LARISSA DI CARVALHO MELO E SILVA

TENDÊNCIAS ATUAIS E EVIDÊNCIAS DISPONÍVEIS SOBRE A TERAPIA COM LASER DE BAIXA INTENSIDADE NA OSTEORRADIONECROSE: UMA REVISÃO DE ESCOPO

Current trends and available evidence on low-level laser therapy for osteoradionecrosis:

A scoping review

BRASÍLIA, 2024

UNIVERSIDADE DE BRASÍLIA

FACULDADE DE CIÊNCIAS DA SAÚDE

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE

LARISSA DI CARVALHO MELO E SILVA

TENDÊNCIAS ATUAIS E EVIDÊNCIAS DISPONÍVEIS SOBRE A TERAPIA COM LASER DE BAIXA INTENSIDADE NA OSTEORRADIONECROSE: UMA REVISÃO DE ESCOPO

Dissertação apresentada como requisito parcial para a obtenção do Título de Mestre em Ciências as Saúde pelo Programa de Pós-Graduação em Ciências da Saúde da Universidade de Brasília.

Orientadora: Profa. Dra. Eliete Neves da Silva Guerra

BRASÍLIA, DISTRITO FEDERAL

2024

LARISSA DI CARVALHO MELO E SILVA

TENDÊNCIAS ATUAIS E EVIDÊNCIAS DISPONÍVEIS SOBRE A TERAPIA COM LASER DE BAIXA INTENSIDADE NA OSTEORRADIONECROSE: UMA REVISÃO DE ESCOPO

Dissertação apresentada como requisito parcial para a obtenção do Título de Mestre em Ciências as Saúde pelo Programa de Pós-Graduação em Ciências da Saúde da Universidade de Brasília.

Aprovado em 1 de novembro de 2024

BANCA EXAMINADORA

Profa. Dra. Eliete Neves da Silva Guerra (Presidente)

Universidade de Brasília

Profa. Dra. Amanda Gomes de Meneses

Universidade do Distrito Federal

Prof. Dr. André Ferreira Leite

Universidade de Brasília

Profa. Dra. Paula Elaine Diniz dos Reis (Suplente)

Universidade de Brasília

Dedico este trabalho a todos os pacientes com câncer, que enfrentam bravamente seus desafios. Que as evidências e as tendências apresentadas aqui contribuam para a melhoria de suas vidas e inspirem novas possibilidades de tratamento.

AGRADECIMENTOS

Este trabalho é o resultado de uma longa trajetória, que só foi possível com o apoio, incentivo e colaboração de várias pessoas e instituições. A cada uma delas, deixo aqui minha sincera gratidão.

Aos meus pais, Julie e Henrique, pelo apoio e fortaleza quando era difícil prosseguir na caminhada. Obrigada pelo incentivo, pelas orações, por torcerem sempre por mim e por fazerem todo o possível dentre as ferramentas disponíveis. Obrigada por tornarem as dificuldades superáveis.

À minha irmã Letícia, minha eterna gratidão. Obrigada por estar ao meu lado, enfrentando desafios semelhantes e celebrando cada conquista comigo. Você, com seu mestrado em botânica, enquanto eu... bem, só consigo manter um cacto vivo por um mês!

À Universidade de Brasília (UnB) e ao Decanato de Pós-Graduação (DPG) por terem sido o alicerce da minha formação acadêmica, oferecendo ensino público, gratuito e de excelência, além de um ambiente que promoveu meu crescimento pessoal e profissional. Também expresso minha profunda gratidão ao Programa de Pós-Graduação em Ciências da Saúde da UnB, por proporcionar uma estrutura sólida para o desenvolvimento desta pesquisa, bem como pelo suporte contínuo e pelas oportunidades de aprendizado e aprimoramento que foram fundamentais para a conclusão deste trabalho.

À Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) pela concessão da bolsa durante meu mestrado, que foi essencial para que eu pudesse me dedicar integralmente à pesquisa e ao aprendizado, viabilizando a realização deste trabalho. Sou igualmente grata ao Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) pelo apoio ao meu mestrado através do projeto Universal intitulado "Modulação do processo de reparo em modelos pré-clínicos de osteorradionecrose" (Processo 406557/2021-7, Chamada CNPq/MCTI/FNDCT nº 18/2021 – UNIVERSAL – Faixa B). O financiamento dessa iniciativa foi fundamental para a execução deste trabalho e para o progresso das pesquisas na área.

Ao Laboratório de Histopatologia da Universidade de Brasília, que foi um ambiente inspirador e colaborativo, contribuindo significativamente para o desenvolvimento deste trabalho. A interação com colegas e a troca de experiências foram essenciais para aprofundar meu conhecimento e enriquecer a minha pesquisa.

À banca examinadora, composta pelos Professores Amanda Meneses, André Leite e Paula Reis, agradeço por suas valiosas sugestões e críticas construtivas, que irão enriquecer a qualidade deste estudo.

À minha orientadora, Profª Dra. Eliete Guerra, minha profunda gratidão. Agradeço pela confiança depositada em mim, pela paciência e pelo incentivo constante. Suas valiosas orientações e seu vasto conhecimento foram fundamentais em todas as fases deste trabalho. Sua dedicação e apoio foram essenciais para o desenvolvimento desta pesquisa. Além disso, sou grata pela amizade e pelos conselhos de vida que me ofereceu, tornando essa jornada ainda mais enriquecedora. Inspiro-me muito em sua trajetória e em sua sabedoria. Obrigada por ser uma mentora exemplar e por me guiar com tanta generosidade ao longo desta caminhada.

Ao grupo de pesquisa, que se reúne semanalmente desde 2020 para compartilhar conhecimento e promover um ambiente de aprendizado mútuo. A cada um de vocês — Bruna, Isabela, Isabella, Juliana, Liandra, Maria Luiza, Mylene, Vitória e Yuri — sou grata pela inspiração e pelo apoio inestimável que me proporcionaram ao longo dessa jornada. A colaboração e o entusiasmo de vocês me motivaram a seguir em frente e a explorar novas possibilidades. Vocês foram fundamentais para o meu crescimento pessoal e acadêmico. Agradeço também a Lídia, técnica do laboratório, por nos auxiliar nos experimentos e pelas conversas descontraídas.

À minha parceira de tantas aventuras acadêmicas e pessoais, Bruna Bastos, por compartilhar não só o trabalho, mas também as incertezas, os momentos de crise e - principalmente - as vitórias. Suas palavras de apoio, as longas conversas e as risadas que tivemos ao longo dessa experiência tornaram o caminho muito mais leve. Obrigada por estar ao meu lado em cada passo.

Por fim, sou grata a todos os amigos e familiares que, direta ou indiretamente, me apoiaram ao longo dessa trajetória. A cada um de vocês, o meu mais sincero obrigada.

"Do início até o último porto, só interessa a viagem: às vezes tem tempestade, ondas enormes cobrem o barco; depois vem a calmaria e podemos desfrutar de um horizonte claro. Mas se durante essa travessia a gente prosseguir desejando o bom, o belo e o verdadeiro, então tudo terá valido a pena."

Lygia Fagundes Telles

RESUMO

A osteorradionecrose (ORN) é uma complicação grave frequentemente observada em pacientes que receberam radioterapia para o tratamento de neoplasias na região da cabeça e pescoço. Essa condição resulta na morte do tecido ósseo devido à diminuição do fluxo sanguíneo, que pode ser exacerbada pela radioterapia. As manifestações da ORN podem levar a dor intensa, dificuldade de cicatrização, fraturas ósseas e perda da função mandibular, afetando significativamente a qualidade de vida dos pacientes. Nesse contexto, a terapia com laser de baixa intensidade surge como uma abordagem terapêutica promissora, demonstrando potencial na prevenção e tratamento da ORN. Este trabalho apresenta uma revisão de escopo sobre as tendências atuais e as evidências disponíveis que sustentam a utilização da terapia com laser de baixa intensidade no manejo da ORN. O objetivo desta pesquisa foi examinar, de maneira abrangente, a aplicação da terapia com laser de baixa intensidade no contexto da ORN, com foco nas evidências científicas disponíveis e nas práticas clínicas atuais. A estratégia de busca foi realizada em 15 de janeiro de 2024, utilizando as bases de dados MEDLINE/PubMed, EMBASE, Web of Science e literatura cinza adicional, sem restrições de idioma ou período de publicação. No total, 19 estudos foram incluídos na análise. Os resultados revelaram que 58% dos estudos se concentraram na utilização da terapia com laser de baixa intensidade para fins terapêuticos, enquanto 21% abordaram a aplicação preventiva e 21% exploraram uma combinação de ambas. Além disso, observou-se que 41% dos estudos incluíram a terapia fotodinâmica antimicrobiana (aPDT), utilizando o azul de metileno como fotossensibilizador. As intervenções complementares à fotobiomodulação foram predominantemente farmacológicas, representando 57% dos estudos, seguidas por 29% de tratamentos cirúrgicos e 11% de bochechos com clorexidina. As investigações *in vivo* frequentemente utilizaram lasers de diodo com densidades de potência baixa na faixa do infravermelho próximo (67%), variando entre 780 e 904 nm, enquanto os relatos de caso também aplicaram lasers de diodo nas faixas vermelha e infravermelha próxima (64%) de 660 a 904 nm. O modo de emissão contínua foi utilizado em 83% dos estudos *in vivo* e em 17% dos relatos de caso. É importante ressaltar que nenhum dos estudos revisados apresentou todos os parâmetros do laser de maneira abrangente, o que representa uma limitação significativa. Conclui-se que a terapia com laser de baixa intensidade possui um potencial considerável tanto para aplicações terapêuticas quanto preventivas na gestão da osteorradionecrose. No entanto, a predominância de relatos de caso e a variabilidade nos parâmetros do laser dificultam a padronização de protocolos de tratamento. Com isso, a falta de dados detalhados sobre os parâmetros do laser enfatiza a necessidade de futuras pesquisas que se concentrem na padronização dos protocolos de terapia com laser de baixa intensidade e na realização de ensaios clínicos bem estruturados e em larga escala. Essas iniciativas são essenciais para uma avaliação mais rigorosa da eficácia da terapia com laser de baixa intensidade, além de promover uma integração confiável dessa técnica na prática clínica, proporcionando - dessa forma - uma alternativa significativa para o tratamento da osteorradionecrose.

Palavras-chave: Terapia com Luz de Baixa Intensidade; Terapia a Laser de Baixa Intensidade; Osteorradionecrose; Terapia Fotodinâmica; Fotobiomodulação.

ABSTRACT

Osteoradionecrosis (ORN) is a severe complication often observed in patients who have received radiotherapy for the treatment of neoplasms in the head and neck region. This condition results in the death of bone tissue due to decreased blood flow, which can be exacerbated by radiotherapy. The manifestations of ORN can lead to intense pain, difficulty in healing, bone fractures, and loss of mandibular function, significantly affecting the quality of life of patients. In this context, low-level laser therapy (LLLT) emerges as a promising therapeutic approach, demonstrating potential in the prevention and treatment of ORN. This work presents a scoping review of current trends and available evidence supporting the use of LLLT in the management of ORN. The objective of this research was to comprehensively examine the application of LLLT in the context of ORN, focusing on the available scientific evidence and current clinical practices. The search strategy was conducted on January 15, 2024, using the databases MEDLINE/PubMed, EMBASE, Web of Science, and additional grey literature, without language or publication period restrictions. A total of 19 studies were included in the analysis. The results revealed that 58% of the studies focused on the use of LLLT for therapeutic purposes, while 21% addressed preventive applications, and 21% explored a combination of both. Furthermore, it was observed that 41% of the studies included antimicrobial photodynamic therapy (aPDT), utilizing methylene blue as the photosensitizer. Complementary interventions to photobiomodulation were predominantly pharmacological, representing 57% of the studies, followed by 29% surgical treatments and 11% chlorhexidine mouth rinses. In vivo investigations frequently utilized diode lasers with low power densities in the near-infrared range (67%), varying from 780 to 904 nm, while case reports also applied diode lasers in the red and near-infrared ranges (64%) from 660 to 904 nm. The continuous emission mode was used in 83% of in vivo studies and in 17% of case reports. It is important to note that none of the reviewed studies comprehensively presented all laser parameters, which represents a significant limitation. It is concluded that LLLT has considerable potential for both therapeutic and preventive applications in the management of osteoradionecrosis. However, the predominance of case reports and variability in laser parameters hinder the standardization of treatment protocols. Consequently, the lack of detailed data on laser parameters emphasizes the need for future research to focus on standardizing LLLT protocols and conducting well-structured, large-scale clinical trials. These initiatives are essential for a more rigorous evaluation of the effectiveness of LLLT, as well as for promoting reliable integration of this technique into clinical practice, thus providing a significant alternative for the treatment of osteoradionecrosis.

Keywords: Low-Level Light Therapy; Low-Level Laser Therapy; Osteoradionecrosis; Photodynamic Therapy; Photobiomodulation therapy.

LISTA DE FIGURAS

Figuras do manuscrito - Capítulo 1:

LISTA DE TABELAS

Tabelas da dissertação:

Tabelas do manuscrito - Capítulo 1: Não aplicável

LISTA DE APÊNDICES

Apêndices da dissertação:

Apêndice 1. Protocolo da revisão de escopo

Apêndices do manuscrito - Capítulo 1:

Appendix A. Search strategies with appropriate key words and MeSH terms.

Appendix B. Summary of overall descriptive characteristics of included studies

Table 1 - Summary of overall descriptive characteristics of *in vivo* included studies (n= 6)

Table 2 - Summary of overall descriptive characteristics of Case report or Series Case Report included studies (n= 11)

Table 3 - Summary of overall descriptive characteristics of Systematic Review included studies (n= 2)

Appendix C. Excluded articles and reasons for exclusion (n=36).

