou inibição de crescimento de células tumorais. (23) Esta modalidade constitui um dos pilares para tratamento oncológico, juntamente com a cirurgia e a quimioterapia, podendo em alguns casos, ser usada para lesões benignas. (19)

O Sistema Único de Saúde (SUS), criado pela Constituição Federal em seu artigo 198 e organizado pela Lei Orgânica da Saúde 8.080 de 1990, garante para seus usuários, de forma gratuita e padronizada todos os tratamentos oncológicos necessários, conforme Lei 12.732 de 2012, o que vem ao encontro do que é preconizado pela Constituição Federal em seu artigo 196 quando trata a saúde como direito fundamental de todos e, ainda inclui a obrigatoriedade de efetivação desse direito como dever do Estado. (23, 24) Conforme a Portaria nº 516 de 2015 do Ministério da Saúde, a técnica de radioterapia conformacional tridimensional 3D é a eleita para utilização em todos os usuários do SUS portadores de câncer, de forma padronizada, (25) com raras exceções, como por exemplo em caso de judicialização da saúde ou quando há necessidade de utilização de técnicas que consigam realizar modulação da radiação desviando de órgãos vitais e impedindo maiores danos ao paciente. (26)

Qualquer que seja o tratamento de escolha, cirúrgico, radioterápico ou quimioterápico, os efeitos colaterais irão existir em menor ou maior gravidade (27), e no caso da radioterapia, mesmo com os avanços na precisão da entrega da dose de radiação, com as novas tecnologias, o conhecimento dos efeitos dos raios X sobre os tecidos biológicos, o aumento da energia dos raios com desenvolvimento tecnológico das máquinas e melhoria, tanto das imagens usadas para planejamento de entrega de energia, como da sua capacidade computacional, não são capazes de impedir manifestações indesejadas (19, 26). A radioterapia não possui seletividade para células canerígenas, atingindo significativamente células normais e provocando perda na renovação celular, (28) o que desencadeia lesão ao tecido sadio adjacente. (23, 28, 29) Por isso, a entrega da dose de radiação é realizada com fracionamento, visando ser mais eficaz para células cancerígenas, alvo da radiação. (23, 28, 29) Mas, os efeitos indesejados são inevitáveis, e em alguns casos, pode permanecer por um longo prazo ou até mesmo, instalar-se permanentemente. (2, 23, 27-29) As consequências mais frequentemente observadas, durante e após a radiação são mucosite, xerostomia e hipossalivação, causando impactos na qualidade de vida do paciente e trazendo limitações que desencadeiam quadros de depressão e ansiedade. (15, 16)

1.4 Xerostomia e hipossalivação

A saliva, constituída por uma variedade de fluidos excretados pelo conjunto de glândulas menores e maiores, parótidas, submandibulares, sublinguais e mais recentemente descoberta, a glândula tubária, (30) além de células epiteliais descamadas, restos alimentares e fluidos do sulco gengival, contribui, entre outros, para manter a homeostasia da cavidade oral. (15, 31) Pode ser dividida em duas categorias, saliva em repouso, varia entre 0,29 ml/min a 0,41 ml/min, e saliva estimulada, com fluxo normal que varia entre 1,6 a 2,0 ml/min. (32) Cerca de 70% da saliva em repouso, deriva-se das glândulas submandibulares e sublinguais, pode-se dizer que é a saliva presente a maior parte do tempo na boca. (32) Enquanto 45 a 50% da saliva estimulada, deriva-se da glândula parótida e está presente na cavidade oral apenas por duas horas, pois está relacionada às funções de alimentação devido a presença da amilase, também secretada por essa glândula. (32)

As glândulas salivares são altamente sensíveis à radiação ionizante e a morte de suas células inicia logo nos primeiros dias de tratamento radioterápico. (15, 31, 33) A redução na

quantidade de fluxo salivar é um sinal denominado hipossalivação, que pode ser medido através da sialometria, enquanto a sensação subjetiva de boca seca, o sintoma percebido pelo paciente, recebe o nome de xerostomia e é um dos efeitos colaterais relatados por cerca de 68 a 85% dos pacientes submetidos a tratamentos para CEC na região de cabeça e pescoço, (2) o que leva a grande impacto negativo na qualidade de vida dos mesmos. (31)

A radiossensibilidade dos tecidos normalmente é determinada pela alta proliferação da células, sendo iniciado o dano assim que houver a redução na taxa de renovação celular. (28, 33, 34) Diferentemente do que ocorre em outros tecidos, as glândulas salivares possuem um ciclo de renovação de suas células relativamente baixo. (27, 31, 33) Porém, fugindo à regra, os danos iniciam-se em horas ou dias após a radiação ionizante, o que torna seriamente comprometida a secreção de água pelas suas células, sem comprometer, no entanto, a secreção de amilase, enzima produzida pela glândula parótida. (27, 31) Estudos mostram que glândulas submandibulares são menos sensíveis à radiação, quando comparadas às glândulas parótidas, o que se justifica ao se observar o relato de saliva grossa e pegajosa pelos pacientes logo nos primeiros dias de tratamento radioterápico, uma vez que são as parótidas as responsáveis pela produção de água, e danos em suas células causaria redução na produção de produto aquoso para a saliva aumentando a concentração de mucina, glicoproteína produzida especialmente pelas glândulas submandibulares, responsáveis pela viscosidade da saliva. (27, 31)

Com base em estudo, (28) a diminuição aguda da secreção de saliva após a radiação da glândula foi justificada não ter sido somente devido à apoptose radioinduzida, (35) perda celular (36, 37) e/ou renovação celular lenta, mas pela disfunção de receptores muscarínicos de acetilcolina presentes em células acinares, que são os responsáveis pela secreção de fluidos salivares. (28, 36, 37)

As taxas de fluxo salivar são dependentes do campo irradiado e da dose média de radiação, diminuindo progressivamente conforme se aumenta a dose, e a sua recuperação ao longo de 2 anos pode ocorrer até um limiar de doses de até 39 Gy, (31) porém já existem relatos de queixa de xerostomia pelos pacientes com doses abaixo de 30 Gy. (38) Doses entre 50 a 70 Gy produzem efeitos danosos em glândulas salivares, permanentemente. (31, 33, 39) Pacientes portadores de câncer de células escamosas em região cérvico-facial são submetidos à radioterapia com doses entre 60 a 70 Gy, podendo-se afirmar que a depender da técnica

radioterápica selecionada, tridimensional ou IMRT, da localização da radiação e da glândula a ser irradiada, parótida ou submandibular, haverá comprometimento glandular com alteração na produção de fluidos ou da qualidade da saliva. (27, 40)

A saliva tem papel fundamental na manutenção da homeostasia bucal, com proteção da cavidade oral e do epitélio gastrointestinal, além de promover o "clearence" oral, contribuir com a digestão, formar a película adquirida, realizar a mineralização dentária, ter ação antimicrobiana, contribuir com o paladar e realizar reparação tecidual, entre outros. (41, 42) O fluxo salivar normal varia de 1,0 a 1,5 ml/min por dia, com pH entre 6,4 a 7,4 e a diminuição na secreção salivar acarreta, entre outros, dificuldade na formação do bolo alimentar, na alimentação e na fala, corrobora para instalação de quadros de ansiedade e depressão, tornando os indivíduos vulneráveis ao ato ou mesmo à ideia do suicídio. (15, 43)

A redução do fluxo salivar desencadeia desequilíbrio da microbiota oral com proliferação de microrganismos oportunistas levando ao desenvolvimento de doenças, como candidíase, herpes, gengivite, além de perda do paladar, dificuldade para falar, disgeusia, odinofagia, ardência bucal, entre outros. (44-47) O sistema de tamponamento realizado pela saliva, fica prejudicado e o aparecimento de doenças, como a cárie dental, durante e após o tratamento radioterápico, torna-se comum. (2, 44, 45)

Nem sempre as alternativas de tratamento capazes de resolver a xerostomia ou hipossalivação, de forma definitiva e eficaz, serão satisfatórias, visto a sua complexidade, além de gerar gastos públicos e/ou privados, com internações, prescrição de medicamentos e outros tratamentos médicos e dentários, decorrentes da enfermidade e suas complicações. (2, 47)

1.5 Fotobiomodulação para xerostomia e hipossalivação

Com objetivo de melhorar a qualidade de vida dos pacientes, existem na literatura alternativas para prevenir e tratar os sinais e sintomas decorrentes da diminuição do fluxo salivar, como drogas colinérgicas como a pilocarpina, responsável por efeitos adversos importantes (48, 49) e betanecol, considerado menos agressivo porém, possui uma vasta lista de contra-indicações (50) ou drogas radioprotetoras, como a amifostina, (51) que são indicadas para prevenir a hipossalivação quando administradas antes da radioterapia, porém o alto custo, os efeitos colaterais e o possível comprometimento do controle tumoral inviabilizam o seu uso. (52, 53)

As salivas artificiais, outra alternativa de tratamento, causam alívio imediato com atenuação dos sintomas da xerostomia, porém seus efeitos são temporários. (51) Abordagens com o uso da acupuntura em pacientes submetidos à radioterapia na região de cabeça e pescoço, relatam os benefícios na redução de xerostomia, hipossalivação e ansiedade do paciente. (54) Técnicas mais avançadas, como a radioterapia de intensidade modulada (IMRT), permitem uma distribuição de doses de forma altamente conformadas, contribuindo para o aumento da dose no alvo do tratamento, enquanto consegue reduzir a dose nos tecidos sadios adjacentes ao tumor, diminuindo a sua toxicidade, porém, o seu alto custo somado à incapacidade em demonstrar aumento de sobrevida global com a sua utilização, inviabilizam o uso desta técnica para pacientes usuários do SUS, na maioria dos serviços prestados no Brasil. (18, 25, 26) A fotobiomodulação, também é citada como forma de tratamento para xerostomia e hipossalivação decorrentes dos tratamentos oncológicos. (27, 55, 56)

A luz do laser de baixa intensidade nos comprimentos de onda, vermelho (660 nm) e infravermelho (808 nm), é absorvida por cromóforos endógenos e desencadeia reações biológicas sem liberar calor, não são tóxicas aos tecidos e levam a mudanças fisiológicas que estimulam a regeneração tecidual, diminuindo a inflamação e controlando a dor. (47, 57) Pacientes submetidos à radioterapia apresentarão complicações decorrentes da radiação ionizante que irão aumentar a morbidade, o que leva ao aumento de utilização de recursos para cuidados em saúde, impactam negativamente na qualidade de vida, além de comprometer a adesão dos mesmos aos protocolos de tratamento, diminuindo os resultados abaixo do ideal. (47) O uso terapêutico do laser, com a fotobiomodulação, contribui para amenizar os efeitos colaterais advindos do tratamento oncológico, favorecendo a adesão do paciente e, consequentemente, o seu prognóstico. (46, 47)