Appendix D. Bibliometric analysis of included studies (n = 19).

Appendix E. Summary of laser parameters characteristics of included studies

Table 1 - Summary of laser parameters of primary *in vivo* studies included (n=6).

Table 2 - Summary of laser parameters of primary case report studies included (n=11).

Appendix F. Summary of Case Report or Series Case Report Studies on Low-Level Laser Therapy for Osteoradionecrosis (n=11).

LISTA DE ANEXOS

Anexos da dissertação:

Anexo1. Artigos como autora e coautora

Anexos do manuscrito: Não aplicável

LISTA DE ABREVIATURAS

3D-CRT - 3D Conformal Radiation Therapy

aPDT - antimicrobial Photodynamic Therapy

HBOT - Hyperbaric Oxygen Therapy

IMRT – Intensity Modulated RT

LLLT – Low-Level Laser Therapy

ORN – Osteoradionecrosis

PBMT - Photobiomodulation Therapy

PENTOCLO - Pentoxifylline-tocopherol-clodronate

PRISMA-P - Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols

PRISMA-ScR - Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews checklist

QoV – Quality of Life

SUMÁRIO

Sumário

1. PREFÁCIO

Esta dissertação de mestrado faz parte do projeto Universal do CNPq "Modulação do processo de reparo em modelos pré-clínicos de osteorradionecrose" (Processo 406557/2021-7, Chamada CNPq/MCTI/FNDCT nº 18/2021 – UNIVERSAL – Faixa B, 2021), coordenado pela Profª Drª Eliete Neves da Silva Guerra, que financiou este trabalho. Este trabalho, intitulado "Tendências Atuais e Evidências Disponíveis sobre a Terapia com Laser de Baixa Intensidade na Osteorradionecrose: Uma Revisão de Escopo" visa contribuir para a compreensão da terapia com laser de baixa intensidade como uma abordagem promissora no tratamento e na prevenção da osteorradionecrose (ORN). A ORN é uma complicação grave que pode ocorrer em pacientes submetidos à radioterapia, levando a sérias sequelas e comprometendo a qualidade de vida dos indivíduos afetados.

Os objetivos deste estudo são investigar as tendências atuais no uso da terapia com laser de baixa intensidade para o manejo da ORN e fornecer uma análise abrangente das evidências disponíveis na literatura. Por meio desta revisão de escopo, buscamos não apenas destacar os resultados positivos, mas também abordar lacunas críticas – especialmente – em relação à padronização de protocolos de tratamento, que é uma questão essencial para a eficácia da terapia com laser de baixa intensidade.

O trabalho está estruturado da seguinte maneira: iniciamos com a introdução, onde apresentamos o contexto e a relevância do tema. Em seguida, delineamos os objetivos da pesquisa e detalhamos os materiais e métodos utilizados. O corpo principal é composto por capítulos que discutem os resultados e análises obtidos. Finalizamos com as considerações finais, onde sintetizamos as principais descobertas e suas implicações. As referências e os anexos complementam o trabalho, oferecendo um suporte robusto às informações apresentadas.

No Capítulo 1, intitulado "Manuscrito", encontra-se o artigo preparado com os resultados desta dissertação, formatado conforme as normas da *Photodiagnosis and Photodynamic Therapy* (IF: 3.1), periódico ao qual submetemos este trabalho. Este manuscrito apresenta pontos inovadores que contribuem significativamente para a compreensão da terapia com laser de baixa intensidade no manejo da osteorradionecrose. Um aspecto central é a análise do papel duplo da terapia com laser de baixa intensidade, tanto no tratamento quanto na prevenção, oferecendo uma visão abrangente das potenciais aplicações terapêuticas. A revisão

também enfatiza a importância da padronização dos protocolos da terapia com laser de baixa intensidade, destacando a necessidade de uniformidade nos parâmetros do laser e regimes de tratamento, abordando uma lacuna crítica na literatura. A inclusão de diversos estudos, que cobrem diferentes dosagens de radioterapia e modelos animais variados, proporciona uma compreensão da eficácia da terapia com laser de baixa intensidade em diferentes cenários e potenciais formas de integrá-la à prática clínica de modo mais confiável. Por fim, a revisão identifica tendências emergentes e direções futuras de pesquisa, promovendo investigações mais direcionadas e metodologicamente sólidas neste campo promissor.

Ao longo do meu mestrado, tive a oportunidade de colaborar em diversas produções acadêmicas, entre as quais destaco o artigo *"Oral manifestations in pediatric patients with leukemia: A systematic review and meta-analysis",* publicado na revista *The Journal of the American Dental Association* (JADA, Qualis A1; IF=3.4), onde figuro como segunda autora. Além disso, outros artigos estão em processo de revisão, incluindo o manuscrito *"Oral manifestations of COVID-19 vaccinated, post-illness and different variants: study of Brazilian population"*, submetido à *Brazilian Oral Research* (Qualis A2, IF=1.5) como primeira autora; e o artigo *"Ionizing radiation in osteoblastic cells: establishment of an in vitro model of osteoradionecrosis",* enviado para a revista *Archives of Oral Biology* (Qualis A1, IF=2.2), como segunda autora. Também contribuí como terceira autora para o artigo *"Worldwide Research Trends on Artificial Intelligence in Head and Neck Cancer: A Bibliometric Analysis",* submetido à *Critical Reviews in Oncology/Hematology* (Qualis A1, IF=5.5), e, como quarta autora, para a revisão metodológica *"3D bioprinting skin equivalents: a methodological review of human keratinocyte and fibroblast-loaded models"*, em processo de revisão na revista *Bioprinting* (Qualis A1, IF=11.5). Nos apêndices e anexos, encontram-se: o protocolo da revisão de escopo e os demais artigos aceitos e em preparação para publicação durante o mestrado.

Este trabalho está sendo defendido como parte de um pedido de ascensão ao doutorado, o que reforça a relevância deste estudo e a continuidade de minhas contribuições acadêmicas nesta área.

Agradeço a todas as pessoas que contribuíram direta e indiretamente para a realização deste projeto e ao grupo de pesquisa que me apoiou durante toda essa jornada. Espero que esta pesquisa inspire e forneça *insights* valiosos para outros pesquisadores que atuam nesse campo tão importante.

2. INTRODUÇÃO

A osteorradionecrose (ORN) do complexo maxilofacial configura-se como uma complicação resultante da radioterapia em tumores de cabeça e pescoço (Chronopoulos et al., 2018). Ela é descrita como sendo o resultado de osso exposto irradiado e que não cicatriza por um período de três a seis meses e sem que haja evidências de tumores persistentes ou recorrentes no local (Chronopoulos et al., 2018; Frankart et al., 2020). Além disso, o espectro do período de tempo de desenvolvimento da ORN após a radioterapia difere significativamente na literatura, podendo ocorrer após alguns meses ou após vários anos (Frankart et al., 2020; Costa et al., 2016). No entanto, o risco de ORN devido a trauma persiste indefinidamente, o que explica casos de ORN ocorrendo até 10 anos após a radioterapia (Franco et al., 2017). A maioria dos casos de ORN, cerca de 70%, ocorre nos primeiros três anos após a conclusão do tratamento radioterápico (de Freitas et al., 2023). No geral, a taxa de incidência de ORN relatada varia de 0 a 14% (De Felice et al., 2020). Geralmente, a ORN é sintomática, causando dor, infecção, trismo, halitose, fístulas intraorais e extraorais, além de fraturas patológicas (Shaw et al., 2020; Costa et al., 2016). Consequentemente, há uma deterioração na qualidade de vida pois impacta em funções como a fala, a mastigação e a deglutição, além de causar deformidades faciais (Beaumont et al., 2021; Kolokythas et al., 2019).

Há uma prevalência maior de lesões de ORN em homens em comparação com mulheres, com uma proporção de 9:1 (Ribeiro et al., 2018). Em Otto et al. (2024), uma prevalência maior de ORN também foi observada entre os homens. Pacientes do sexo masculino apresentaram maiores escores de qualidade de vida (QoV) antes e depois do tratamento cirúrgico em comparação com pacientes do sexo feminino. No entanto, após a cirurgia, as pacientes do sexo feminino apresentaram maior melhora em sua QoV em comparação com seus escores pré-operatórios. Isso é esperado, pois maiores taxas de incidência de câncer de cabeça e pescoço são observadas entre os homens em comparação com as mulheres (Ferley et al., 2020). Os principais fatores de risco para câncer oral e alguns tumores orofaríngeos estão relacionados ao estilo de vida, como tabagismo e consumo excessivo de álcool, com risco aumentado em indivíduos que usam tabaco e bebem álcool (Sung et al., 2020). Em resumo, essas descobertas destacam a importância de considerar o sexo ao avaliar a ORN e seu impacto na qualidade de vida dos pacientes.

As doses máximas de radioterapia maiores que 60–75 Gy estão associadas ao desenvolvimento de ORN (Ferreira et al., 2019). A radioterapia pode causar oclusão vascular e necrose óssea, particularmente na mandíbula, onde a prevalência de ORN é maior devido ao menor suprimento sanguíneo, maior densidade óssea e maior incidência de tumores (Franco et al., 2017; Robijns et al., 2022). A introdução de técnicas como radioterapia conformada 3D (3D-CRT) e radioterapia de intensidade modulada (IMRT) reduziu a incidência de ORN para menos de 5%, em comparação com taxas anteriores de até 15% (Owosho et al., 2017; Robijns et al., 2022). No entanto, a ORN continua sendo uma complicação comum, especialmente em pacientes que passam por extrações dentárias pós-radioterapia ou têm doença periodontal grave (Marcondes et al., 2022; Peterson et al., 2010). O cuidado odontológico adequado antes, durante e depois da radioterapia é essencial para prevenir a ORN (Robijns et al., 2022). A prevalência de ORN em pacientes tratados com quimiorradioterapia foi de 6,8% (Peterson et al., 2010). No entanto, é importante observar que poucos estudos tentaram estabelecer uma associação entre a prevalência de ORN e o tipo de terapia do câncer.

No que concerne à patogênese da ORN, ela ainda não é bem estabelecida e suscita debates na comunidade científica. Entretanto, suporta-se a teoria vascular, na qual a radiação ionizante promove uma arterite, com desenvolvimento de uma região de hipóxia, hipocelular e hipovascular, o que inviabiliza o processo de reparo (Chronopoulos et al., 2018; Frankart et al., 2021; Leonetti et al., 2020). Delanian & Lefaixb (2004) propuseram um modelo, no qual há uma inflamação precoce precedida de fibrose e de remodelação, cuja resultante é a necrose tecidual a partir da atuação de espécies reativas de oxigênio (ROS) e TGF-β-1. Assim, em virtude da menor vascularização, a mandíbula é o osso facial mais afetado (Costa et al., 2016). Ademais, apresentam-se como fatores de risco para a ORN, a má higiene oral, a dose de radiação, a mandibulectomia, as extrações dentárias, a má nutrição e o abuso de álcool e de tabaco (Liu et al., 2020; Costa et al., 2016). Dessa forma, é de suma relevância o estudo da ORN e de um tratamento apropriado, com uma abordagem terapêutica multimodal, considerando as características do paciente e a gravidade da doença (Raggio & Winters, 2018; Costa et al., 2016). No processo de reparo, a produção de IL-1β, TNF-a e IL-6 pelos osteoblastos aumenta sinergicamente o RANKL e também pode contribuir para a estimulação, diferenciação e formação de osso (Bautista-Carbajal et al., 2023).

Nesse contexto, ainda não está estabelecido na literatura um tratamento ideal ou diretrizes consensuais a respeito da melhor intervenção para a ORN (Morechi et al., 2016;

Camolesi et al., 2021). A terapia de fotobiomodulação é uma modalidade de tratamento que provou ser eficaz na aceleração da cicatrização de feridas, alívio da dor, redução da sensibilidade dentinária e da gravidade da xerostomia e frequência do herpes labial (Sonis et al., 2016; Pellicioli et al., 2014). De igual modo, a terapia fotodinâmica antimicrobiana (aPDT) é utilizada para controlar o dano ósseo e está diretamente associada ao controle microbiológico (Pedroni et al., 2020). A PBMT opera com emissão de fótons a partir de uma luz laser de baixa intensidade que transfere baixa energia para os tecidos e não gera calor (Pellicioli et al., 2014). A exposição dos tecidos à luz do laser de baixa intensidade induz a modulação das funções celulares ativando várias vias envolvidas no crescimento e sobrevivência celular, proliferação, migração e transcrição (Pellicioli et al., 2014; Marques et al., 2016). Os lasers vermelhos, que são bem absorvidos pela mucosa oral rica em hemoglobina, e os lasers infravermelhos próximos, que penetram em tecidos mais profundos como as glândulas salivares, desempenham um papel importante nesses efeitos positivos (Pedroni et al., 2020).

Atualmente, a fotobiomodulação é considerada um tratamento não invasivo eficaz e recomendado pela MASCC/ISOO (Associação Multinacional de Cuidados de Suporte em Câncer e a Sociedade Internacional de Oncologia Oral) para muitas desordens orais, tais como mucosite, xerostomia, alteração de paladar e disfagia (Kalhori et al., 2019; Bensadoun, 2018; Bensadoun et al, 2020; Elad et al., 2020). A fotobiomodulação, com comprimento de onda entre 600 a 1000 nm, portanto, tem sido empregada para estimular a cicatrização, prevenir e tratar sinais decorrentes dos mecanismos de inflamação e de exacerbação de resposta imune (Zadik et al, 2019; Aguiar et al, 2021). No osso irradiado, a fotobiomodulação foi capaz de acelerar a regeneração óssea, aumentar o número de osteócitos, controlar a resposta inflamatória e aumentar a vascularização (Escudero et al., 2019). Esses resultados destacam a importância da fotobiomodulação como uma abordagem terapêutica promissora no manejo de complicações orais e na promoção da regeneração óssea em pacientes submetidos a tratamentos oncológicos.

Além disso, a PBMT e a terapia fotodinâmica antimicrobiana (aPDT) foram utilizadas como coadjuvantes ao procedimento cirúrgico no tratamento de ORN e em 12 meses de seguimento nenhuma recidiva foi observada (Magalhães et al., 2020). O tratamento conservador com aPDT também foi eficaz no controle da lesão, uma vez que tem sido utilizada para controlar e diminuir a colonização bacteriana dentro das lesões ósseas expostas, o que aumentariam as possibilidades de reparo ósseo (Pedroni et al., 2020). Considerando o papel crucial da disbiose na fisiopatologia da ORN, a aPDT foi proposta devido à sua eficácia contra

diversos microrganismos patogênicos (Campos et al., 2021). A aPDT é eficaz na eliminação de microrganismos oportunistas sem causar resistência microbiana (Magalhães et al., 2020). Essas terapias aumentam a eficácia do tratamento e previnem a recorrência de ORN, além de potencializar a ação de antibióticos e antifúngicos, reduzindo a dose necessária para efeitos bactericidas (Magalhães et al., 2020). Portanto, a PBMT e a aPDT podem ser agentes eficazes para prevenir e tratar ORN.

Os meios terapêuticos com emissão de luz têm se tornado cada vez mais relevantes na Odontologia, oferecendo uma variedade de opções para tratamento e regeneração de tecidos, podendo ser feitos com lasers de baixa intensidade, de alta intensidade e com LEDs. A terapia com laser de baixa intensidade, que opera com comprimentos de onda geralmente entre 600 e 1000 nm, utiliza luz coerente e monocromática para promover a bioestimulação celular (Farkas et al., 2013). Esse processo resulta na produção de ATP, uma molécula essencial para a energia celular, acelerando a regeneração dos tecidos e reduzindo a inflamação. A terapia com laser de baixa intensidade é aplicada em diversos contextos, incluindo cicatrização de feridas, tratamento de aftas, herpes, disfunções temporomandibulares e xerostomia. Além disso, demonstra eficácia no manejo de mucosite em pacientes oncológicos, podendo necessitar de múltiplas sessões.

Além disso, também é utilizado o laser de alta intensidade, que opera em comprimentos de onda variáveis, incluindo diodo, CO_2 e neodímio (Nd). Esta tecnologia é especialmente projetada para realizar vaporização, coagulação e corte de tecidos com notável precisão, o que permite a remoção de tecidos danificados ou doentes enquanto minimiza os danos aos tecidos adjacentes (Porcaro et al., 2015). Como resultado, é amplamente aplicada em diversas situações clínicas, incluindo cirurgias de tecidos moles, onde a precisão é crucial, além de ser eficaz na desinfecção de canais radiculares, remoção de cáries e tratamento de hipersensibilidade dentinária. As vantagens do uso do laser de alta intensidade são significativas. Entre elas, destaca-se a redução do sangramento durante os procedimentos, o que contribui para um campo cirúrgico mais limpo e visível. Ademais, a necessidade de anestesia é frequentemente reduzida, uma vez que o laser pode proporcionar uma experiência menos dolorosa para o paciente. Os tempos de recuperação também tendem a ser mais curtos, permitindo que os pacientes retornem às suas atividades normais mais rapidamente (Qualliotine et al.,2023). Por essas razões, o laser de alta intensidade se torna uma opção valiosa e eficaz em procedimentos cirúrgicos, oferecendo benefícios tanto para os profissionais de saúde quanto para os pacientes.

Já os LEDs (diodos emissores de luz), que operam em comprimentos de onda que variam entre 400 e 700 nm, emitem luz incoerente e policromática. Essa luz é absorvida pelos cromóforos presentes nas células, desencadeando um processo conhecido como fotobiomodulação. Esse processo é crucial, pois estimula a produção de colágeno, uma proteína essencial para a estrutura e reparo dos tecidos, e também contribui para a redução da inflamação, promovendo um ambiente favorável à cicatrização. Devido a essas propriedades, os LEDs são frequentemente utilizados em uma variedade de aplicações clínicas, como no tratamento de inflamações, no alívio da dor e na aceleração da cicatrização de feridas (Rech et al., 2022). Uma das principais vantagens dos LEDs é o seu custo relativamente baixo em comparação a outras tecnologias, como lasers de alta intensidade. Essa característica torna os LEDs uma opção acessível tanto para profissionais quanto para pacientes. A facilidade de uso é outro aspecto positivo, já que os dispositivos de LED podem ser aplicados em consultórios e até mesmo em casa, oferecendo segurança para aplicações frequentes (Prado et al., 2023). No entanto, é importante ressaltar que, embora os LEDs sejam valiosos em diversos contextos terapêuticos, a penetração tecidual é geralmente menor em comparação aos lasers, o que pode limitar a eficácia em situações que requerem tratamento com maior penetrância. Em suma, a terapia com laser de baixa intensidade é especialmente adequada para bioestimulação e tratamentos não invasivos, enquanto a terapia com laser de alta intensidade se destaca em procedimentos cirúrgicos precisos. Os LEDs, por sua vez, são ideais para tratar superfícies e áreas maiores, proporcionando uma abordagem econômica e prática para diversas condições clínicas. As informações detalhadas sobre as diferentes tecnologias e suas aplicações podem ser consultadas na Tabela 1.

Tabela 1 – Comparação de abordagens terapêuticas de emissão de luz na Odontologia

Abordagem Terapêutica	**Comprimento de onda (nm)**	**Características**	**Aplicações**	**Vantagens**	**Desvantagens**
Laser de Baixa Intensidade	600 - 1000	Luz coerente e monocromática; bioestimulação celular	Cicatrização de feridas, tratamento de aftas, herpes,	Acelera a regeneração tecidual, reduz	Pode requerer múltiplas sessões para eficácia

			disfunções temporomandibulares, xerostomia, mucosite	inflamação, várias aplicações	
Laser de Alta Intensidade	Variável (Diodo, CO2, Nd)	Luz coerente e monocromática; alta precisão	Vaporização, coagulação, corte de tecidos, desinfecção de canais radiculares, remoção de cáries, hipersensi-bilidade dentinária	Menor sangramento, reduzida necessidade de anestesia, tempos de recuperação mais curtos	Custo elevado, necessidade de treinamento para uso adequado
LEDs	400 - 700	Luz incoerente e policromática; menor penetração tecidual	Tratamento de inflamações, alívio da dor e cicatrização de feridas superficiais	Custo mais baixo, facilidade de uso, segurança para aplicações frequentes	Menor eficácia em profundidade, penetração tecidual reduzida

Os efeitos biológicos da terapia com laser de baixa intensidade em tecidos irradiados são determinados por diversos parâmetros do laser, incluindo o comprimento de onda, a densidade de potência, o tamanho do feixe ou ponto, o método de administração (se pulsado ou contínuo) e a duração da exposição (Robijns et al., 2022). Esses aspectos podem influenciar tanto a eficácia quanto a segurança do tratamento. O comprimento de onda, por exemplo, impacta a profundidade da penetração do laser e sua absorção pelos tecidos-alvo (Farkas et al.,

2013). Diferentes comprimentos de onda interagem de maneira diversa com os cromóforos presentes nas células, como a água e a hemoglobina, o que afeta a absorção de energia pelos tecidos-alvo. Lasers com comprimentos de onda na faixa de 600 a 1000 nm, por exemplo, são ideais para penetrar mais profundamente em tecidos moles e ósseos, atingindo estruturas celulares sem causar danos superficiais excessivos (Farkas et al., 2013). Quanto maior o comprimento de onda, maior a penetração, porém há uma redução na quantidade de energia absorvida na superfície, o que pode ser útil em casos onde se deseja tratar tecidos mais profundos sem sobrecarregar as camadas externas.

A densidade de potência é outro parâmetro crucial e é definida pela quantidade de energia aplicada por unidade de área alvo. Ela é calculada com base na potência do laser e no tamanho do feixe ou ponto, o que, por sua vez, influencia diretamente a concentração de energia nos tecidos. Um ponto de feixe menor resulta em maior densidade de potência, o que pode ser benéfico para tratamentos localizados e superficiais. No entanto, como o foco é mais intenso, pode-se reduzir a profundidade de penetração dos fótons, uma vez que eles se dispersam mais rapidamente, resultando em uma ação terapêutica mais concentrada em camadas superficiais. Isso possibilita a realização de um tratamento eficaz com uma quantidade mínima de energia superficial, diminuindo, assim, o risco de complicações. Já um feixe maior pode proporcionar uma maior penetração, mas com uma distribuição mais dispersa da energia, adequada para tratamentos mais difusos e profundos (Farkas et al., 2013). Assim, a escolha do tamanho do ponto deve ser cuidadosamente considerada de acordo com a natureza do tecido a ser tratado.

O modo de administração do laser — se contínuo ou pulsado — também desempenha um papel determinante nos resultados terapêuticos. Os lasers contínuos fornecem energia de maneira constante, o que pode aumentar o risco de superaquecimento e danos aos tecidos, especialmente se usado por períodos prolongados. Já o laser pulsado emite energia em intervalos regulares, permitindo que o tecido tenha tempo de dissipar o calor entre os pulsos, o que pode reduzir o risco de danos térmicos. Esse método permite maior controle sobre a dose acumulada e pode ser particularmente útil em tratamentos que exigem maior precisão e minimização de efeitos adversos (Carroll & Humphreys, 2006).

A duração da exposição é outra variável crítica e está diretamente relacionada à quantidade total de energia aplicada aos tecidos. Tempos de exposição mais longos permitem a acumulação de energia nos tecidos-alvo, potencialmente aumentando os efeitos terapêuticos,

mas também o risco de efeitos colaterais, como superaquecimento ou dano celular. A energia total entregue durante o tratamento é o produto da potência do laser pelo tempo de exposição, e ambos devem ser ajustados conforme a condição clínica a ser tratada (Carroll & Humphreys, 2006). Além disso, é importante considerar o número de pontos de aplicação e a área total tratada, para garantir uma distribuição uniforme da dose ao longo da área afetada, melhorando os resultados globais do tratamento.

Outros parâmetros, como a energia radiante, a fluência e a irradiância, desempenham papéis cruciais no sucesso da terapia com laser de baixa intensidade. A energia radiante refere-se à quantidade total de energia emitida pelo laser durante uma sessão de tratamento e é um fator determinante na eficácia da terapia. Medida em joules, a energia deve ser cuidadosamente calibrada para cada tipo de tecido e condição clínica, pois uma quantidade insuficiente pode resultar em um efeito terapêutico subótimo, enquanto uma superexposição pode causar danos aos tecidos (Hadis et al., 2016). A fluência descreve a densidade de energia que atinge uma área específica do tecido ao longo da sessão, expressa em joules por centímetro quadrado (J/cm^2) e calculada dividindo-se a energia total pela área tratada. Esse parâmetro é fundamental, uma vez que a resposta biológica ao laser é altamente dependente da quantidade de energia absorvida pelos tecidos. Uma fluência adequada pode otimizar a ativação de processos celulares e bioquímicos desejados, como a promoção da cicatrização, a redução da inflamação e o alívio da dor (Esteves-Pereira et al., 2024).

A irradiância, que se refere à densidade de potência aplicada sobre a área de tratamento e é expressa em watts por centímetro quadrado (W/cm^2), indica a quantidade de energia que o tecido recebe por unidade de tempo e pode impactar diretamente a profundidade e a eficiência da terapia. Irradiâncias mais altas podem proporcionar uma resposta terapêutica mais rápida, mas aumentam o risco de superaquecimento local, enquanto irradiâncias mais baixas, embora mais seguras, podem exigir um tempo de tratamento mais prolongado para alcançar os efeitos desejados (Esteves-Pereira et al., 2024). A combinação apropriada desses parâmetros, juntamente com o local anatômico da aplicação, o número de sessões e o intervalo entre os tratamentos, é essencial para garantir que a dose de luz seja corretamente dosada e otimizada para os efeitos desejados nos tecidos biológicos. O local da aplicação influencia a penetração do laser, dado que diferentes tecidos possuem características de absorção distintas. Além disso, a programação adequada do número de sessões e dos intervalos entre os tratamentos é crucial

para permitir que os tecidos se recuperem e respondam ao estímulo, maximizando assim os benefícios terapêuticos da terapia com laser de baixa intensidade (Robijns et al., 2022).

Por fim, a ausência de uma descrição detalhada dos parâmetros utilizados nos estudos sobre a terapia com laser de baixa intensidade pode comprometer significativamente a transparência dos resultados obtidos e limitar a replicabilidade dos achados clínicos. Essa falta de clareza pode gerar incertezas quanto à eficácia real da terapia, impactando negativamente a confiança de profissionais de saúde e pacientes em relação à terapia com laser de baixa intensidade como uma opção de tratamento válida (Esteves-Pereira et al., 2024). A dificuldade em reproduzir os resultados em diferentes contextos clínicos ou por outros pesquisadores também pode levar a inconsistências nos dados, dificultando a construção de um corpo sólido de evidências que sustente o uso da terapia. Para que os benefícios clínicos da terapia com laser de baixa intensidade sejam adequadamente documentados e aplicados, é crucial que os estudos forneçam informações detalhadas e padronizadas sobre os parâmetros utilizados, conforme apresentado na Tabela 2. Esta tabela inclui elementos como energia radiante, fluência, irradiância, duração do tratamento e método de administração. Essa abordagem não apenas facilita a comparação entre diferentes investigações, mas também permite a otimização das práticas clínicas, garantindo que os profissionais possam implementar a terapia com laser de baixa intensidade de forma eficaz e segura, maximizando assim os resultados terapêuticos para os pacientes.