Existem protocolos variados para fotobiomodulação demonstrando que a sua utilização melhora o reparo tecidual e contribui para regeneração de tecidos, em diferentes fases, como a fase em que o tecido está inflamado, quando as células de defesa migram para a lesão, durante a fase proliferativa, quando estimula os fibroblastos e macrófagos (47, 57), e na fase de remodelação, com a reposição de colágeno na matriz extracelular da ferida, características que corroboram muito na cicatrização das mucosites. (47) Nas glândulas salivares, a PBM contribui para o aumento da microcirculação local, a proliferação de suas células e aumenta a respiração celular. (51, 56) A luz do laser atua sobre o citocromos c oxidase da cadeia respiratória da mitocôndria, induzindo a produção de adenosina trifosfato (ATP), fonte de

energia essencial para todas as reações biológicas. (47), favorece a síntese de proteínas e aumenta o nível de cálcio dentro da célula. (51, 56) Estudo relatam que a fotobiomodulação estimula a função de células glandulares que ainda não sofreram danos pela radiação (51, 56), podendo ser uma alternativa de estímulo para aumento de secreção de saliva, o que contribui para reduzir a hipossalivação e a sensação de boca seca. (27) Porém, os estudos sobre os mecanismos dos seus efeitos terapêuticos não estão ainda muito bem elucidados (46) e a diferente forma de atuação do laser de baixa intensidade nas células depende da dose e do comprimento de onda utilizada. (47)

Além disso, a PBM favorece liberação de espécies reativas de oxigêncio (ROS), reduzindo o estresse oxidativo, o que atenua o dano tecidual, gera fatores de crescimento em fibroblastos, (47, 57) favorece o sistema imunológico reduzindo as citocinas pró-inflamtórias e quimiocinas, contribui para a reparação e regeneração tecidual. (47) Porém, se a quantidade de ROS for alta, pode induzir a apoptose celular devido aos efeitos dos danos no DNA, além da efetivação de vias pré-apópticas nas células. (58-60)

A fotobiomodulação é responsável por uma grande variedade de resultados e a falta de um parâmetro em relação ao comprimento de onda a ser utilizado (vermelho ou infravermelho), energia, densidade de energia, potência do aparelho, densidade de potência, frequência e periodicidade para aplicação, mitiga a investigação em busca de protocolos terapêuticos precisos e altamente reprodutíveis para prevenir e tratar a disfunção de glândulas salivares irradiadas em pacientes tratados com câncer de cabeça e pescoço. (51, 56, 61)

Baseado em estudos realizados, os quais a terapia com utilização de laser de baixa intensidade parece colaborar como ferramenta eficiente para minimizar a gravidade da mucosite oral (46, 47, 57), hipossalivação e xerostomia decorrente de radiação ionizante ou de outras modalidades de tratamento oncológico, (27, 51) o presente estudo propõe uma análise com um protocolo de fotobiomodulação para tratamento de xerostomia e hipossalivação, justificando-se nos achados do estudo (57), o qual a combinação de ondas de 660 nm e 808 nm, com dose de energia de 9J por ponto entregues à mucosa ou densidade de energia de 300 J/cm^2, sugerem melhores resultados clínicos na recuperação de feridas, reparação tecidual e celular.(57) O benefício da combinação dos comprimentos de onda já havia sido demonstrado, (27, 62) entretanto a maioria dos estudos realizados e das revisões sistemáticas não entram em um consenso em relação à dose, ao comprimento de onda mais adequado ou à potência do aparelho, sem também avaliar o efeito da fotobiomodulação na prevenção e

manejo da hipossalivação e xerostomia em pacientes submetidos ao tratamento oncológico para câncer de cabeça e pescoço. (46, 56, 61) É notório a necessidade de mais estudo que visem a busca de um protocolo terapêutico eficaz. (46, 56, 61)

2. OBJETIVOS

2.1 Objetivo geral

- Verificar a eficácia da fotobiomodulação combinando os comprimentos de onda vermelho e infravermelho no tratamento da xerostomia e hipossalivação em pacientes portadores de carcinoma de células escamosas na região de cabeça e pescoço.

2.2 Objetivos específicos:

- Investigar se a fotobiomodulação modifica volume, densidade e pH da saliva em pacientes submetidos tratamento oncológico na região de cabeça e pescoço.

- Verificar se a fotobiomodulação reduz a frequência e intensidade da xerostomia e da hipossalivação.

- Verificar os escores de ansiedade e depressão e o impacto na qualidade de vida do paciente relacionada à xerostomia e hipossalivação durante tratamento oncológico e fotobiomodulação.

3 PRODUTO CIENTÍFICO

Photobiomodulation in the treatment of xerostomia and hyposalivation in patients with squamous cell carcinoma in the head and neck region – a randomized controlled clinical trial, formatado segundo as normas para publicação em periódico Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, Qualis A2, enviado.

3.1 Produto: *Photobiomodulation in the treatment of xerostomia and hyposalivation in patients with squamous cell carcinoma in the head and neck region – a randomized controlled clinical trial,* formatado segundo as normas para publicação em periódico Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, Qualis A2, enviado.

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Abstract

Objective:

The aim of this study was to verify the effectiveness of photobiomodulation combining red and infrared wavelengths in the treatment of xerostomia and hyposalivation in patients with squamous cell carcinoma in the head and neck region.

Study design:

This was a two-arm, single-blind, parallel clinical study. Patients with head and neck squamous cell carcinoma (HNSCC) (N = 111) were screened for eligibility, and 85 were included in the study. The study design included one control group that did not receive laser therapy intervention (n = 44) and one group that received the intervention (n = 41). The primary expected outcome was the reduction of radiation-induced xerostomia and hyposalivation after cancer treatment. The secondary outcome was the reduction of depression and anxiety.

Results:

The proposed photobiomodulation protocol did not reduce xerostomia scores, did not increase the volume or density of saliva, did not change salivary pH, nor did it reduce the scores of the Beck Anxiety Inventory (BAI) or the Beck Depression Inventory (BDI) after radiotherapy.

Conclusion:

Photobiomodulation with the protocol used in this study did not show effectiveness in reducing ansiety and depression scores, and also did not show a statistically significant difference between the compared groups in terms of saliva volume, density and pH.

Letter of Submission

January 04 TH, 2022
Attention Professor Mark W. Lingen
Editor-in-Chief ***Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology***
Dear Dr. Lingen

We have pleasure to submit for publication in the ***Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*** the manuscript entitled "***Photobiomodulation in the treatment of xerostomia and hyposalivation in patients with squamous cell carcinoma in the head and neck region – a randomized controlled clinical trial***" written by

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The salivary glands are highly radiosensitive, and damage to these cells is inevitable in most cases, with manifestations in the first days of radiation resulting in hyposalivation and promoting changes that hinder basic functions of the oral cavity and negatively impact the quality of life of patients. The objective of this study was to investigate the effects of laser therapy on xerostomia and salivary flow in patients undergoing radiotherapy treatment for squamous cell carcinoma in the head and neck region. The laser therapy protocol used in this study did not reduce xerostomia or increase saliva volume, and it did not alter salivary pH in patients subjected to radiotherapy for HNSCC. In addition, there were no changes in the BAI or BDI scores.

Thanks for attention.

Sincerely,

Prof. André Luiz Sena Guimarães

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Statement of Clinical Relevance

Statement of clinical relevance

The present study demonstrated that the photobiomodulation used with this protocol did not reduce xerostomia, did not increase the salivary volume of patients and did not change the pH of saliva in irradiated patients with head and neck SCC. The results of the present study suggest that laser therapy with the parameters used does not serve as an alternative complementary treatment for patients with SCC of the head and neck.

Title Page

Photobiomodulation in the treatment of xerostomia and hyposalivation in patients with squamous cell carcinoma in the head and neck region – a randomized controlled clinical trial

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Possible Conflict of Interest: No /

Manuscript (.doc format)

Photobiomodulation in the treatment of xerostomia and hyposalivation in patients with squamous cell carcinoma in the head and neck region – a randomized controlled clinical trial

Objective. The objective of this study was to verify the effectiveness of photobiomodulation combining red and infrared wavelengths in the treatment of xerostomia and hyposalivation in patients with squamous cell carcinoma in the head and neck region.

Study design. This was a two-arm, single-blind, parallel clinical study. Patients with head and neck squamous cell carcinoma (HNSCC) (N = 111) were screened for eligibility, and 85 were included in the study. The study design included a control group that did not receive the PBM intervention (n = 44) and a group that received the intervention (n = 41). The expected primary outcome was a reduction in xerostomia and hyposalivation after radiotherapy. The secondary outcome was a reduction in depression and anxiety.

Results. The proposed PBM protocol did not reduce xerostomia scores, did not increase saliva volume and density, did not alter salivary pH, or reduced Beck Anxiety Inventory (BAI) or Beck Depression Inventory (BDI) scores after radiotherapy.

Conclusion. The laser therapy protocol used in this study did not reduce xerostomia or increase saliva volume, and it did not alter salivary pH in patients subjected to radiotherapy for HNSCC. In addition, there were no changes in the BAI or BDI scores.

Keywords: Salivary glands. Radiotherapy. Low-intensity light therapy. Xerostomia.