Tabela 2 – Parâmetros para a terapia com laser de baixa intensidade

Parâmetros	**Símbolo**	**Definição**	**Unidade de Medida**	**Aplicação**
Comprimento de onda	λ	Distância entre dois picos consecutivos da onda eletromagnética, determina quais cromóforos absorverão a luz.	Nanômetros (nm)	Ajuste de penetração e absorção tecidual

Potência de saída	Φ	Quantidade de energia fornecida pelo dispositivo.	Watts (W)	Influencia a dose total recebida
Área do feixe (spot size)	A	Área total sobre a qual o feixe de laser é entregue.	Centímetros quadrados (cm^2)	Define a área de tratamento
Modo de emissão	-	Forma como o laser é emitido, contínua ou pulsada.	-	Influencia o padrão de entrega de energia
Energia radiante	Q	Quantidade total de energia entregue ao tecido durante a sessão.	Joules (J)	Determina a quantidade de energia transferida
Fluência	H	Quantidade de energia entregue por unidade de área do tecido	Joules por centímetro quadrado (J/cm^2)	Determina a densidade de energia no tecido
Irradiância ou densidade de potência	E	Potência entregue por unidade de área do tecido.	Watts por centímetro quadrado (W/cm^2)	Regula a densidade de potência aplicada
Localização anatômica	-	Região do corpo onde a luz é aplicada.	-	Define a área de aplicação terapêutica
Número de sessões	-	Quantidade de vezes que o tratamento é realizado.	Sessões	Determina o plano terapêutico
Intervalo entre tratamentos	-	Período de tempo entre as sessões de tratamento.	Dias/Semanas/Meses	Influencia o processo de

				recuperação tecidual
Forma de aplicação	-	Contato direto, com pressão ou fibra óptica intersticial.	-	Define o modo de entrega da luz ao tecido
Duração da exposição	*t*	Tempo total em que o laser é aplicado em cada sessão	Segundos (s)	Efeito na intensidade do tratamento
Tipo de laser	-	Classificação do laser utilizado (por exemplo, diodo, CO2)	-	Características de penetração e absorção

Observa-se na literatura diferentes opções de manejo da osteorradionecrose. Dentre as terapias propostas, a utilização do laser de baixa intensidade tem provocado interesse na comunidade científica – sobretudo – devido ao seu efeito no reparador e analgésico. Apesar de já ser recomendado seu uso em alguns casos, ainda não se encontram protocolos estabelecidos e padronizados para sua aplicação. Desse modo, espera-se investigar os efeitos da fotobiomodulação e da terapia fotodinâmica no processo de reparo e como elas podem contribuir para um melhor entendimento das funções fisiológicas e do efeito terapêutico na osteorradionecrose.

3. OBJETIVOS

3.1.Objetivo Geral

Avaliar os efeitos da terapia com laser de baixa intensidade no tratamento e prevenção da osteorradionecrose do complexo maxilofacial.

3.2.Objetivos Específicos

- Realizar uma revisão de escopo da literatura científica sobre o uso do laser de baixa intensidade na prevenção e tratamento da osteorradionecrose do complexo maxilofacial, identificando as tendências atuais e evidências disponíveis;
- Analisar os parâmetros e os métodos empregados nos estudos incluídos, incluindo a eficácia e a segurança das abordagens terapêuticas, para fornecer uma visão abrangente sobre o estado atual da pesquisa nessa área;
- Organizar e apresentar os dados coletados de forma clara e acessível, utilizando gráficos e tabelas, para facilitar a compreensão das informações relevantes sobre o impacto da fotobiomodulação e da terapia fotodinâmica na osteorradionecrose;
- Identificar lacunas na pesquisa atual e sugerir direções para estudos futuros, visando a melhoria das práticas clínicas e a otimização dos tratamentos para osteorradionecrose.

4. MÉTODOS

4.1.Protocolo e registro

Esta revisão de escopo foi conduzida conforme a metodologia proposta pelo Joanna Briggs Institute (JBI) para revisões de escopo (Peters et al., 2020). O protocolo foi desenvolvido de acordo com as diretrizes do *Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols* (PRISMA-P) (Shamseer et al., 2015) e da lista de verificação *Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews* (PRISMA-ScR) (Tricco et al., 2018). O protocolo passou por revisão por pares e foi registrado na plataforma Open Science Framework (OSF) sob o código de identificação (https://doi.org/10.17605/OSF.IO/72WGJ).

4.2.Critérios de elegibilidade

4.2.1. População, conceito e contexto

O acrônimo PCC (População, Conceito e Contexto) foi utilizado para formular a seguinte pergunta de pesquisa: "Quais são as tendências atuais e as evidências disponíveis sobre o uso de terapia com laser de baixa intensidade no manejo da osteorradionecrose?". Os elementos da pergunta foram definidos da seguinte maneira: P) Animais ou humanos com osteorradionecrose; C) Tendências atuais e evidências do uso do laser de baixa intensidade no tratamento da osteorradionecrose; e C) Tratamento ou prevenção da osteorradionecrose.

4.2.2. Tipos de fontes

Foram incluídas revisões sistemáticas, estudos observacionais e de intervenção que investigaram o uso de terapia a laser para tratar ou prevenir a osteorradionecrose decorrente de radioterapia. Não foram impostas restrições de idioma ou período de publicação. Além disso, não houve limitações quanto ao comprimento de onda utilizado ou à técnica de aplicação do laser de baixa intensidade. Os critérios de exclusão foram: 1) Estudos que não atendiam aos critérios de inclusão (isto é, laser de baixa intensidade — fotobiomodulação e/ou terapia fotodinâmica — não foi utilizada para tratar osteorradionecrose); 2) Estudos que avaliaram osteonecrose relacionada a medicamentos; 3) Resumos de conferências, cartas ao editor ou revisões narrativas; e 4) Estudos em humanos ou animais que não receberam radioterapia.

4.3.Fontes de informação e de busca

Uma estratégia de busca abrangente foi desenvolvida e aplicada em três bases de dados principais: MEDLINE/PubMed (via National Library of Medicine), EMBASE e Web of Science Core Collection (WoSCC). Essas bases de dados foram escolhidas devido à sua abrangência e relevância na literatura científica relacionada à terapia a laser e osteorradionecrose. Para garantir uma cobertura completa, foram realizadas também pesquisas na literatura cinzenta, utilizando plataformas como Google Scholar e ProQuest Dissertations and Theses Citation Index (PQDT). Além disso, foi realizada uma busca manual nas listas de referências dos estudos incluídos (conforme detalhado no Apêndice A), permitindo a identificação de trabalhos adicionais que poderiam não ter sido capturados nas buscas eletrônicas. A busca foi realizada em 15 de janeiro de 2024. As referências obtidas foram importadas para um software de gerenciamento de referências (EndNote X7; Thomson Reuters, Filadélfia, PA, Estados Unidos), em que os documentos duplicados foram cuidadosamente identificados e removidos, garantindo a integridade da base de dados final.

4.4.Seleção de fontes de evidência

O processo de seleção das fontes de evidência foi realizado em duas fases distintas. Na primeira fase, dois revisores independentes (LDCM e BBS) examinaram os títulos e resumos de todas as referências identificadas, utilizando um software online projetado para facilitar essa análise (Rayyan, Qatar Computing Research Institute). Essa ferramenta permitiu uma avaliação rápida e eficaz, garantindo que as referências fossem filtradas com precisão. Na segunda fase, os mesmos revisores aplicaram os critérios de elegibilidade ao texto completo dos estudos selecionados. Quando divergências surgiram durante esse processo, um terceiro autor foi consultado para ajudar a resolver as diferenças por meio de discussões de consenso (ENSG), assegurando a validade e a robustez da seleção final. A seleção definitiva das evidências foi baseada no texto completo das publicações analisadas. Para a caracterização dos estudos incluídos, foram coletadas as seguintes informações: autor, ano, país, indicação de uso do laser, dose de radioterapia, avaliação, animais e grupos experimentais, tipo de câncer, características clínicas, tratamentos associados, tempo de acompanhamento, número de estudos incluídos, desenho dos estudos incluídos, número de estudos a laser, tamanho da amostra e principal resultado ou conclusões (conforme detalhado no Apêndice B).

4.5.Resumo descritivo

Um resumo qualitativo foi conduzido que envolveu o agrupamento e a comparação dos dados relatados nos estudos incluídos na revisão. O objetivo principal desse resumo foi avaliar as evidências disponíveis sobre o uso do laser de baixa intensidade no tratamento e prevenção da osteorradionecrose resultante da radioterapia. Este processo incluiu a análise detalhada do tipo específico do laser de baixa intensidade utilizado em cada estudo, bem como os parâmetros associados a essa terapia. Os resultados secundários examinaram fatores adicionais, como a região afetada pelo câncer, sexo, idade dos pacientes, fatores de risco relacionados e a dose de radiação utilizada tanto na radioterapia quanto na quimiorradioterapia. Os resultados foram apresentados em forma de porcentagens e prevalência, sendo ilustrados por meio de gráficos para facilitar a visualização. Para a elaboração desses gráficos, foram utilizadas ferramentas licenciadas, incluindo Microsoft Excel, Microsoft PowerPoint e BioRender. Além disso, a ferramenta de software VOSviewer (versão 1.6.17) foi empregada para criar e explorar mapas baseados em dados de rede, facilitando a análise de conexões entre os diferentes estudos. Essa ferramenta é comumente utilizada em estudos de análise bibliométrica e foi adaptada especificamente para esta revisão de escopo. Adicionalmente, o intervalo de confiança de 95% foi calculado utilizando uma calculadora estatística online (OpenEpi; www.OpenEpi.com), garantindo a robustez dos resultados apresentados.

5. CAPÍTULO 1: Manuscrito

Artigo preparado e submetido na revista *Photodiagnosis and Photodynamic Therapy* (IF: 3.1)

Current trends and available evidence on low-level laser therapy for osteoradionecrosis: A scoping review

ABSTRACT

Background: This scoping review explored current trends and available evidence in Low-Level Laser Therapy (LLLT) in the treatment and prevention of osteoradionecrosis.

Methods: The search strategy was conducted in MEDLINE/PubMed, EMBASE, Web of Science, and grey literature on January 15, 2024, without language or time restrictions.

Results: 19 studies were included. The application of LLLT protocols was 58% for therapeutic use, 21% for preventive use, and 21% for a combination of both. Regarding the use of antimicrobial photodynamic therapy (aPDT), 41% of the studies employed this technique, which utilized methylene blue as the photosensitizer. For treatments associated with photobiomodulation, 57% reported pharmacological treatment, 29% surgical treatment, 11% prescribed chlorhexidine mouthwashes, and 4% other therapies. In vivo studies used diode lasers emitting low incident power densities in the near-infrared wavelength (67%) at 780 to 904 nm. In comparison, case reports also used diode lasers emitting low incident power densities in the red and near-infrared wavelength (64%) at 660 to 904 nm. The continuous emission mode was utilized in 83% of in vivo studies and 17% of the case reports. None of the studies included in this review reported all laser parameters.

Conclusions: In general, studies suggested that LLLT can be used for therapeutic and preventive applications in the management of osteoradionecrosis. However, clinical studies are case reports and the variability in laser parameters across the included studies poses challenges for establishing standardized treatment protocols. The lack of comprehensive data on laser parameters underscores the need for future research to focus on standardizing LLLT protocols and conducting well-designed, large-scale clinical trials. This approach will help to better

evaluate the effectiveness of LLLT and potentially integrate it more reliably into clinical practice.

Keywords: Osteoradionecrosis; Laser therapy; Photobiomodulation therapy; Photodynamic Therapy; Low-Level Light Therapy; Low-Level Laser Therapy; LLLT; Review.

INTRODUCTION

Osteoradionecrosis of the maxillofacial complex is a complication resulting from radiotherapy in head and neck tumors [1]. It is characterized by exposed bone that has been irradiated and fails to heal over three to six months without evidence of persistent or recurrent tumors at the site [1,2]. The period for osteoradionecrosis to develop after the end of radiotherapy can vary significantly, occurring either months or even years later [2,3]. There is a greater prevalence of osteoradionecrosis in the mandible compared to maxillary tumors in the oral cavity [4]. The reported osteoradionecrosis incidence rate ranges from 2 to 22% [5,6]. Several factors increase the risk of developing osteoradionecrosis, including radiation dose, trauma, periodontal disease, tumor location and size, type and technique of radiation, infections, immune defects, and malnutrition [7,8]. The removal of compromised teeth just after radiotherapy and inadequate dental care are also significant factors [9]. Symptoms of osteoradionecrosis may include pain, infection, trismus, halitosis, intraoral and extraoral fistulas, and pathological fractures [3,10]. Consequently, osteoradionecrosis negatively impacts the quality of life, affecting functions such as speech, chewing, and swallowing, and leading to facial deformities [11,12].