INTRODUCTION

The vast majority of patients with head and neck cancer undergo radiotherapy (RT), which has deleterious side effects (1). The salivary glands are highly radiosensitive, and damage to these cells is inevitable in most cases, with manifestations in the first days of radiation resulting in hyposalivation (1-3) and promoting changes that hinder basic functions of the oral cavity and negatively impact the quality of life of patients (2). Long-term effects of radiation include the accumulation of inflammation; development of fibrosis is the main characteristic of damage in the salivary glands, which may or may not regenerate in one to two years, (4) depending on the radiation dose administered, (5) the selected RT technique, and the irradiated area and gland. (6-8)

Whole saliva is a mixture of fluids from the major salivary glands (parotid, submandibular, and sublingual glands), which account for 90% of the total amount of saliva, and from the minor glands, which contribute the remaining 10% (7). Under resting conditions, the submandibular glands, which are composed of serous and mucous cells, produce two-thirds of the mucin-rich saliva and contribute to the sensation of salivary viscosity. (7) The sublingual glands produce 1% to 2% of the salivary product and are composed mainly of mucous cells; they contribute to the feeling of hydration of the oral cavity. (7, 9) The parotid glands, formed by serous cells, produce a watery fluid and, when stimulated, produce approximately 50% of the total volume of saliva. (7, 10) The minor salivary glands, composed of mucous cells, play a significant role in lubricating the mucosa despite their relatively small contribution to the total volume of saliva. (7, 11)

The sensation of dry mouth occurs when the unstimulated salivary flow rate decreases by at least 45% to 50%. (7, 12, 13) Salivary flow rates at rest of $\leq$ 0.1 ml/min and stimulated salivary flow rates of $\leq$ 0.5 ml/min cause pathologic low saliva secretion, a condition called hyposalivation. (7, 9)

Reduced salivary flow leads to xerostomia, or the sensation of dry mouth, one of the most frequent side effects seen in patients with cancer in the head and neck region and differentially affecting about 60% to 90% of patients. (14) A range of interventions is available for the prevention and treatment of gland hypofunction. (2, 15) Drugs such as pilocarpine and cevimeline are being recommended as first line treatment for hyposalivation and xerostomia in cancer patients. (2, 5, 16, 17) However, these treatments have side effects. (5) Bethanechol has similar activity to pilocarpine but with longer lasting effects; the few studies on its activity in the treatment of radiation-induced hyposalivation show that it provides minimal improvement of salivary flow and xerostomia.(5) Alternative treatment

options include taking chewing gum, (18) sialogogues (2, 17), and artificial saliva forms; (2, 5, 17) all these provide temporary effect and few to no benefits (2, 16). Amifostine, a radioprotective drug, has also been described in the literature as preventing salivary flow reduction, but its high cost and harmful side effects make its use unfeasible. (2, 5, 17, 19)

Interventions such as acupuncture showed benefits in hyposalivation with an increase in salivary flow volume and density, in addition to decreasing anxiety scores for patients with reports of xerostomia, but showed no change in salivary pH. (1)

PBM has been shown to be beneficial in treating the symptoms of xerostomia and signs of hyposalivation in cancer patients or those with autoimmune diseases such as Sjögren's Syndrome, etc. (20, 21) However, the lack of an evidence-based protocol (20, 21) makes it difficult to manage, prevent, and treat xerostomia and hyposalivation in cancer patients. (16) Therefore, it is necessary to establish PBM parameters that can be effectively reproduced in order to prevent or treat the harmful effects that further complicate patients' quality of life. (21)

PATIENTS AND METHODS

Ethical approval

The study was conducted in accordance with Resolution No. 466/2012 of the National Health Council, which approves the guidelines and regulatory standards for research involving human subjects, according to the ethical standards of the institutional and international ethics committees, and also with the Helsinki Declaration of 1964 and its subsequent amendments. The study was reviewed by the involved institutions and the Research Ethics Committee - CEP, http://plataformabrasil.saude.gov.br/ (opinion no. 3.234.287) and CAAE no. 01518618.8.0000.5146. The study was registered in the Brazilian Registry of Clinical Trials ReBEC, available at http://www.ensaiosclinicos.gov.br, on March 28 of 2021 with UTN no. U1111-12599-9624 / RBR-9bt3cbj under the title "Evaluation of the use of low power laser therapy for the treatment of dry mouth in patients of cancer in the head and neck region." Data were collected at Dilson Godinho de Quadros Hospital between December 2018 and March 2021.

Study design

This was a two-arm, single-blind, randomized, controlled, parallel-treatment clinical study that followed the CONSORT guidelines to avoid bias. (22) The lack of a protocol with scientific evidence for PBM (23-25) motivated the search for an effective protocol that would bring benefits to patients.

Sample size calculation

The sample size was calculated based on standard practice, as described in the literature, carried out in a very similar way to the present study, however, with the difference of having used acupuncture intervention to decrease xerostomia and increase salivary flow, in addition to improve anxiety scores. (1) The online chi-square sample size calculator available at http://clincalc.com was used. The sample size calculation provided data for two study groups with independent samples suggesting a number of 85 participants divided between 41 in the intervention group and 44 in the non-intervention group, who received different treatments and the primary binomial outcome. (i.e., only two outcomes were possible in this study). The calculation was performed to achieve an alpha level of 0.05, a beta level of 0.2 and a study power of 0.8, with a confidence interval of 95%.

Allocation concealment and blinding

Before the start of the study, allocation concealment was performed by an investigator who was not involved in the study, with the allocation sequence randomly generated using the Research Randomizer software. This sequence was included in the informed consent form (ICF) for later identification of the groups using an ID reveal method (that is, scratching the sealed code after patients consented to participate). Patients were recruited from a sample that was poised to start RT treatment. The individuals were invited to participate in the study after they were provided with aclear explanation of all the study steps and after reading the ICF. After patients confirmed their participation in the study, they were invited to sign the consent form. The allocation sequence in the ICF randomly assigned patients using a 1:1 ratio and provided knowledge of the group to which a patient was assigned (intervention or no-intervention). Both the recruiter and the patient were blinded to this information, and this was only available to the researcher responsible for administering the laser therapy after the participant signed and scratched the ID code on the ICF, thus ensuring randomization. Access to the identity of the group in which the participant was included occurred after he/she signed the ICF and was provided solely to the researcher responsible for the intervention to avoid interference of allocation and recruitment with the study results.

Inclusion criteria

Eligibility criteria included participants of both sexes aged over 18 years, histopathologically confirmed diagnosis of squamous cell carcinoma in the oral cavity, lips, oropharynx, larynx, hypopharynx, nasopharynx or occult primary site, and treatment with RT alone (3D conformational technique or IMRT with radiation doses between 60 to 70 Gy) or in combination with chemotherapy and/or surgery.

Exclusion criteria

Participants who did not participate or were not collaborative in all low-level laser intervention sessions, previous RT in the head and neck region, having performed 10 sessions of RT treatment at the time of randomization, or refusal to participate were the exclusion criteria.

Intervention with photobiomodulation

The researchers who administered the laser treatment were certified in laser therapy by the Ministry of Education and Culture (MEC) and authorized by the Class Council - Regional Council of Dentistry (CRO). The patients in the intervention group received low-power laser therapy with a Laser Duo device (MMOptics®, MMOptics Ltda, São Carlos, São Paulo,

Brazil, RRID: SCR_015955) that was validated and authorized for dental use by ANVISA/MS (registration no. 8005142002) and had the following technical characteristics: a semiconductor light-emitting laser (GaA1As and InGaAIP), an output laser beam area at the laser pen tip of 3 mm^2, power of 100 mW and a spot size of 0.030 cm^2. Light transmission was performed in continuous mode, and irradiation was performed using a punctual contact technique directly on the tissue at a 90° angle of light incidence (in relation to irradiated tissue) when possible, and at wavelengths of 660 nm (red laser) and 808 nm (infrared laser), starting the intervention with the length of 660 nm in 15 points and, only after, 15 different points, but in the same gland, of the length infrared waveform. The proposed protocol was based on that of a previous study, (26) using a energy of 9.0 J (300 J/cm^2) per application point, distributed in the major salivary glands as follows: three extra-oral points for each parotid gland, three extra-oral points for each submandibular gland (Figure 2A), and three intra-oral points for the sublingual glands (Figure 2B), totaling 15 points, i.e., a total dose of 135 J was delivered to the tissues. The treatment was performed twice a week (Tuesdays and Thursdays) during the radiotherapy treatment period, mostly with the 3D conformational radiotherapy technique, and in only 5 participants (2 in the intervention group and 3 in the without intervention) with the modality of Intensity Modulated Radiotherapy (IMRT), the first intervention being right after the allocation and signature of the TCLE, remembering that, as an inclusion criterion, the participant could only be there until the 10th session of RT. The last laser intervention did not always coincide with the last RT session, since it happened only twice a week and radiotherapy from Monday to Friday. The cases of mucositis and radiodermatitis lesions in both groups were treated with photobiomodulation, in the protocol proposed by Soares et al, 2018. Therefore, a portable DUO laser device was used, with a semiconductor light emitter (GaAIAs and InGaAIP), optical power laser beam of 100mW, laser beam output area of the pen nozzle of 3 mm^2, spot area of 0.030 cm^2, continuous mode of operation of the equipment (light transmission), in the wavelengths of 660nm and 808 nm, being delivered to the tissues an energy of 9 J per point, energy density of 300 J/cm^2, power density of 3.33 J/cm^2. The form of irradiation was punctual, with an angle of incidence of light, in relation to the tissues, at 90°. The objective was to ensure adherence to treatment and ensure the participant's well-being and quality of life. The severity of mucositis was varied for each participant and the protocol used was according to the appearance of the lesions and the patient's complaint. The dose of PBM used for mucositis, therefore, was varied according to the reality of each one, and following the aforementioned parameters. No interference or

statistical difference was demonstrated between participants in the groups. PBM in tumors was avoided as suggested by studies. (25-27)

To avoid harm to the patient, they were asked to wear protective goggles during all sessions, the laser device was covered with plastic, and the applications were performed by qualified professionals.

Groups

The intervention group was composed of participants who received PBM, while the comparison group (no intervention) was composed of participants who did not receive photobiomodulation and no other type of intervention for xerostomia and hyposalivation during the research.

Outcomes and measured parameters

The primary outcome expected after photobiomodulation was the reduction or maintenance of baseline xerostomia and hyposalivation scores (salivary flow volume, saliva density and pH were evaluated) with comparison of results between groups or comparison of initial and final results of participants in the same group. The expected secondary outcome was a reduction in anxiety and depression scores. The participant included in the research was before starting radiotherapy or until the 10th session of the treatment, had no contact with the researcher, and therefore, no guidance or intervention had been carried out. Participants were evaluated regarding their clinical and socioeconomic characteristics and regarding the use of medications or previous comorbidities with anamnesis questionnaires. After their inclusion in the study, they received guidance on oral hygiene, hydration and, when possible and necessary, were referred to the Basic Health Units for adaptation of the previous oral environment. No participant received oral stents or root prostheses and those who used oral prostheses were instructed not to make the mask for treatment, using the prosthesis. Participants were followed up without prescription of oral lubricants or chemical or mechanical sialogogues in order to avoid factors that could interfere with the PBM intervention. The parameters for evaluating the study variables were acquired in two stages: the first evaluation was performed before the beginning of the PBM intervention among patients who were up to the 10th RT session and the second evaluation was performed at or near the end of the RT treatment.

Saliva collection and analysis

Unstimulated sialometry was performed in both groups as adapted from previous studies (28), and the patients' salivary flow was quantitatively and qualitatively determined through objective analyzes (measurements of pH, weight and volume before the 10th radiotherapy session and close to the last treatment session). (29) It was decided that saliva would be collected without stimulation because some patients were edentulous, which would make the use of sialagogues difficult. Patients were instructed not to eat for one hour before collection. They were placed in a resting position with their heads tilted down and instructed to spit out, letting the saliva flow to the front of the mouth for five minutes and then spit it out into a collection container. (29) The saliva collected was weighed on a calibrated precision scale before each weighing. After the foam was discarded, with vibration to break the formed balls, the saliva was transferred to a 5 ml syringe for volume determination (in ml). Subsequently, the pH of the saliva was measured and recorded using a pH meter that was also calibrated daily with buffer solutions of known pH (4.02 and 6.86). We searched the medical records for evidence of the use of medications that could trigger xerostomia and interfere with saliva production, in order to avoid confounding bias. (30) All sample collections were performed in a standardized way, that is, in the morning, between 8 am and 11 am to avoid circadian effects (11, 31) and diurnal variations in salivary flow. (32)

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Questionnaires

The Xerostomia Inventory, (33, 34) the Beck Anxiety Inventory (BAI) and the Beck Depression Inventory (BDI) (33) were administered to identify signs and symptoms associated with xerostomia, anxiety, and depression, respectively.

Statistical analysis

Statistical analysis was performed using the PASW® software version 18.0 for Windows®. Kolmogorov-Smirnov and Shapiro-Wilk tests were performed to evaluate the distribution of data; the analyses showed that the data were non-parametrically distributed. Subsequently, the Mann-Whitney U test was performed.

RESULTS

Both groups had the same initial clinical characteristics

A total of 111 patients were screened for eligibility, and 85 patients were included in the study. The intervention group consisted of 41 participants; the others were excluded due to death (n = 5), withdrawal from the study due to reports of fatigue resulting from the time of the intervention by the participants (n = 7) and interruption of cancer treatment (n = 6). The non-intervention group included 44 patients; the others were excluded due to death (n = 3), withdrawal from the study who reported not intending to continue to participate in the research (n = 3) and interruption of cancer treatment (n = 2). The study flowchart is shown in Figure 1.

The group that received the intervention consisted of 41 patients (32 men and 9 women) between 40 and 83 years of age (mean = 59.61; SD = 10.7). Regarding the distribution of malignant tumors, 17 were located in the oral cavity, 12 in the oropharynx, and 12 in the larynx. Among all patients in the treatment group, 18 were treated with RT and chemotherapy; f5 were treated with RT, chemotherapy, and surgery; and 18 were treated with RT and surgery. The non-intervention group consisted of 44 patients (35 men and 9 women) aged 34 to 79 years (mean = 59.66; SD = 9.967). In the non-intervention group, the distribution of lesions was as follows: 14 in the oral cavity, 15 in the oropharynx, 7 in the hypopharynx, 5 in the larynx, 2 in the nasopharynx, and 1 in an unknown primary site. In this group, all patients were treated with RT: 2 patients were treated exclusively with RT, 24 patients were treated with RT and chemotherapy; 7 patients were treated with RT, chemotherapy, and surgery, and 11 patients were treated with RT and surgery. The groups did not differ regarding clinical findings that could affect the incidence of xerostomia (Table 1).

The risks of applying low-power lasers are considered minimal and associated with the inadequate use of personal protective equipment (PPE). However, no patient was harmed, and those who complained of discomfort due to fatigue were promptly excluded from the study.

Xerostomia score

The Xerostomia Inventory was used to collect reports of xerostomia symptoms. (33, 34) There was no statistical difference between the groups regarding the final xerostomia scores (Figure 3A).

There was no increase in saliva volume and density and no change in salivary pH in both groups (Figure 3B, 3C, and 3D).

Objective analyses for xerostomia and were performed using sialometry (28, 29) that showed no significant differences in saliva volume and density before and after RT among the study participants (1) i.e., the volume and density levels of saliva were not significantly different between patients treated with laser therapy at the applied dose and wavelength (Figure 3B and 3C) and those who did not receive the intervention. There was no significant difference between groups regarding saliva density after RT (figure 3C). RT treatment and PBM (Figure 3D) did not alter the pH of saliva.

Reduction of anxiety and depression

The BAI and BDI (33) were applied to determine if there was an effect of laser therapy on the degree of anxiety and depression, respectively. No significant differences were observed between the groups before ($p= 0.587$ and $p= 0.825$, respectively) or after laser treatment ($p= 0.485$ and $p= 0.158$, respectively; Table 2).

DISCUSSION

The unwanted effects of RT in the head and neck region interfere with the basic functions of the oral cavity and have a negative impact on patients' quality of life. (7) The present study was based on a study (26) that analyzed the effect of low-power laser on the prevention and treatment of radiation-induced xerostomia in patients with head and neck cancer.

Alternative therapies such as low-power laser therapy have been used to minimize the deleterious effects of RT treatment. (21) However, despite many experiments, the use of laser therapy is controversial. (35, 36) The biochemical and cellular changes caused by the use of laser therapy have benefits that include tissue repair; reduction of pain, inflammation and edema; and minimization of damage to irradiated healthy cells adjacent to the tumor. (21, 24, 27, 35-37) PBM is a non-invasive, simple, painless, inexpensive, and well-tolerated treatment that does not harm patients.(23, 24, 27, 38) Photobiomodulation does not have carcinogenic effects and does not induce malignant transformation of healthy epithelial tissue cells or fibroblasts.(27) However, despite many positive reports in the literature, parameter specifications including dosage, wavelength, fluence, power density, pulse, and duration remain cunclear. (21, 24, 27, 35-37) Well-established laser therapy parameters are crucial for treatment efficacy. (19, 23, 24)

Studies performed in mammalian cells have shown a more effective response to biphasic dose delivery to tissues with low-level laser energy, resulting in a better therapeutic outcome, (35-37) which suggests that a high power density or long duration of irradiation can inhibit the action of the laser on the tissues. (35-37) However, research with human cells has shown that the combination of red and infrared laser wavelengths with an energy of 9J (300 J⁄cm2) delivered to tissues increases fibroblast proliferation within 24 hours and promotes tissue repair, (26) which allows for periodic photobiomodulation twice a week (Tuesdays and Thursdays) and the maintenance and recovery of fibroblasts throughout the week in cases of oral mucositis. (26) These data verify the security and efficiency of the proposed protocol. PBM was performed in a group of 41 participants, while a placebo group of 44 participants did not receive the intervention, with the aim of analyzing the effects of photobiomodulation on salivary glands of patients who received RT in radiotherapy techniques, 3D three-dimensional conformal radiotherapy and IMRT, in the head and neck region.

Other studies report that PBM contributes to the increase of local microcirculation, which leads to the proliferation of acinar cells in salivary glands and increases cellular respiration. (19, 23) In addition, it favors the production of ATP, protein synthesis and raises the level of

intracellular calcium. (19, 23) There is evidence that photobiomodulation can contribute to improving cell function in remaining glands that have not yet suffered radiation damage sufficiently capable of leading to a hypofunction of their cells. (19, 23)

In a study conducted during RT treatment, (19) low-power laser with combined wavelengths targeted major and minor salivary glands, but at a dose lower than that proposed herein, and was shown to be a promising and effective agent in mitigating salivary hypofunction in patients with head and neck cancer, resulting in increased salivary flow rate. In another study conducted after receiving RT, (23) the use of low-power laser with a wavelength of 808 nm (infrared) resulted in significantly increased salivary flow and pH and decreased xerostomia, however, there was no comparison group in this study. (23)

Research (31) conducted with laser therapy (with one wavelength) in patients undergoing cancer treatment and with mucositis lesions showed an effect of non-ionizing radiation on salivary flow and indicated that laser therapy mitigates hypofunction of the salivary glands. (21, 31) In the present study, there were no differences between the groups regarding saliva volume and pH or reduction of self-reported xerostomia symptoms among the participants that received laser therapy for mucositis lesions; however, a combination of wavelengths (red and infrared) was used.

Many studies have used more advanced RT techniques to reduce xerostomia, such as intensity-modulated radiation therapy, partially sparing the parotid glands. (4, 7, 32, 39) With regard to the amount of saliva production, the salivary flow of spared parotid glands appears to increase significantly over time, compared to that of glands irradiated using conventional techniques. (7, 30, 35) However, complaints of xerostomia by the patients did not necessarily cease to exist, but experiences of xerostomia became inconsistent and complex. (32) This phenomenon may explain the fact that, in that study, the patients' subjective sensations of dry mouth remained even with the use of an RT technique that spares the parotid gland. (7)

Thus, sparing parotid glands alone is not a guarantee of decreased xerostomia. (7) Therefore, the role of the submandibular glands in unstimulated production of saliva stands out (7, 32, 40) as one of the most important in complaints of dry mouth, (7, 32, 41-43) because the presence of mucin, produced by the submandibular glands and minor salivary glands in a smaller quantity, acts as a selective barrier of permeability of the oral mucosa and contributes to keeping tissues hydrated and, in turn, contributes to the individual's subjective feeling of oral hydration. (7, 32, 44) Studies in which the location of the submandibular gland was surgically changed during radiation to a non-irradiated area resulted in significant improvements in salivary flow production and in symptoms of dry mouth reported by the

patient.(32, 45, 46) However, one study did not demonstrate improvement in the quality of life of patients who underwent surgery for gland transfer compared to those who did not. (45) In addition, the indication for the procedure has limitations. (17)

Other studies suggest a lower radiosensitivity of the submandibular gland compared to the parotid glands, which is compatible with the common symptoms of thick and sticky saliva throughout RT treatment and after its completion, relating to the faster fall in the production of the aqueous content of the saliva produced by the parotid glands compared to the fall in mucin secretion, which occurs predominantly in the submandibular and minor salivary glands. (7, 32, 47)

In the present study, there was no significant difference between patients who used drugs responsible for the reports of dry mouth sensation and those who underwent surgical removal of submandibular glands or others.

Radiation doses were similar in the two study groups, as were the related probable causes of xerostomia and hyposalivation; however, the use of this photobiomodulation protocol in the treatment and the radiotherapy treatment did not interfere with salivary pH.

It was demonstrated that the combination of the two wavelengths did not result in statistical differences between the two groups regarding the complaint of xerostomia or the signs of hyposalivation such as saliva volume and pH. Regarding the depression and anxiety scores of the patients, there was also no statistical difference for the scores of the compared groups. It is important to emphasize that further studies should be carried out to clarify the benefits of photobiomodulation and establish a protocol capable of preventing and treating lesions in the salivary glands of cancer patients.