In this context, the literature still needs to establish an ideal treatment or consensus guidelines regarding the best intervention for osteoradionecrosis. Further clarification is needed regarding the effectiveness of alternative therapies such as the pentoxifylline-tocopherol-clodronate (PENTOCLO) combination, ultrasound, and hyperbaric oxygen therapy (HBOT) [13]. The selection of an appropriate treatment for osteoradionecrosis is contingent upon the extent of the necrotic tissue. A range of potential interventions may be considered to enhance the likelihood of a favorable clinical outcome. However, in instances where the injury is more advanced, surgical procedures may be the optimal treatment choice. These procedures typically involve the debridement of necrotic tissue and bone reconstruction [14]. Photobiomodulation therapy (PBMT) is a treatment modality that has proven to be effective in accelerating wound healing, relieving pain, reducing dentin sensitivity, and reducing the severity of xerostomia and frequency of cold sores [15,16]. PBMT operates with the emission of photons from a low-intensity laser light that transfers low energy to the tissues and does not generate heat [16]. Exposure of tissues to low-intensity laser light induces the modulation of cellular functions by activating several pathways involved in cell growth and survival, proliferation, migration, and transcription [16,17]. Thus, it is essential to study osteoradionecrosis and appropriate treatment, with a multimodal therapeutic approach, considering the patient's characteristics and disease severity [3,18].

Currently, low-level laser therapy (LLLT) is considered an effective non-invasive treatment recommended by the Multinational Association of Supportive Care in Cancer

(MASCC) and the International Society of Oral Oncology (ISOO) for various oral disorders, such as mucositis, xerostomia, taste alterations, and dysphagia [19,20,21,22]. LLLT uses a wavelength between 600 to 1000 nm to stimulate healing and prevent signs resulting from inflammatory mechanisms and exacerbated immune responses [23,24]. It has also been shown to accelerate bone regeneration, increase the number of osteocytes, control inflammatory responses, and enhance vascularization in irradiated bone [25]. In addition, PBMT and antimicrobial photodynamic therapy (aPDT) were used as adjuncts to surgical procedures in the treatment of osteoradionecrosis, with no recurrence observed during a 12-month follow-up [26]. Conservative treatment with aPDT has also been effective to control lesions by reducing bacterial colonization within exposed bone lesions, thereby enhancing the possibilities of bone repair [27]. Therefore, both PBMT and aPDT can serve as effective agents for preventing and treating osteoradionecrosis.

The utilization of LLLT has garnered significant interest within the scientific community, primarily due to its reparative and analgesic effects. Consequently, this scoping review aims to explore the available evidence and delineate the effects of LLLT in the treatment of osteoradionecrosis due to radiotherapy and answer the question: “What are the current trends and available evidence regarding LLLT for the management of osteoradionecrosis?”

MATERIAL AND METHODS

Protocol and registration

The proposed scoping review (ScR) followed the JBI methodology for scoping reviews [28]. A protocol was created following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P) [29] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews checklist (PRISMA-ScR) [30]. The protocol underwent peer review and was registered on the Open Science Framework (OSF) under the identification code (https://doi.org/10.17605/OSF.IO/72WGJ).

Eligibility criteria

Participants, Concept, and Context

The acronym PCC (Population, Concept, and Context) was used to formulate the question: “What are the current trends and available evidence on LLLT in the management of osteoradionecrosis?”, which: P) Animal or human with osteoradionecrosis; C) Current trends and evidence of LLLT in the management of osteoradionecrosis; and C) Treatment or prevention of osteoradionecrosis.

Types of sources

We included systematic reviews, and observational, and interventional studies that investigated laser therapy to treat and or prevent osteoradionecrosis due to radiotherapy. There were no language restrictions or limitations based on publication time. Additionally, there were

no constraints regarding the type of wavelength protocol used or the application technique for LLLT. The exclusion criteria were as follows: 1) Studies that did not meet the inclusion criteria (i.e., LLLT —photobiomodulation and or photodynamic therapy —was not used for osteoradionecrosis management); 2) Studies that evaluated medication-related osteonecrosis; 3) Conference abstract, letter to the editor or and narrative reviews; and 4) Studies in humans or animals that do not receive radiotherapy.

Information sources and search

A search strategy was developed and applied to three databases: MEDLINE/PubMed (via National Library of Medicine), EMBASE, and Web of Science Core Collection (WoSCC). Additional research was also conducted in the grey literature, including Google Scholar and ProQuest Dissertations and Theses Citation Index (PQDT), and a manual search of reference lists from included studies (Appendix A). The search was carried out on January 15, 2024. The references were imported into a reference software manager (EndNote X7; Thomson Reuters, Philadelphia, PA, United States), and the duplicate documents were excluded.

Selection of sources of evidence

The selection process occurred in two phases. In phase one, two independent reviewers (LDCM and BBS) screened the titles and abstracts of all identified references using online software (Rayyan, Qatar Computing Research Institute). In the second stage, the same two reviewers applied the eligibility criteria to the full text of the studies. When necessary, a third author was consulted to resolve any disagreements through consensus discussions (ENSG). The final selection was based on the full text of the publication. For the characterization of the included studies, the following information was collected: author, year, country, laser use indication, radiotherapy dose, evaluation, animals and experimental groups, cancer type, clinical characteristics, associated treatments, follow-up time, number of studies included, design of included studies, number of laser studies, sample size, and main result or conclusions (Appendix B).

Descriptive summary

A qualitative summary was conducted by grouping and comparing data reported in the included studies. The primary objective was to assess the available evidence of LLLT in the treatment and prevention osteoradionecrosis due to radiotherapy. This involved examining the specific type of LLLT used and its associated parameters. Secondary outcomes included factors such as the affected region, sex, age, related risk factors, and the radiation dose used in both radiotherapy and chemoradiotherapy. The results are presented as percentages and prevalence among the findings and illustrated by graphics. Licensed tools such as Microsoft Excel, Microsoft PowerPoint, and BioRender were used for the graphics. Additionally, the software tool VOSviewer (version 1.6.17) was employed, facilitating the creation and exploration of maps based on network data. This is a tool used for Bibliometric Analysis studies and was adapted for these ScR. In addition, the 95% confidence interval was calculated by an online statistical calculator (OpenEpi; www.OpenEpi.com) [31].

RESULTS

Selection of sources of evidence

From 1,101 references identified through database searches, 971 remained after removing duplicates. These records were then assessed against eligibility criteria in two selection phases. In the first phase, titles and abstracts were read, leading to the selection of 53 studies for full-text review in the second phase. Thereafter, 19 studies were finally included for descriptive synthesis. Figure 1 illustrates the PRISMA 2020 flow diagram for the eligible articles. Two additional references were included based on expert recommendation and a manual search was conducted on the reference lists of the included studies. Seven articles were excluded as we could not retrieve them despite our efforts to contact their corresponding authors via listed emails, online searches, and consultation with academic networks. Studies that did not meet the eligibility criteria were excluded (Appendix C).

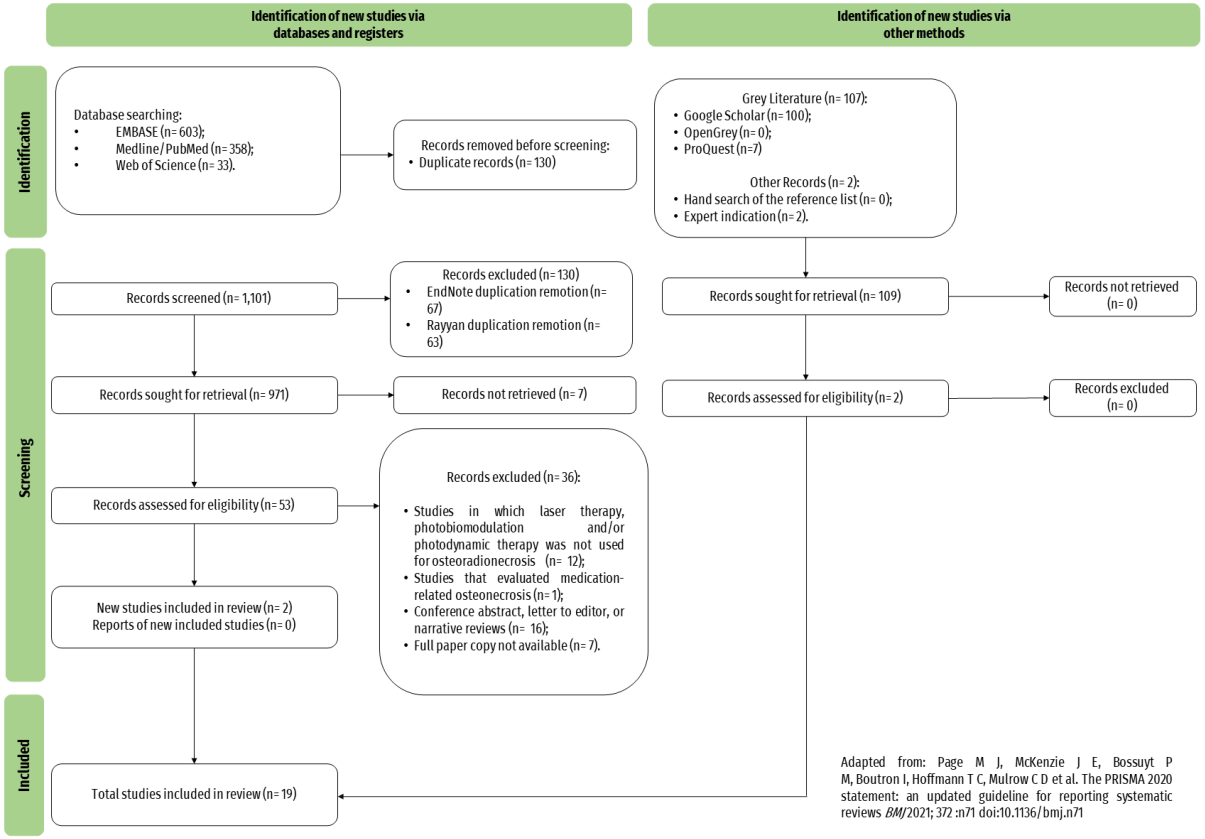


Figure 1: Flow diagram of literature search and selection criteria adapted from PRISMA (Page et al. 2021).

Bibliometric analysis and characteristics of sources of evidence

The 19 studies included were well localized, with limited distribution across continents, showing a preference for the use of LLLT in Brazil (84%; CI 95%: 62.4 -94.5%) [4,5,6,26,27,32,33,34,35,36,37,38,39,40,41,42] Egypt (11%; CI 95%: 3 -31.4%) [43,44], and Italy (5%; CI 95%: 9.3 -24.6%) [45] (Figure 2A). In Bibliometric Analysis, the domain visualization, driven by keyword analysis, was achieved through diagram representation, providing insights into the dynamics of the literature and potential interconnections (Figure 2B). The publications of the included studies range from 2007 to 2023, with 2021 (21%; CI 95%: 8.5 -43.3%) being the year with the most publications in LLLT and osteoradionecrosis [5,27,34,35,41] (Figure 2C). From the nineteen studies analyzed comprised eleven case reports (58%; CI 95%: 36.3 -76.8%) [4,5,6,26,27,34,37,39,41,42,45], six *in vivo* studies (32%; CI 95%: 15.4 -54%) [32,33,3640,43,44], and two systematic reviews (11%; CI 95%: 3 -31.4%) [35,38], and all of them were published in English (Figure 2D). The bibliometric analysis of the included studies can also be accessed (Appendix D).

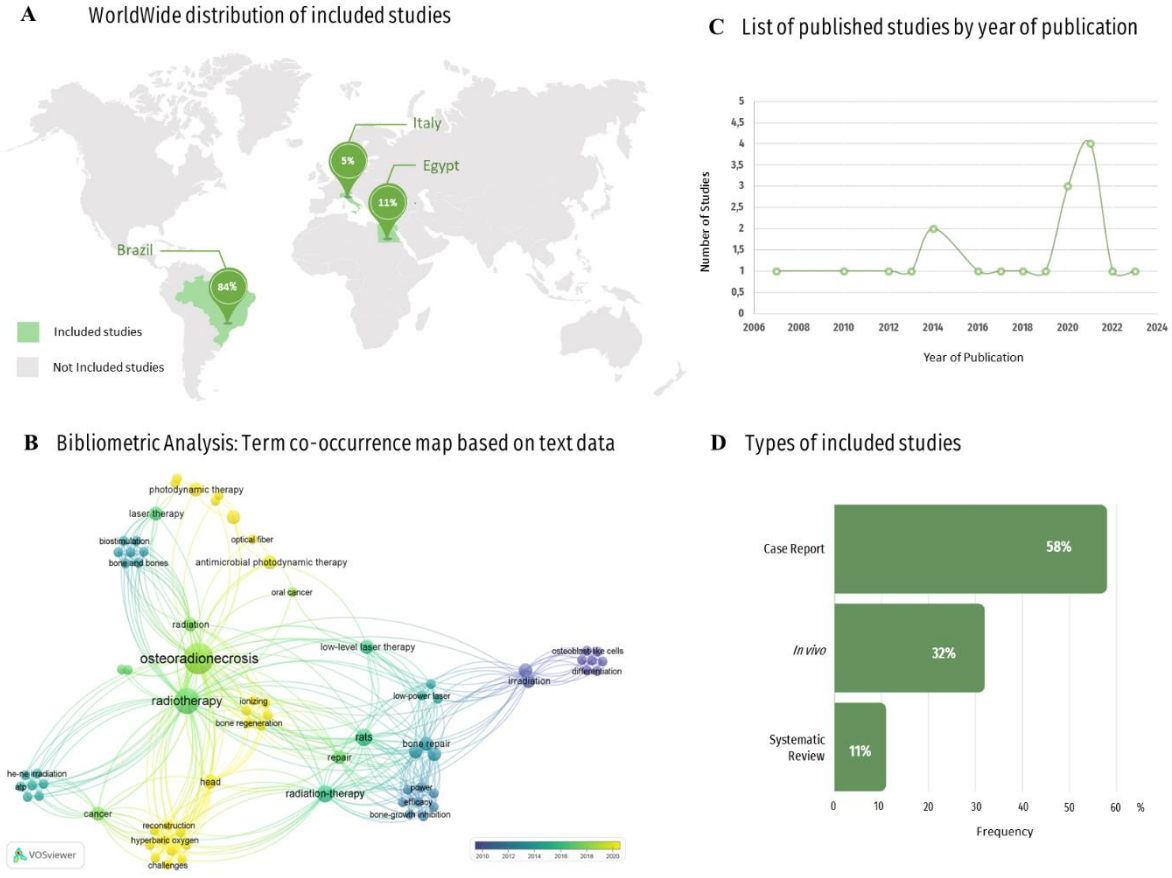


Figure 2: (A) Worldwide distribution of selected studies about the use of laser therapy in management of osteoradionecrosis in North America, South America, Europe, and Africa (n = 19); (B) Overlay map of term co-occurrence based on text data over time for papers included (n=19); (C) Timeline list showcasing the included studies by year of their publication, providing a visual overview of research progress over time (n=19); (D) Distribution of analyzed studies by type, including case reports (58%), *in vivo* studies (32%), and systematic reviews (11%) (n=19).