REFERENCES

1. Menezes A, Sanches GLG, Gomes ESB, Soares RG, Durães CP, Fonseca LL, et al. The combination of traditional and auricular acupuncture to prevent xerostomia and anxiety in irradiated patients with HNSCC: a preventive, parallel, single-blind, 2-arm controlled study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2021;131(6):675-83.
2. Jasmer KJ, Gilman KE, Muñoz Forti K, Weisman GA, Limesand KH. Radiation-Induced Salivary Gland Dysfunction: Mechanisms, Therapeutics and Future Directions. J Clin Med. 2020;9(12).
3. Cardoso CM, de Jesus SF, de Souza MG, Santos EM, Santos CKC, Silveira CM, et al. Is HIF1-a deregulated in malignant salivary neoplasms? Gene. 2019;701:41-5.
4. Barazzuol L, Coppes RP, van Luijk P. Prevention and treatment of radiotherapy-induced side effects. Molecular oncology. 2020;14(7):1538-54.
5. Lovelace TL, Fox NF, Sood AJ, Nguyen SA, Day TA. Management of radiotherapy-induced salivary hypofunction and consequent xerostomia in patients with oral or head and neck cancer: meta-analysis and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014;117(5):595-607.
6. Hernandez-Segura A, Nehme J, Demaria M. Hallmarks of Cellular Senescence. Trends Cell Biol. 2018;28(6):436-53.
7. Jensen SB, Pedersen AM, Vissink A, Andersen E, Brown CG, Davies AN, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. Support Care Cancer. 2010;18(8):1039-60.
8. Millsop JW, Wang EA, Fazel N. Etiology, evaluation, and management of xerostomia. Clin Dermatol. 2017;35(5):468-76.
9. Schneyer LH. Source of resting total mixed saliva of man. Journal of applied physiology. 1956;9(1):79-81.
10. Dawes C, Ong BY. Circadian rhythms in the flow rate and proportional contribution of parotid to whole saliva volume in man. Archives of oral biology. 1973;18(9):1145-53.
11. Dawes C, Wood CM. The contribution of oral minor mucous gland secretions to the volume of whole saliva in man. Archives of oral biology. 1973;18(3):337-42.
12. Dawes C. Physiological factors affecting salivary flow rate, oral sugar clearance, and the sensation of dry mouth in man. Journal of dental research. 1987;66 Spec No:648-53.
13. Ghezzi EM, Lange LA, Ship JA. Determination of variation of stimulated salivary flow rates. Journal of dental research. 2000;79(11):1874-8.
14. Rosen BS, Hawkins PG, Polan DF, Balter JM, Brock KK, Kamp JD, et al. Early Changes in Serial CBCT-Measured Parotid Gland Biomarkers Predict Chronic Xerostomia After Head and Neck Radiation Therapy. International journal of radiation oncology, biology, physics. 2018;102(4):1319-29.
15. Plemons JM, Al-Hashimi I, Marek CL. Managing xerostomia and salivary gland hypofunction: executive summary of a report from the American Dental Association Council on Scientific Affairs. J Am Dent Assoc. 2014;145(8):867-73.
16. Mercadante V, Al Hamad A, Lodi G, Porter S, Fedele S. Interventions for the management of radiotherapy-induced xerostomia and hyposalivation: A systematic review and meta-analysis. Oral Oncol. 2017;66:64-74.
17. Vissink A, Burlage FR, Spijkervet FK, Jansma J, Coppes RP. Prevention and treatment of the consequences of head and neck radiotherapy. Critical reviews in oral biology and medicine : an official publication of the American Association of Oral Biologists. 2003;14(3):213-25.

18. Furness S, Worthington HV, Bryan G, Birchenough S, McMillan R. Interventions for the management of dry mouth: topical therapies. Cochrane Database Syst Rev. 2011(12):Cd008934.
19. Gonnelli FA, Palma LF, Giordani AJ, Deboni AL, Dias RS, Segreto RA, et al. Low-Level Laser for Mitigation of Low Salivary Flow Rate in Head and Neck Cancer Patients Undergoing Radiochemotherapy: A Prospective Longitudinal Study. Photomedicine and laser surgery. 2016;34(8):326-30.
20. Dompe C, Moncrieff L, Matys J, Grzech-Leśniak K, Kocherova I, Bryja A, et al. Photobiomodulation-Underlying Mechanism and Clinical Applications. Journal of clinical medicine. 2020;9(6).
21. Louzeiro GC, Teixeira DDS, Cherubini K, de Figueiredo MAZ, Salum FG. Does laser photobiomodulation prevent hyposalivation in patients undergoing head and neck radiotherapy? A systematic review and meta-analysis of controlled trials. Critical reviews in oncology/hematology. 2020;156:103115.
22. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg. 2012;10(1):28-55.
23. Palma LF, Gonnelli FAS, Marcucci M, Dias RS, Giordani AJ, Segreto RA, et al. Impact of low-level laser therapy on hyposalivation, salivary pH, and quality of life in head and neck cancer patients post-radiotherapy. Lasers Med Sci. 2017;32(4):827-32.
24. Robijns J, Censabella S, Bulens P, Maes A, Mebis J. The use of low-level light therapy in supportive care for patients with breast cancer: review of the literature. Lasers Med Sci. 2017;32(1):229-42.
25. Zecha JA, Raber-Durlacher JE, Nair RG, Epstein JB, Elad S, Hamblin MR, et al. Low-level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 2: proposed applications and treatment protocols. Support Care Cancer. 2016;24(6):2793-805.
26. Soares RG, Farias LC, da Silva Menezes AS, de Oliveira ESCS, Tabosa ATL, Chagas PVF, et al. Treatment of mucositis with combined 660- and 808-nm-wavelength low-level laser therapy reduced mucositis grade, pain, and use of analgesics: a parallel, single-blind, two-arm controlled study. Lasers Med Sci. 2018;33(8):1813-9.
27. Zecha JA, Raber-Durlacher JE, Nair RG, Epstein JB, Sonis ST, Elad S, et al. Low level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 1: mechanisms of action, dosimetric, and safety considerations. Support Care Cancer. 2016;24(6):2781-92.
28. Navazesh M. Methods for collecting saliva. Ann N Y Acad Sci. 1993;694:72-7.
29. Shetty SR, Bhowmick S, Castelino R, Babu S. Drug induced xerostomia in elderly individuals: An institutional study. Contemporary clinical dentistry. 2012;3(2):173-5.
30. Mithani SK, Mydlarz WK, Grumbine FL, Smith IM, Califano JA. Molecular genetics of premalignant oral lesions. Oral diseases. 2007;13(2):126-33.
31. Simões A, de Campos L, de Souza DN, de Matos JA, Freitas PM, Nicolau J. Laser phototherapy as topical prophylaxis against radiation-induced xerostomia. Photomedicine and laser surgery. 2010;28(3):357-63.
32. Murdoch-Kinch CA, Kim HM, Vineberg KA, Ship JA, Eisbruch A. Dose-effect relationships for the submandibular salivary glands and implications for their sparing by intensity modulated radiotherapy. International journal of radiation oncology, biology, physics. 2008;72(2):373-82.
33. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. Journal of consulting and clinical psychology. 1988;56(6):893-7.

34. da Mata AD, da Silva Marques DN, Freitas FM, de Almeida Rato Amaral JP, Trindade RT, Barcelos FA, et al. Translation, validation, and construct reliability of a Portuguese version of the Xerostomia Inventory. Oral diseases. 2012;18(3):293-8.
35. Hamblin MR, Demidova TN, editors. Mechanisms of low level light therapy. Mechanisms for low-light therapy; 2006: International Society for Optics and Photonics.
36. Huang YY, Sharma SK, Carroll J, Hamblin MR. Biphasic dose response in low level light therapy - an update. Dose Response. 2011;9(4):602-18.
37. Huang YY, Chen AC, Carroll JD, Hamblin MR. Biphasic dose response in low level light therapy. Dose Response. 2009;7(4):358-83.
38. Saleh J, Figueiredo MA, Cherubini K, Braga-Filho A, Salum FG. Effect of low-level laser therapy on radiotherapy-induced hyposalivation and xerostomia: a pilot study. Photomedicine and laser surgery. 2014;32(10):546-52.
39. Eisbruch A. Reducing xerostomia by IMRT: what may, and may not, be achieved. J Clin Oncol. 2007;25(31):4863-4.
40. Ship JA, Fox PC, Baum BJ. How much saliva is enough? The Journal of the American Dental Association. 1991;122(3):63-9.
41. Eisbruch A, Kim HM, Terrell JE, Marsh LH, Dawson LA, Ship JA. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. International Journal of Radiation Oncology* Biology* Physics. 2001;50(3):695-704.
42. Jellema AP, Doornaert P, Slotman BJ, Leemans CR, Langendijk JA. Does radiation dose to the salivary glands and oral cavity predict patient-rated xerostomia and sticky saliva in head and neck cancer patients treated with curative radiotherapy? Radiotherapy and Oncology. 2005;77(2):164-71.
43. Saarilahti K, Kouri M, Collan J, Kangasmäki A, Atula T, Joensuu H, et al. Sparing of the submandibular glands by intensity modulated radiotherapy in the treatment of head and neck cancer. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2006;78(3):270-5.
44. Tabak LA. In defense of the oral cavity: structure, biosynthesis, and function of salivary mucins. Annual review of physiology. 1995;57(1):547-64.
45. Scrimger RA, Seikaly H, Vos LJ, Harris J, O'Connell D, Ghosh S, et al. Combination of submandibular salivary gland transfer and intensity-modulated radiotherapy to reduce dryness of mouth (xerostomia) in patients with head and neck cancer. Head Neck. 2018;40(11):2353-61.
46. Seikaly H, Jha N, Harris JR, Barnaby P, Liu R, Williams D, et al. Long-term outcomes of submandibular gland transfer for prevention of postradiation xerostomia. Archives of Otolaryngology–Head & Neck Surgery. 2004;130(8):956-61.
47. Konings AW, Coppes RP, Vissink A. On the mechanism of salivary gland radiosensitivity. International journal of radiation oncology, biology, physics. 2005;62(4):1187-94.
48. Deasy JO, Moiseenko V, Marks L, Chao KS, Nam J, Eisbruch A. Radiotherapy dose-volume effects on salivary gland function. International journal of radiation oncology, biology, physics. 2010;76(3 Suppl):S58-63.

Figures Legend

Figure 1-The study flowchart is illustration.

Figure 2-Esquematic intervention

(A) Scheme of irradiation sublingual salivary gland intraorally.

(B) Extra oral irradiation of parotid and submandibular glands

Figure 3 – Final parameters

(A) Final score in xerostomia

(B) Final saliva volume

(C) Final saliva density

(D) Final saliva pH

There was no statistical difference between the xerostomia scores, volume, density and pH of saliva between the groups compared at the end of the intervention.

Table 1-Comparison of initial clinical characteristics between groups

No initial clinical differences were observed in comparison of intervention and without intervention groups.

Table 2- Comparison of anxiety and depression levels between intervention and non-intervention groups.

No differences were observed between the scores of the initial and final anxiety and depression inventories when comparing the intervention and non-intervention groups.

Table 3 - Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC)

Maximum dose and average dose limits so that ionizing radiation damages do not occur in parotid glands according to the Quantec table. (48) Adapted table

Compliance with ethical standards

The authors declare no conflicts of interest related to this study.

SUPPLEMENTARY MATERIAL

CONSORT 2010 checklist of information to include when reporting a randomised trial.

*** Conflict of Interest Statement**

This study was supported by grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), the Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) and Hospital Dilson Godinho, Montes Claros, MG Brazil. Dr. Guimarães, Dr. Santos and Dr. de Paula are research fellows of the CNPq. Dr Farias is research fellow of FAPEMIG.

Conflicts of interest

The authors deny any conflicts of interest related to this study.

Ethical approval process number: 3.234.287

CAAE no. 01518618.8.0000.5146

Brazilian Clinical Trial registration: UTN no. U1111-12599-9624／RBR-9bt3cbj

Figure 1 - The study flowchart is illustration.

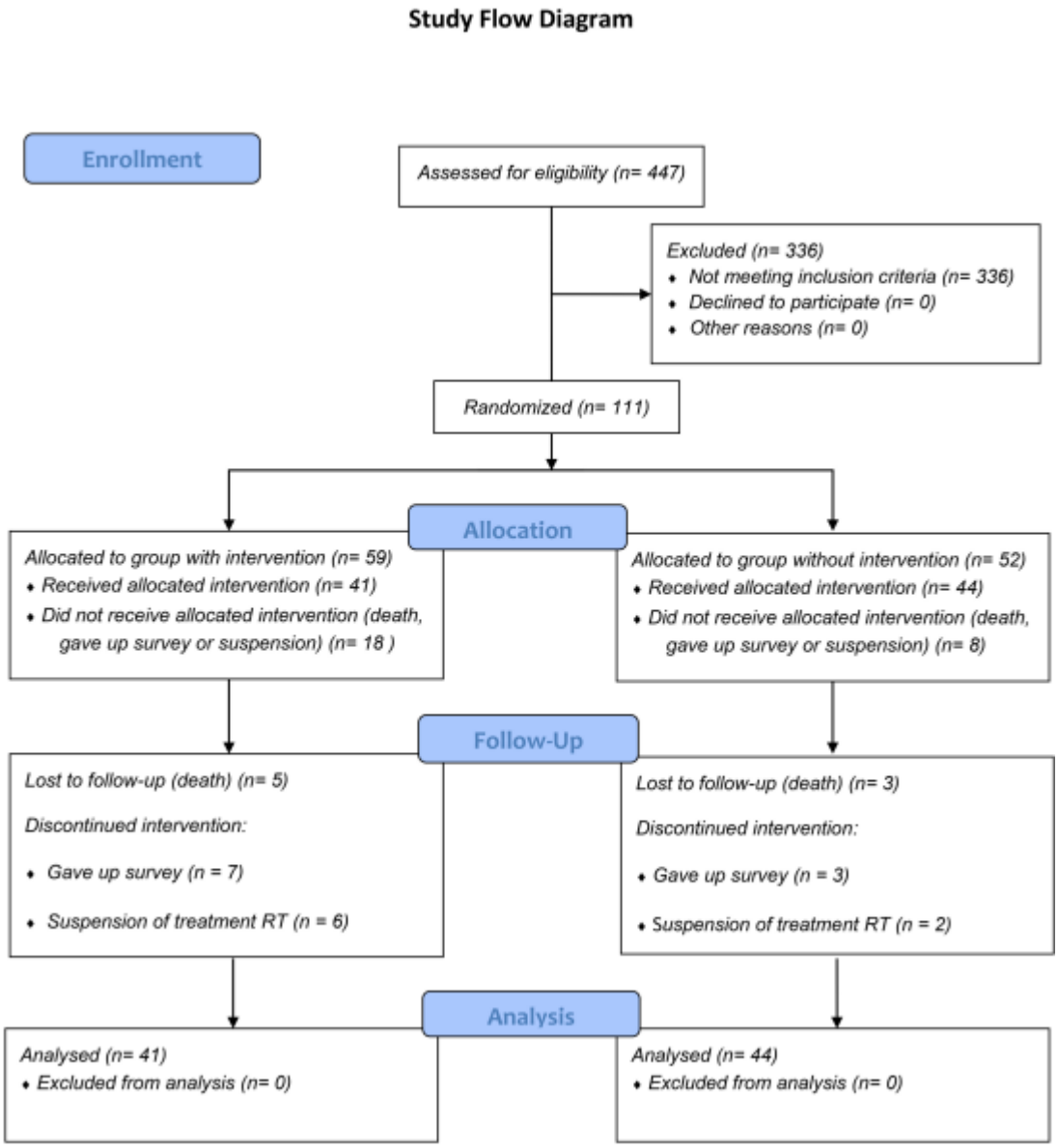


Figure 2 - Esquematic intervention

(A) Scheme of irradiation sublingual salivary gland intraorally.

(B) Extra oral irradiation of parotid and submandibular glands

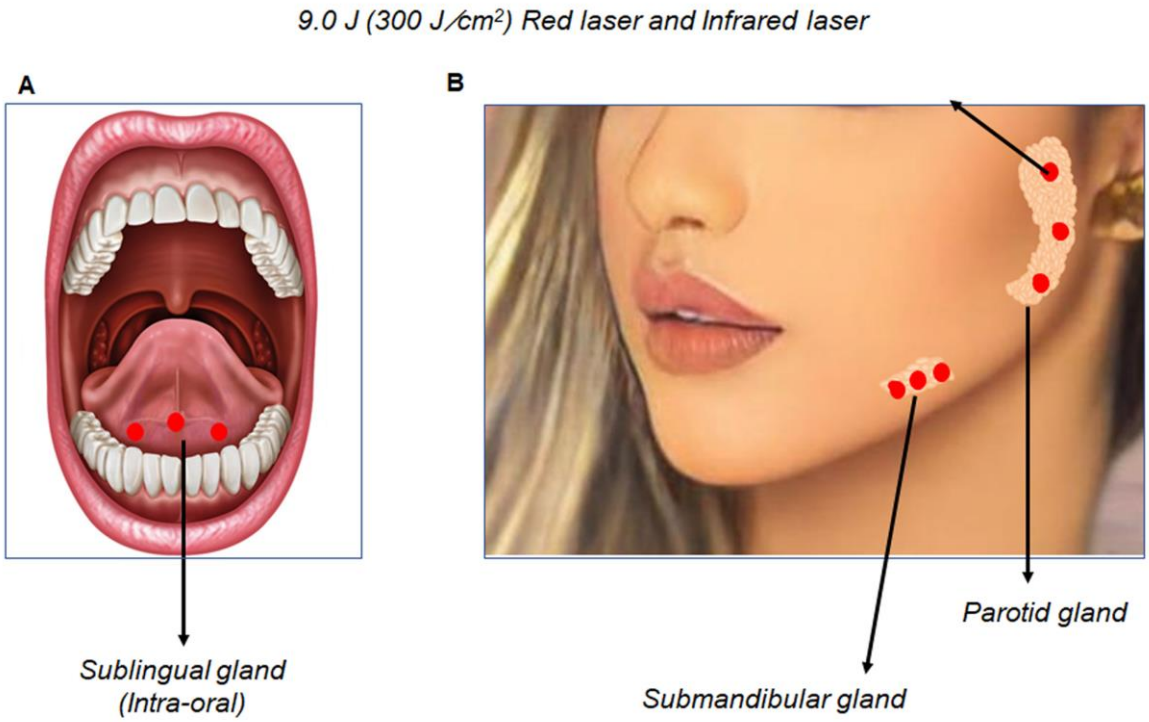
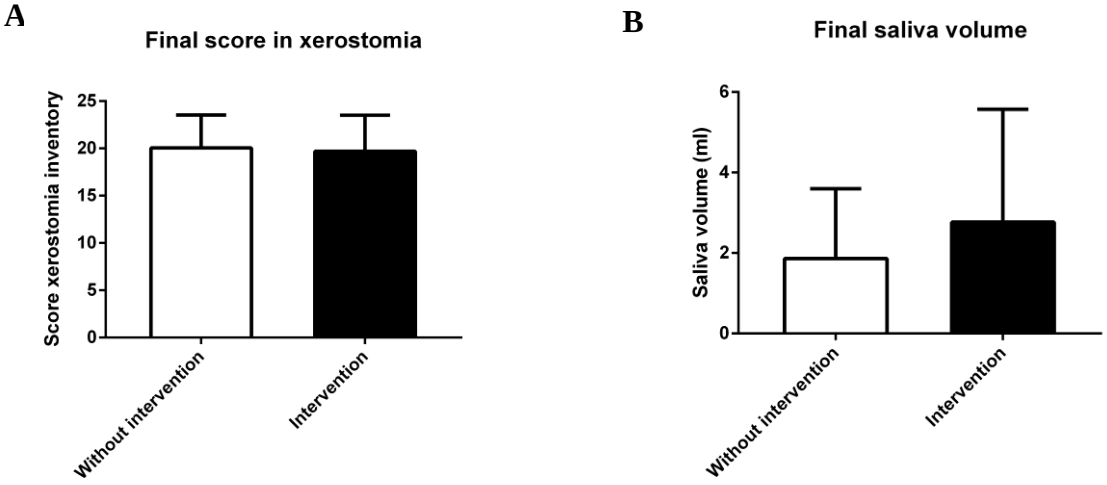
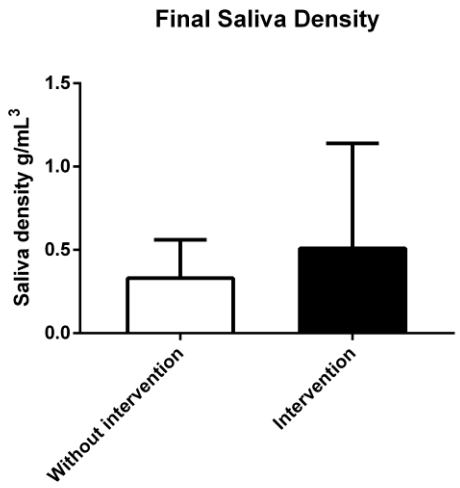


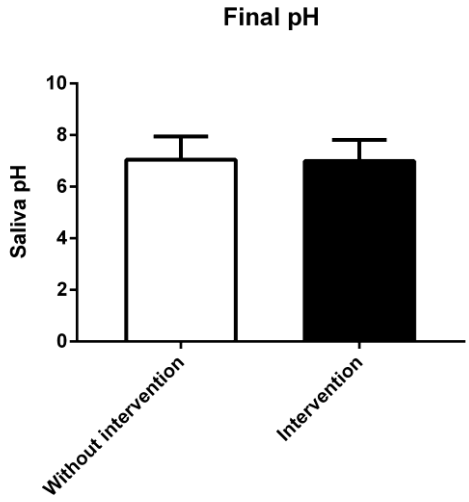
Figure 3 - Final parameters



C



D



There was no statistical difference between the xerostomia scores, volume, density and pH of saliva between the groups compared at the end of the intervention.