Characteristics of animal models and cases reports

Regarding the animal model species, all the animals recruited were male and, 67% (CI 95%: 30 -90.3%) employed Wistar rats [32,33,36,40], while 33% (CI 95%: 9.7 -70%) utilized Swiss Albino rats [43,44]. The most prevalent type of cancer in case reports was Oral Squamous Cell Carcinoma (OSCC) (75%; CI 95%: 46.7-91%) affecting the mandible, floor of the mouth, left cervical, laryngeal, oropharyngeal, and tongue [5,6,26,27,34,37,39,41,45]. In the case reports, 64% (CI 95%: 35.4-85%) were male, aged 41 to 65 [4,6,26,27,39,41,45], while 36% (CI 95%: 15.2-64.6%) were female, aged 16 to 62 [5,34,37]. In the series of cases conducted by Ribeiro et al (2018) [42], 90% were male, while 10% were female, aged 40 to 71 (Appendix B).

Radiotherapy doses and osteoradionecrosis diagnosis interval

The total radiotherapy dose utilized in the *in vivo* studies was 6 Gy in two studies [43,44] and 30 Gy in four studies [32,33,36,40]. In the context of case reports, the total doses administered ranged from 45 to 92 Gy, with 45% (CI 95%: 21.3-72%) of these cases being associated with chemotherapy [5,6,27,34,39]. The time interval between cancer diagnosis and osteoradionecrosis diagnosis ranged from 1 to 16 years and was less than or equal to two years in 45% (CI 95%: 21.3-72%) [5,6,27,39,42]. This difference was greater than two years in three studies (27%; CI 95%: 10-56.5%) [34,37,45] and was not reported in three studies (27%; CI 95%: 10-56.5%) [4,26,41] (Appendix B).

LLLT indication: Therapeutic, preventive, and combined uses

Regarding the indication for the use of LLLT, the frequence was 58% (CI 95%: 36.3-77%) for therapeutic use [4,27,32,33,34,35,37,39,40,42,45], 21% (CI 95%: 8.5-43.3%) for preventive use [4,6,41,44], and 21% (CI 95%: 8.5-43.3%) for the combination of therapeutic and preventive use (36; 38; 43; 26) (Figure 3A). Antimicrobial photodynamic therapy (aPDT) was employed in 41% (CI 95%: 21.6-64%) of the studies, all of which utilized methylene blue as the photosensitizer [5,6,26,27,34,37,42]. The reported concentrations of methylene blue were 0.01% in 35% (CI 95%: 17.3-21.6%) [5,6,26,27,37,42] of the studies and 0.02% in 6% (CI 95%: 1-27%) [34] (Figure 3B). No *in vivo* studies used aPDT. This technique was only applied in case reports.

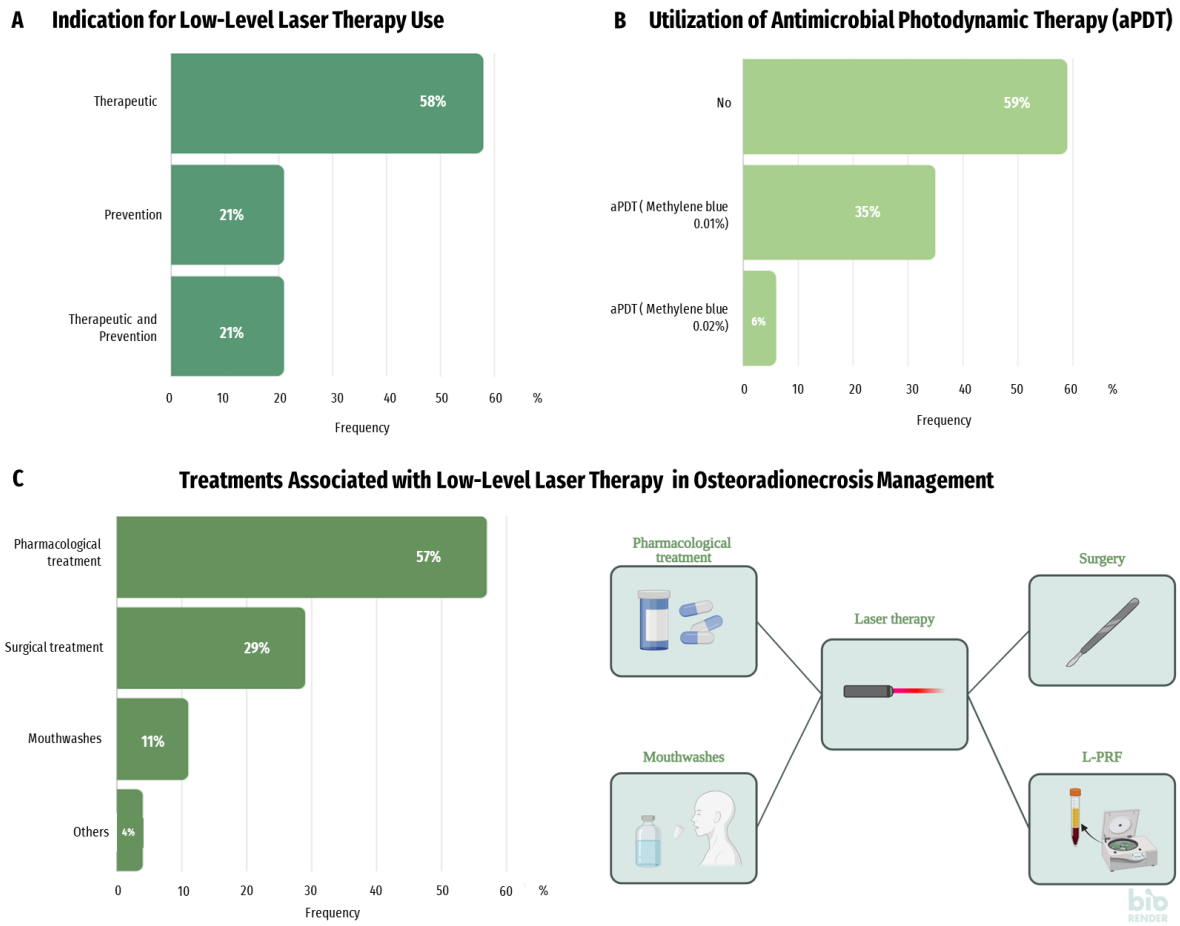


Figure 3: (A) Frequency of Low-Level Laser Therapy (LLLT) usage indication categorized into therapeutic (58%), preventive (21%), and combined therapeutic and preventive (21%) purposes among the analyzed studies (n=19); (B) Frequency of antimicrobial photodynamic therapy (aPDT) utilization in included studies (n=19); (C) Distribution of treatment modalities associated with Low-Level Laser Therapy (LLLT) in the management of Osteoradionecrosis (ORN).

Treatments associated with LLLT for osteoradionecrosis management

Regarding treatments associated with LLLT in the management of osteoradionecrosis, 57% (CI 95%: 39-73.5%) reported the use of pharmacological treatment such as antibiotic therapy, AINE therapy, PENTO protocol and analgesic therapy [4,5,6,26,27,34,39,41,45], 29% (CI 95%: 15.3-47%) surgical treatment (tooth extractions, superficial sequestrectomy, and partial mandibulectomy) [4,6,26,27,34,37,39,45], 11% (CI 95%: 3.7-27.2%) prescribed mouthwashes (chlorhexidine) [4,26,39] and 4% (CI 95%: 6.3-17.7%) other therapies (Leukocyte and Platelet Rich Fibrin: L-PRF) [4] (Figure 3C).

LLLT in systematic reviews

The included systematic reviews indicated LLLT for therapeutic and prevention purposes. In Camolesi et al.'s study (2021) [35], out of the 110 studies examined, only one employed laser, but it was not included in the reported analyses. Conversely, in de Oliveira et al.'s study (2022) [38], all six included studies conducted analyses on PBMT uses in the healing process of irradiated rat bones (Appendix B).

Analysis of laser parameters in LLLT studies

For the analysis of laser parameters, systematic reviews were excluded [35,38], as the studies included in the two reviews that assessed the use of low-level laser therapy had already been included. Therefore, only 17 studies were considered in the analysis. The summary of laser parameters of primary *in vivo* studies and case report studies included can be assessed in Appendix E.

Most of the low-level laser systems used in the *in vivo* studies were GaAlAs (83%; CI 95%: 43.6-97%) [32,33,36,40,44] and Ga-As (17%) [43]. The studies utilized diode lasers emitting low incident power densities in the near-infrared (67%; CI 95%: 30-90.3%) wavelength varying at 780 to 904 nm [33,40,43,44]. In case reports, 73% (CI 95%: 43.4-90.2%) of the LLLT lasers used were InGaAlP (red) AlGaAs (near-infrared) [4,5,6,26,27,34,37,39,42]. They also used diode lasers emitting low incident power densities in the wavelength red and near-infrared varying at 660 to 904 nm (64%; CI 95%: 35.4-85%) [5,6,26,34,37,39,42], near-infrared (18%; CI 95%: 5.1-48%) [4,27], and not repotted (18%; CI 95%: 5.1-48%) [41,45].

Regarding the emission mode of the laser photon beam, the continuous mode was utilized in 83% (CI 95%: 43.6-97%) of *in vivo* studies [32,33,36,43,44], while it was used in 17% of case reports [37]. The emission mode was not reported in 17% (CI 95%: 3-56.3%) of *in vivo* studies [40] and 91% (CI 95%: 62.3-98.4%) of case reports [4,5,6,26,27,34,39,41,42,45]. None of the studies employed the pulsed mode (Figures 4A and 4B). The distance between the laser tip and the application point was also investigated. In *in vivo* studies, 33% (CI 95%: 70%) involved direct contact with punctual application [43,44], while 67% (CI 95%: 30-90.3%) combined contact with punctual application and transcutaneous use [32,33,36,40]. In case reports, 25% (CI 95%: 9-53.2%) utilized direct contact with punctual application [5,6,27], 8% (CI 95%: 1.5-35.4%) employed a non-contact (unfocused mode) approach [45], and 58% (CI 95%: 32-80.7%) did not provide specific details [4,26,34,37,39,41,42] (Figure 4C and 4D).