Table 1

Table 1-Comparison of initial clinical characteristics between groups

	Without intervention (n=44)		*With ntervention group (n=41)*		
	Nº	*%*	*Nº*	*%*	*P valu e*
Sex					
Male	35	79.5%	32	78.0%	
Female	9	20.5%	9	22.0%	0.87
Age (y)					
Range	34-79		40-83		
Mean (SD)	60	(10.0)	60	(10.7)	0.92
Smoking status					
Non Smoker	5	11.4%	5	12.2%	
Smorker or ex-smoker	39	88.6%	36	87.8%	0.90
Alcohol use disorder					
Never drank	2	4.5%	3	7.3%	
Alcoholic or ex-alcoholic	42	95.5%	38	92.7%	0.59
Treatment					
RT	2	4.5%	0	0%	
RT+CT	24	54.5%	18	43.9%	
RT+CT+SUR	7	15.9%	5	12.2%	
RT+SUR	11	25.0%	18	43.9%	0.19
Chemotherapy scheme					

No medicine	13	29.5%	18	43.9%	
Cisplatin	28	63.6%	23	56.1%	
Cisplatin and fluorouracil	1	2.3%	0	0.0%	
Cisplatin and docetaxel	1	2.3%	0	0.0%	
Cisplatin, docetaxel and fluouracil	1	2.3%	0	0.0%	0.38
RT dose					
≥ 60Gy and ≤ 62 Gy	13	29.5%	12	29.3%	
66 Gy	7	15.9%	7	17.1%	
70 Gy	24	54.5%	22	53.7%	0.99
Technic RT					
3D	41	93.2%	39	95.1%	
IMRT	3	6.8%	2	4.9%	1.00
Anatomic site					
Oral cavity	14	31.8%	17	41.5%	
Oropharynx	15	34.1%	12	29.3%	
Hypopharynx	7	15.9%	0	0%	
Larynx	5	11.4%	12	29.3%	
Nasopharynx	2	4.5%	0	0.0%	
Occult primary	1	2.3%	0	0.0%	0.01
Cancer staging					
Stage I	0	0.0%	0	0.0%	
Stage II	4	9.1%	4	9.8%	
Stage III	11	25%	7	17.1%	
Stage IV	29	65.9%	30	73.2%	0.61
Use of medication that causes xerostomia					
Yes	30	68.2%	29	70.7%	
No	14	31.8%	12	29.3%	0.80

No initial clinical differences were observed in comparison of intervention and without intervention groups.

Table 2- Comparison of anxiety and depression levels between intervention and non-intervention groups.

	Without intervention (n=44)		*With ntervention group (n=41)*		
	Nº	*%*	*Nº*	*%*	*P value*
Anxiety					
Low anxiety	39	88.6%	37	90.20%	
Moderate anxiety	5	11.4%	3	7.3%	
High anxiety	0	0.0%	1	2.4%	0.49
Depression					
Minimal depression	12	27.3%	9	22.0%	
Mild depression	17	38.6%	24	58.5%	
Moderate depression	7	15.9%	6	14.6%	
Severe depression	8	18.2%	2	4.9%	0.16

No differences were observed between the scores of the initial and final anxiety and depression inventories when comparing the intervention and non-intervention groups.

Table 3 -

QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Parotid	Bilateral whole parotid glands	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <25	<20	For combined parotid glands¶
	Unilateral whole parotid gland	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <20	<20	For single parotid gland. At least one parotid gland spared to <20 Gy¶
	Bilateral whole parotid glands	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <39	<50	For combined parotid glands (per Fig. 3 in paper) ¶

Abbreviations: 3D-CRT = 3-dimensional conformal radiotherapy

†All at standard fractionation (i.e., 1.8–2.0 Gy per daily fraction) unless otherwise noted. Vx is the volume of the organ receiving ≥ x Gy. Dmax = Maximum radioation dose.

¶ Severe xerostomia is related to additional factors including the doses to the submandibular glands.

Dose average limits so that ionizing radiation damages do not occur in parotid glands according to the Quantec table. Adapted table

SUPPLEMENTARY MATERIAL

CONSORT 2010 checklist of information to include when reporting a randomised trial.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	01
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	01
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	02
	2b	Specific objectives or hypotheses	03
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	04
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	04
Participants	4a	Eligibility criteria for participants	05
	4b	Settings and locations where the data were collected	04
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	04 e 06
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	07
	6b	Any changes to trial outcomes after the trial commenced, with reasons	09
Sample size	7a	How sample size was determined	04
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	05
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	05
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	05
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	05

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	05
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	09
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	04
	13b	For each group, losses and exclusions after randomisation, together with reasons	04
Recruitment	14a	Dates defining the periods of recruitment and follow-up	04
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Flow chart
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	4 and 5
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	09
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	06
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	N/A
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	09
Other information			
Registration	23	Registration number and name of trial registry	04
Protocol	24	Where the full trial protocol can be accessed, if available	04
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Acknowledgment

This study was supported by grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), the Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) and Hospital Dilson Godinho, Montes Claros, MG Brazil. Dr. Guimarães, Dr. Santos and Dr. de Paula are research fellows of the CNPq. Dr Farias is research fellow of FAPEMIG.

Conflicts of interest

The authors deny any conflicts of interest related to this study.

4. CONSIDERAÇÕES FINAIS

Qualquer que seja a modalidade de tratamento escolhida para o paciente oncológico, seja cirúrgico, quimioterápico ou radioterápico, os efeitos colaterais acontecerão, em maior ou menor gravidade. A radioterapia na região de cabeça e pescoço está associada a complicações que podem levar a quadros de ansiedade e depressão e impactam diretamente e de forma negativa a qualidade de vida do paciente.

A fotobiomodulação tem sido citado pela literatura como um potencial colaborador no manejo de hipossalivação e xerostomia causadas pelos tratamentos oncológicos. Porém, a falta de um protocolo definido dificulta o seu uso.

O presente estudo foi baseado em pesquisa com células humanas que verificou a ação do laser em fibroblastos, seguido de ensaio clínico randomizado para minimizar danos da mucosite oral (57) e buscou verificar o efeito da fotobiomodulação em glândulas salivares, para verificar o impacto no tratamento da hipossalivação e da xerostomia decorrentes do tratamento oncológico, em especial durante a radioterapia, propondo um protocolo terapêutico.

Porém, não foi demonstrada diferença significativa entre os grupos analisados em relação ao uso do laser de baixa intensidade para tratamento de hipossalivação e xerostomia em pacientes oncológicos com utilização do protocolo proposto. Corroborando com essa afirmativa, o resultado dos inventários de xerostomia, além do BDA e BDI também demonstraram não haver diferença significativa na queixa de sensação de boca seca, ansiedade e depressão entre o grupo que recebeu intervenção e o grupo sem intervenção.

Como limitação para este estudo foi impossível cegar o pesquisador durante o tratamento.

Devido às características específicas das glândulas salivares, como por exemplo, apresentar radiossensibilidade com danos logo nos primeiros dias de tratamento oncológico, mesmo possuindo renovação celular lenta em comparação aos outros tipos de células, ou devido ao

fato da radiação ionizante provocar danos em seus recepetores muscarínicos de acetilcolina ao invés de danos nos DNAs e, consequentemente, morte celular por apoptose, o mecanismo de ação do laser sobre essas células também pode apresentar efeitos específicos. Portanto, mais estudos são necessários em busca do entendimento sobre a ação da fotobiomodulação sobre células acinares, se há algum tipo de reparo dos recpetores das células remanescentes e/ou a possibilidade de reversão da fibrose celular ocasionada pela radiação ionizante, a fim de tratar a hipossalivação e a xerostomia trazendo benefícios para os pacientes.

REFERÊNCIAS

1. Mattiuzzi C, Lippi G. Current Cancer Epidemiology. Journal of epidemiology and global health. 2019;9(4):217-22.
2. Sasportas LS, Hosford DN, Sodini MA, Waters DJ, Zambricki EA, Barral JK, et al. Cost-effectiveness landscape analysis of treatments addressing xerostomia in patients receiving head and neck radiation therapy. Oral surgery, oral medicine, oral pathology and oral radiology. 2013;116(1):e37-51.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018;68(6):394-424.
4. Brasil M, INCA. Classificação de tumores malignos: TNM. 2004.
5. Saúde Md. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2020: Incidência de Câncer no Brasil. Rio de Janeiro. Inca RJ; 2019.
6. Porter RACEWOS. CAWSON'S ESSENTIALS OF
ORAL PATHOLOGY
AND ORAL MEDICIN. 7 ed. Toronto2002. 412 p.
7. Patil S, Awan KH, Arakeri G, Aljabab A, Ferrari M, Gomes CC, et al. The relationship of "shisha" (water pipe) smoking to the risk of head and neck cancer. Journal of oral pathology & medicine : official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology. 2019;48(4):278-83.
8. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1. 0. Cancer incidence and mortality worldwide: IARC CancerBase. 2013;11.
9. Almangush A, Pirinen M, Heikkinen I, Mäkitie AA, Salo T, Leivo I. Tumour budding in oral squamous cell carcinoma: a meta-analysis. Br J Cancer. 2018;118(4):577-86.
10. Society AC. Cancer facts & figures 2019: American Cancer Society; 2019.
11. Baker F, Ainsworth SR, Dye JT, Crammer C, Thun MJ, Hoffmann D, et al. Health risks associated with cigar smoking. Jama. 2000;284(6):735-40.
12. Shapiro JA, Jacobs EJ, Thun MJ. Cigar smoking in men and risk of death from tobacco-related cancers. J Natl Cancer Inst. 2000;92(4):333-7.
13. de Carvalho GD, de Souza LF, Ferreira TO, Bento G, Haddad MF. Prótese bucomaxilofacial: a Odontologia além da boca. ARCHIVES OF HEALTH INVESTIGATION. 2019;8(6).
14. Rodrigues RGS, Rodrigues DS, de Oliveira DC. Reabilitação com prótese bucomaxilofacial: revisão de literatura. Revista Saúde Multidisciplinar. 2019;5(1).
15. Paula JMd, Sonobe HM, Nicolussi AC, Zago MMF, Sawada NO. Symptoms of depression in patients with cancer of the head and neck undergoing radiotherapy treatment: a prospective study. Revista latino-americana de enfermagem. 2012;20:362-8.
16. Santos MAd. Cancer and suicide among the elderly: psychosocial determinants of risks, psychopathology and opportunities for prevention. Ciencia & saude coletiva. 2017;22(9):3061-75.
17. Edition S, Edge S, Byrd D. AJCC cancer staging manual. AJCC cancer staging manual. 2017.
18. Wissinger E, Griebsch I, Lungershausen J, Foster T, Pashos CL. The economic burden of head and neck cancer: a systematic literature review. Pharmacoeconomics. 2014;32(9):865-82.
19. Pinillos L, Pinto JA, Sarria G. History of the development of radiotherapy in Latin America. Ecancermedicalscience. 2017;11:784.

20. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA: a cancer journal for clinicians. 2017;67(2):93-9.
21. Wissinger E, Griebsch I, Lungershausen J, Foster T, Pashos CL. The economic burden of head and neck cancer: a systematic literature review. PharmacoEconomics. 2014;32(9):865-82.
22. Blecha FP, dos Santos Guedes MT. Tratamento de radiodermatite no cliente oncológico: subsídios para intervenções de enfermagem. Revista Brasileira de Cancerologia. 2006;52(2):151-63.
23. Pedraza Muriel V. The impact on oncology of the interaction of radiation therapy and radiobiology. Clin Transl Oncol. 2006;8(2):83-93.
24. do Brasil SF. Constituição da república federativa do Brasil. Brasília: Senado Federal, Centro Gráfico. 1988.
25. da União DO. MINISTÉRIO DA SAÚDE SECRETARIA DE ATENÇÃO À SAÚDE PORTARIA SAS/MS Nº 516, DE 17 DE JUNHO DE 2015. 2015.
26. Lal P, Nautiyal V, Verma M, Yadav R, Das KM, Kumar S. Objective and subjective assessment of xerostomia in patients of locally advanced head-and-neck cancers treated by intensity-modulated radiotherapy. Journal of cancer research and therapeutics. 2018;14(6):1196.
27. Simões A, de Campos L, de Souza DN, de Matos JA, Freitas PM, Nicolau J. Laser phototherapy as topical prophylaxis against radiation-induced xerostomia. Photomedicine and laser surgery. 2010;28(3):357-63.
28. Coppes RP, Meter A, Latumalea SP, Roffel AF, Kampinga HH. Defects in muscarinic receptor-coupled signal transduction in isolated parotid gland cells after in vivo irradiation: evidence for a non-DNA target of radiation. Br J Cancer. 2005;92(3):539-46.
29. Newhauser WD, Berrington de Gonzalez A, Schulte R, Lee C. A Review of Radiotherapy-Induced Late Effects Research after Advanced Technology Treatments. Front Oncol. 2016;6:13.
30. Valstar MH, de Bakker BS, Steenbakkers RJ, de Jong KH, Smit LA, Nulent TJK, et al. The tubarial salivary glands: A potential new organ at risk for radiotherapy. Radiotherapy and Oncology. 2021;154:292-8.
31. Murdoch-Kinch CA, Kim HM, Vineberg KA, Ship JA, Eisbruch A. Dose-effect relationships for the submandibular salivary glands and implications for their sparing by intensity modulated radiotherapy. Int J Radiat Oncol Biol Phys. 2008;72(2):373-82.
32. Sreebny LM. Saliva in health and disease: an appraisal and update. International dental journal. 2000;50(3):140-61.
33. Jensen SB, Pedersen AM, Vissink A, Andersen E, Brown CG, Davies AN, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. Support Care Cancer. 2010;18(8):1039-60.
34. Haber AH, Rothstein BE. Radiosensitivity and rate of cell division: "law of Bergonié and Tribondeau". Science. 1969;163(3873):1338-9.
35. Paardekooper G, Cammelli S, Zeilstra L, Coppes R, KONINGS AT. Radiation-induced apoptosis in relation to acute impairment of rat salivary gland function. International journal of radiation biology. 1998;73(6):641-8.
36. Coppes R, Zeilstra L, Kampinga H, Konings A. Early to late sparing of radiation damage to the parotid gland by adrenergic and muscarinic receptor agonists. British journal of cancer. 2001;85(7):1055-63.

37. Coppes RP, Roffel AF, Zeilstra LJ, Vissink A, Konings AW. Early radiation effects on muscarinic receptor-induced secretory responsiveness of the parotid gland in the freely moving rat. Radiation research. 2000;153(3):339-46.
38. Tsuni H. Quantitative dose-response analysis of salivary function following radiotherapy using sequential RI-sialography. International Journal of Radiation Oncology* Biology* Physics. 1985;11(9):1603-12.
39. Eisbruch A, Rhodus N, Rosenthal D, Murphy B, Rasch C, Sonis S, et al., editors. How should we measure and report radiotherapy-induced xerostomia? Seminars in radiation oncology; 2003: Elsevier.
40. Millsop JW, Wang EA, Fazel N. Etiology, evaluation, and management of xerostomia. Clin Dermatol. 2017;35(5):468-76.
41. Andersen BL, Karlsson JA, Anderson B, Tewfik HH. Anxiety and cancer treatment: response to stressful radiotherapy. Health Psychology. 1984;3(6):535.
42. de Souza MG, Gomes ESB, Costa LB, Andrade ADS, de Jesus SF, de Paula DPS, et al. Might anxiety disorders promote head and neck cancer development? IBRO reports. 2020;9:9-13.
43. Bottino SMB, Fráguas R, Gattaz WF. Depressão e câncer. Archives of Clinical Psychiatry (São Paulo). 2009;36:109-15.
44. Li L-x, Tian G, He J. The standardization of acupuncture treatment for radiation-induced xerostomia: a literature review. Chinese journal of integrative medicine. 2016;22(7):549-54.
45. Porter S, Scully C, Hegarty A. An update of the etiology and management of xerostomia. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2004;97(1):28-46.
46. Zecha JA, Raber-Durlacher JE, Nair RG, Epstein JB, Elad S, Hamblin MR, et al. Low-level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 2: proposed applications and treatment protocols. Support Care Cancer. 2016;24(6):2793-805.
47. Zecha JA, Raber-Durlacher JE, Nair RG, Epstein JB, Sonis ST, Elad S, et al. Low level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 1: mechanisms of action, dosimetric, and safety considerations. Support Care Cancer. 2016;24(6):2781-92.
48. Burlage FR, Faber H, Kampinga HH, Langendijk JA, Vissink A, Coppes RP. Enhanced proliferation of acinar and progenitor cells by prophylactic pilocarpine treatment underlies the observed amelioration of radiation injury to parotid glands. Radiotherapy and Oncology. 2009;90(2):253-6.
49. Burlage FR, Roesink JM, Kampinga HH, Coppes RP, Terhaard C, Langendijk JA, et al. Protection of salivary function by concomitant pilocarpine during radiotherapy: a double-blind, randomized, placebo-controlled study. International Journal of Radiation Oncology* Biology* Physics. 2008;70(1):14-22.
50. Cotomacio C, Campos L, Simões A, Jaguar G, Crosato E-M, Alves F. Influence of bethanechol on salivary parameters in irradiated patients. Medicina oral, patologia oral y cirugia bucal. 2017;22(1):e76.
51. Gonnelli FA, Palma LF, Giordani AJ, Deboni AL, Dias RS, Segreto RA, et al. Low-Level Laser for Mitigation of Low Salivary Flow Rate in Head and Neck Cancer Patients Undergoing Radiochemotherapy: A Prospective Longitudinal Study. Photomed Laser Surg. 2016;34(8):326-30.
52. Buentzel J, Micke O, Adamietz IA, Monnier A, Glatzel M, de Vries A. Intravenous amifostine during chemoradiotherapy for head-and-neck cancer: a randomized placebo-

controlled phase III study. International Journal of Radiation Oncology* Biology* Physics. 2006;64(3):684-91.
53. Vissink A, Burlage FR, Spijkervet FK, Jansma J, Coppes RP. Prevention and treatment of the consequences of head and neck radiotherapy. Crit Rev Oral Biol Med. 2003;14(3):213-25.
54. Menezes A, Sanches GLG, Gomes ESB, Soares RG, Durães CP, Fonseca LL, et al. The combination of traditional and auricular acupuncture to prevent xerostomia and anxiety in irradiated patients with HNSCC: a preventive, parallel, single-blind, 2-arm controlled study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2021;131(6):675-83.
55. Lopes CdO, Mas JRI, Zângaro RA. Low level laser therapy in the prevention of radiotherapy-induced xerostomia and oral mucositis. Radiologia Brasileira. 2006;39:131-6.
56. Palma LF, Gonnelli FAS, Marcucci M, Dias RS, Giordani AJ, Segreto RA, et al. Impact of low-level laser therapy on hyposalivation, salivary pH, and quality of life in head and neck cancer patients post-radiotherapy. Lasers Med Sci. 2017;32(4):827-32.
57. Soares RG, Farias LC, da Silva Menezes AS, de Oliveira ESCS, Tabosa ATL, Chagas PVF, et al. Treatment of mucositis with combined 660- and 808-nm-wavelength low-level laser therapy reduced mucositis grade, pain, and use of analgesics: a parallel, single-blind, two-arm controlled study. Lasers Med Sci. 2018;33(8):1813-9.
58. Hamblin MR, Demidova TN, editors. Mechanisms of low level light therapy. Mechanisms for low-light therapy; 2006: International Society for Optics and Photonics.
59. Huang YY, Chen AC, Carroll JD, Hamblin MR. Biphasic dose response in low level light therapy. Dose Response. 2009;7(4):358-83.
60. Huang YY, Sharma SK, Carroll J, Hamblin MR. Biphasic dose response in low level light therapy - an update. Dose Response. 2011;9(4):602-18.
61. Robijns J, Censabella S, Bulens P, Maes A, Mebis J. The use of low-level light therapy in supportive care for patients with breast cancer: review of the literature. Lasers Med Sci. 2017;32(1):229-42.
62. Campos L, Simões A, Sá PHRN, Eduardo CDP. Improvement in quality of life of an oncological patient by laser phototherapy. Photomedicine and laser surgery. 2009;27(2):371-4.