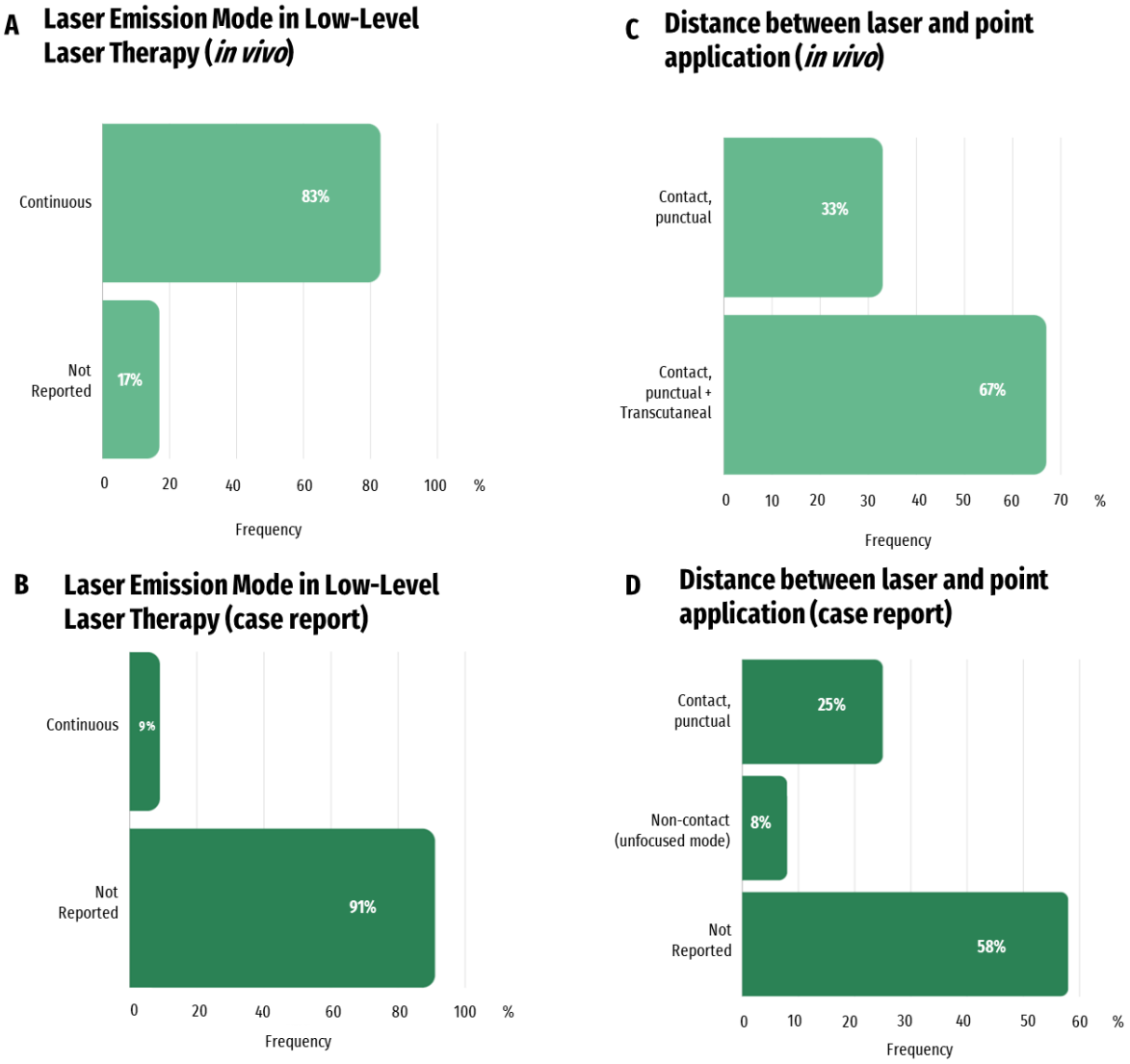


Figure 4: (A) Frequency of utilization of laser emission modes in Low-Level Laser Therapy (LLLT) in *vivo* studies; (B) Frequency of utilization of laser emission modes in Low-Level Laser Therapy (LLLT) case report studies; (C) Frequency of the distance between the laser tip and the application point in Low-Level Laser Therapy (LLLT) *in vivo* studies; (D) Frequency of the distance between the laser tip and the application point in Low-Level Laser Therapy (LLLT) case report studies.

The energy per point in Joules (J) ranged from 2–6 J in *in vivo* studies [32,33,40,43], and was not reported in two studies [36,44]. And it ranged from 2–9 J in case reports that performed aPDT [5,6, 26,27,34,37] and, from 1–6 J in case reports that did PBMT [4,5,6,26,27,34,37,39]. The output power ranged from 30–100 mW in *in vivo* studies [32,33,36,40,43,44], from 40–100 mW in case reports that did aPDT [5,6,26,27,34,37,42], and from 30–500 mW in case reports that did PBMT [4,5,6,26,27,34,37,39,42,45] (Figure 5A and 5B).

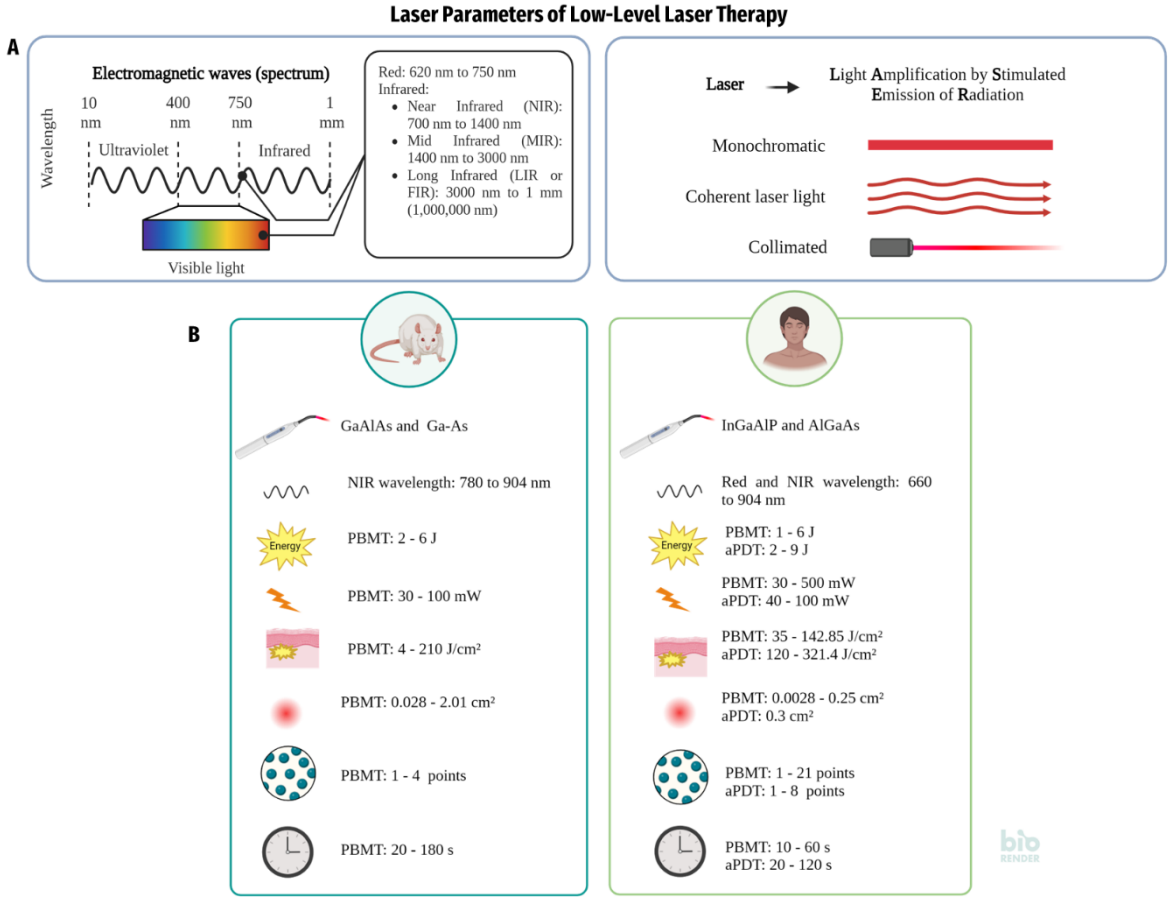


Figure 5: Low-power laser parameters. (A) Graphical representation of the electromagnetic spectrum, highlighting the wavelengths of visible and non-visible light to the human eye, as well as the characteristics of laser light beams; (B) Comparison of laser parameters between *in vivo* studies and case reports included in the review.

Only two studies reported an irradiance value of 3.57 W/cm² [27,32]. Fluence in *in vivo* studies ranged from 4 - 210 J/cm² (32; 33; 36; 40) and was not reported in two studies [43,44]. In case reports, fluence ranged from 120 - 321.4 J/cm² in aPDT [5,26,42] and 35 - 142.85 J/cm² in PBMT [4,5,27,39,42] (Appendix E).

The cross-sectional area of the lesion to be irradiated varied from 0.028 - 2.01 cm² in *in vivo* studies [32,33,36,43,40,44]. Only one study reported a cross-sectional area of 0.3 cm² for aPDT [5], while in PBMT, the studies expressed these values, which were 0.0028 cm² [4,39]. The diameter of the laser device spot ranged from 0.028 - 2.01 cm² in *in vivo* studies [32,33,40,43,44]. Only one study reported a spot diameter of 0.3 cm² for aPDT [5], while in PBMT, the variation was 0.0028 - 0.25 cm² [4,27,39,42,45].

The number of laser application points varied from 1-4 in *in vivo* studies [32,33,43,44]. For aPDT, the number of points varied from 1-8 [6,26,34,42,45], while in PBMT, the variation was 1 -21 points [6,26,34,42]. The distance between the applied points was 1 cm, which was reported in only two *in vivo* studies [43; 40]. For aPDT, the distance between points was about 1 cm [6,26], while in PBMT, the variation was 1 - 2 cm [6,26,27,45]. Some studies reported that the application was made around or inside the lesion, without sizing it [4,5,39]. The

exposure time per point ranged from 20 - 180 s in *in vivo* studies [32,33,36,40,43]. For aPDT, the exposure time per point varied from 20 - 120 s [4,5,6,27,42], while in PBMT, the variation was 10 - 60 s [4,6,26,27,39,42] (Appendix E).

The frequency of laser application varied between studies. *In vivo*, there was a variation of three to seven LLLT sessions every 48 hours [32,33,36,40,43], while one study reported that LLLT was performed immediately after extraction once [44]. For aPDT, the application protocol was once a week for one month [6,26], once a week for eight months [37], and three times a week without reporting the number of months [27]. As for PBMT, the protocol was 7 to 15 days after surgery [34], once a week for a month [6,45], three times a week for a month [26], twice a week, without reporting the number of months [27], for two months without reporting the frequency of the week [37], once a week for three months [39], three sessions every 48 hours without reporting for how many months [4] (Appendix E).

To illustrate the clinical applications and outcomes of LLLT for osteoradionecrosis, a comprehensive supplemental material is available (Appendix F). This appendix offers a detailed overview of each study, covering aspects such as patient information, previous treatments, treatments to prevent or treat osteoradionecrosis, indication for laser use (therapeutic or preventive), parameters of LLLT, follow-up, side effects, and outcomes. Most of the studies reviewed indicated that laser therapy had beneficial effects, with a good prognosis for the patients. The side effects found in case reports and case series studies varied according to the treatment and protocols used. Bernaola-Paredes et al. (2021) observed nausea and vomiting related to the PENTO protocol, which included pentoxifylline and tocopherol [34]. De Freitas et al. (2023) reported that the use of the Er:YAG laser presented minimal side effects due to its low thermal energy, preventing damage to surrounding tissues [37]. Campos et al. (2021), Franco et al. (2017), Magalhães et al. (2020), Moreschi et al. (2016), Palma et al. (2021), Pedroni et al. (2020), Ribeiro et al. (2018), and Tateno et al. (2020) did not report significant side effects, indicating that LLLT and aPDT were well tolerated by patients [4, 5, 6, 26, 27, 41, 42, 45]. Overall, LLLT has been shown to be safe, with few adverse effects reported [4, 5, 6, 26, 27, 34, 37, 41, 42, 45].

Thus, we summarized the results that the depth of light penetration in tissues depends on various factors, including wavelength, spot diameter, and power density. For this purpose, we developed a graphical representation of the light-tissue interaction and penetration capability (Figure 6).

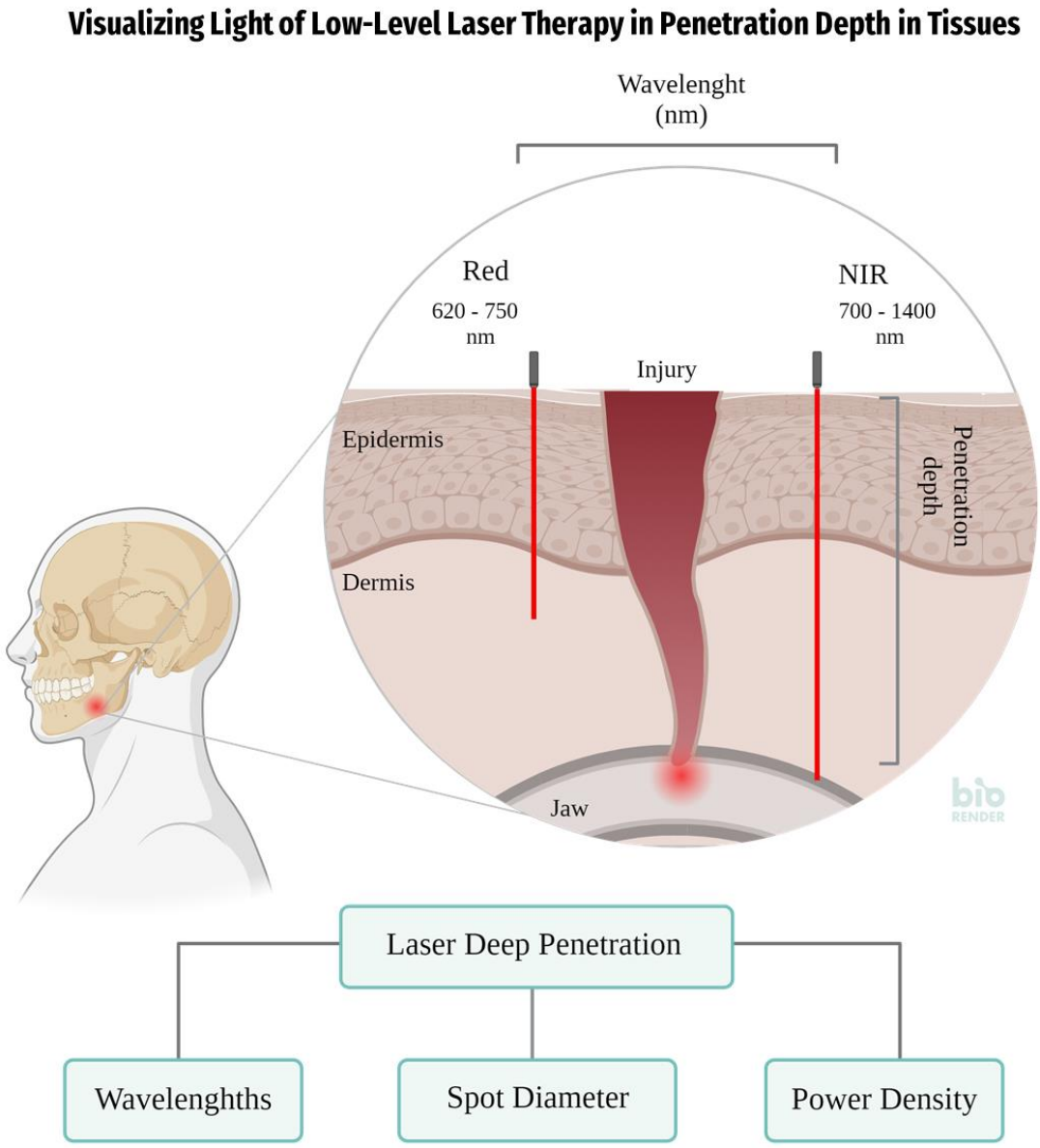


Figure 6: Graphical representation of light-tissue interaction and penetration capability. The depth of light penetration in tissues depends on various factors, including wavelength, spot diameter, and power density.

DISCUSSION

The biological effects of LLLT on irradiated tissues depend on laser parameters, including wavelength, power density, beam or spot size, type of delivery (pulsed or continuous), and duration of exposure [9]. These parameters can directly influence the efficacy and safety of the treatment. However, our research found that many *in vivo* studies and case reports needed complete data on the low-power lasers. None of the studies included in this ScR reported all parameters. The wavelength determines how deeply the laser penetrates and how well it is

absorbed by target tissues [46]. Power and spot size are separate parameters that together determine power density, which indicates the amount of energy and heat delivered to the target area. Reducing the spot size decreases penetration depth due to faster photon dispersion, resulting in more superficial treatment. This allows effective treatment with minimal surface energy, lowering the risk of complications [46]. Laser light can be continuous or pulsed, with continuous wave lasers capable of causing non-selective injuries. In contrast, pulsed delivery allows for more selective damage, depending on the duration of exposure to the beam [47]. The exposure time, derived from the total emitted energy and laser power, should be specified clearly, and can significantly influence therapeutic outcomes. Besides that, describing the number of application points and the total treatment area provides a comprehensive view of the laser dose distribution in the treated tissues [47]. In this sense, detailed reports of laser parameters allow the replication of studies by other researchers and help to establish standardized treatment protocols. Furthermore, the lack of reporting of laser parameters may make difficult the comparison between studies and generalization of results.

LLLT can impact cells and tissues significantly, making it a valuable tool for biomodulation. Particularly beneficial post-operatively, LLLT facilitates faster healing, reduces pain, restores neural function, and improves bone remodeling and repair [4]. Red lasers, which are highly absorbed in the hemoglobin-rich oral mucosa, and near-infrared lasers, which penetrate deeper tissues like the salivary glands, play a role in these positive effects [27]. The World Association for Laser Therapy (WALT) suggests using an intraoral visible red (630-680 nm) or transcutaneous near-infrared (800-1100 nm) wavelength LED/laser device with a power density of 10-150 mW/cm². This treatment, delivering a total dose of 2 J/cm² per field, should be repeated 3 to 4 times a week for 4 to 6 weeks or until clinical improvements are observed [9]. Given these guidelines and the proven benefits of LLLT, it stands out as an essential modality in enhancing patient recovery and oral health.

Considering that dysbiosis has a crucial role in the pathophysiology of osteoradionecrosis, aPDT has been proposed due to its effectiveness against various pathogenic microorganisms [5]. Additionally, PBMT is known to produce anti-inflammatory, analgesic, and biomodulator effects, leading to pain relief, faster healing, and improved wound healing, especially when applied preoperatively [37]. Such a combination of phototherapies is cost-effective, non-invasive, and seems to have no side effects [5]. In our findings, all studies that performed aPDT used methylene blue, in different concentrations, as a photosensitizer. Methylene blue, a commonly used dye in aPDT, has a well-documented safety record and has been utilized in a wide range of human clinical infections, which, when activated by low-energy light of the appropriate wavelength, generates singlet oxygen and free radicals [27]. Furthermore, aPDT has shown promise in eliminating opportunistic microorganisms without leading to microbial resistance [26]. These therapeutic options aim to contribute to the treatment effectiveness and prevention of osteoradionecrosis recurrence, as well as the management of mucous membrane infections by enhancing the antimicrobial effects of antibiotics and antifungals while reducing the antimicrobial dose needed to achieve a bactericidal/fungicidal effect [26]. In summary, aPDT, with its ability to produce reactive oxygen species that lead to microbial death, coupled with PBMT, offers a non-invasive and effective treatment option for osteoradionecrosis lesions [27].

In vivo studies that used aPDT to manage osteoradionecrosis as an outcome have not yet been described in the literature. However, studies investigating the photodynamic effects

on endodontic pathogens have shown promising results, achieving considerable elimination rates [48]. In the study by Dharmaratne et al. (2020) [49], a full-thickness wound model with *in vivo* murine infection by methicillin-resistant *Staphylococcus aureus* (MRSA) was used to support the use of aPDT as a therapeutic modality for MRSA skin infection. A future-forward option is to combine aPDT treatment with conventional antimicrobials to achieve additive or synergistic therapeutic effects, and potentially overcome antimicrobial resistance. This approach could expand the use of aPDT and reduce the amount of antibiotics needed, thereby mitigating the issue of multidrug resistance [50].

The potential benefits of LLLT in managing osteoradionecrosis extend beyond the clinical outcomes, profoundly affecting patients' quality of life. Effective treatment options for osteoradionecrosis are critical due to the debilitating nature of the condition, which can significantly impair daily functioning and overall well-being. By potentially enhancing bone repair and alleviating radiation-induced damage, LLLT offers a promising avenue to reduce pain, accelerate healing, and improve functional recovery [5,27,34,37,39,41,42,45]. Additionally, the literature indicates that LLLT reduces and modulates inflammation and promotes tissue regeneration, demonstrating its therapeutic effect in already established cases of osteoradionecrosis, while also pointing out that its preventive prophylactic potential can reduce the incidence of osteoradionecrosis in patients undergoing radiotherapy [23,25]. These improvements can lead to a decrease in treatment-related discomfort, minimize the need for more invasive interventions, and enhance the patient's quality of life. Given the significant impact that effective management can have on patients' daily lives, it is crucial to continue exploring and validating LLLT protocols. Furthermore, most included *in vivo* studies indicated that LLLT promotes the formation of new bone tissue, osteocytes, osteoblasts, and vascular networks [32,33,36,43,40,44]. Analysis of the included studies revealed significant results that highlight the potential of LLLT in treating and preventing osteoradionecrosis by improving bone healing after exposure to ionizing radiation. However, addressing the current gaps in research and standardizing treatment approaches could lead to more effective and accessible therapies, fostering better outcomes and improved quality of life for those affected by this challenging condition.

Despite the lack of consensus in the literature regarding osteoradionecrosis treatment due to the absence of a universally accepted classification and limited understanding of its pathophysiology, management strategies typically aim to halt the progression and alleviate symptoms. These strategies combine conservative measures with invasive procedures such as surgical resection when necessary [27,37,39]. Conservative management approaches included conventional drug therapy with antibiotics, enhanced oral hygiene, HBOT, PBMT, aPDT, and drug protocols like pentoxifylline-tocopherol (PENTO) and pentoxifylline-tocopherol-clodronate (PENTOCLO) [4,34,37]. The PENTO protocol is well tolerated, although adjustments may be required in some cases due to its acute toxicity [34]. Some studies reported the use of therapeutic mouthwashes with chlorhexidine to reduce oral bacterial load and prevent infections [4,26,39].

The side effects reported in case reports varied depending on the treatments and protocols used. Bernaola-Paredes et al. (2021) described a 62-year-old Afro-descendant woman with stage pT1N0M0 cancer who developed advanced ORN in 2020. Her treatment included radiotherapy, antifibrotic therapy (PENTO protocol), surgery, and antimicrobial photodynamic

therapy (aPDT) with methylene blue. LLLT was applied using specific parameters: a wavelength of 660 nm and a power of 100 mW. After 12 months of follow-up, side effects such as nausea and vomiting, related to the PENTO protocol, were observed [34]. Campos et al. (2021) described a 57-year-old woman treated for ORN in 2020 with radiotherapy and aPDT. LLLT was administered using a wavelength of 808 nm for PBMT and 660 nm for aPDT, with no reported side effects [5]. De Freitas et al. (2023) reported a similar case, adjusting parameters as necessary to accommodate patient response [37]. Other studies reported variations in LLLT protocols to adapt to different stages of ORN, suggesting the need for personalized approaches in treatment to maximize efficacy while minimizing side effects. Overall, LLLT appears effective in reducing ORN symptoms, demonstrating flexibility in its application and significant potential for managing complex cases [5, 34, 37].

The study results show that the PENTO protocol effectively stabilized advanced-stage ORN when combined with adjuvant therapies and surgery [4,34]. PBMT and aPDT with optical fibers appear well-suited for treating restricted areas like fistula tracts, while LLLT and HLLT offer viable therapeutic alternatives for resolving ORN, particularly in cases where more invasive procedures may not be feasible or desirable [26, 37]. One patient, however, died of a heart attack before ORN could be controlled, emphasizing the complexity of managing comorbidities alongside ORN treatment [34]. The protocol successfully prevented ORN in an adolescent, with no pathological signs one year after extractions, demonstrating its potential in younger populations [4]. Adjuvant therapy combining aPDT and LLLT with surgery and antibiotics also proved successful, with no recurrence after a year [4]. Additionally, LLLT paired with systemic antibiotics presents a conservative treatment option for patients who are contraindicated for surgery or those with a high risk of surgical complications. Perioperative systemic antibiotics also seem effective in preventing ORN after extractions in irradiated patients, suggesting the importance of timely intervention and careful monitoring [4]. Also, PBMT and aPDT have shown potential in controlling ORN lesions and alleviating pain, with both therapies appearing to contribute positively as adjuvants in treatment plans. They also seem to assist in promoting healing and may help in preventing ORN after multiple extractions in post-radiotherapy patients, especially when used alongside antibiotics and surgical care. However, further research is needed to better understand their role in managing complex ORN cases [4, 27, 34, 37, 39, 41].

In surgical management, extensive surgical resections followed by microvascularized free flap reconstructions are commonly performed for advanced lesions [34]. Our findings indicate that surgical treatment included dental extractions to remove necrotic or severely compromised teeth, superficial sequestrectomy to remove superficial necrotic bone tissue, and partial mandibulectomy to resect segments of the affected mandibular bone [4,6,26,27,34,37, 39,45]. Additionally, others explored the potential of Leukocyte and Platelet-Rich Fibrin (L-PRF) to promote tissue healing and bone regeneration [4]. However, the use of L-PRF in tooth extractions for post-radiotherapy head and neck cancer patients did not demonstrate any additional benefit relative to the proposed surgical and medication protocols [51].

There is evidence to suggest that using isolated therapies alone may not be enough to completely regress lesions. So, combining adjuvant techniques is necessary for better outcomes [26,34]. High-power lasers (HILT, high-intensity laser treatment), such as the Er: YAG laser, are employed to remove bone tissue due to their photothermal effects, which reduce heat transmission to neighboring structures [37,52]. While LLLT is used for its biostimulative effects, the CO_2 laser provides a less traumatic alternative for debridement compared to

mechanical cutting [53]. Overall, the literature identifies seven potential influencing factors that impact the laser surgery process: wavelength, pulse duration, water and air cooling, laser power, laser scanning speed, and laser line energy [54]. The management of osteoradionecrosis includes a variety of therapies from local irrigation, non-surgical debridement, and antibiotic therapy to major surgical interventions such as sequestrectomy or segmental mandibulectomy with reconstruction [4,26,39,42,55]. Despite the range of therapeutic options available, no clear consensus exists, highlighting the need for individualized treatment plans based on the severity of the condition [27,55].

This ScR has some limitations that should be considered when interpreting the results. Firstly, there is a lack of standardization in laser parameters among the included studies, which is a significant issue. The variability in doses, durations, and frequencies of LLLT sessions makes direct comparisons difficult and hinders the ability to draw definitive conclusions. Additionally, the differences in radiotherapy dosages across studies can affect the outcomes, as varying doses may result in diverse levels of osteoradionecrosis severity, impacting the effectiveness of LLLT treatment. Another limitation is the diversity of animal models used in experimental studies; distinct species and experimental conditions can show variable responses to LLLT, which reduces the generalizability of the results to human clinical practice. It is also important to highlight that many of the included studies are case reports, a study type that lacks a control group and therefore does not allow for comparisons. While these reports may suggest that laser treatment is beneficial, the positive outcomes may reflect a naturally favorable prognosis, which could have occurred even without laser therapy. As such, it is not possible to definitively state that laser is effective when no comparative analysis is conducted. Moreover, publication bias is strongly present in this context, as case reports where laser therapy did not yield positive results are unlikely to be published. Lastly, the methodological heterogeneity among the studies, including differences in inclusion criteria and outcome assessment methods, limits the ability to synthesize the results cohesively and robustly. The current research also has limitations, including a lack of clinical trials, small sample sizes, and inconsistent treatment protocols. These factors make it even more challenging to assess the efficacy of LLLT. As this is a ScR, we do not carry out a quality assessment based on the risk of bias, and no critical quality assessment was performed. Recognizing these limitations is essential for guiding future research that can address these issues and provide more robust evidence on the efficacy of LLLT in managing osteoradionecrosis.

This ScR presents innovative points that significantly contribute to understanding LLLT in osteoradionecrosis. A key point is the analysis of the dual role of LLLT in treatment and prevention, offering a comprehensive view of its potential applications. The review also emphasizes the importance of standardized LLLT protocols, highlighting the need for uniformity in laser parameters and treatment regimens, and addressing a critical gap in the literature. The inclusion of various studies, covering different radiotherapy dosages and diverse animal models, provides an understanding of the effectiveness of LLLT in different scenarios. Finally, the review identifies emerging trends and future research directions, promoting more targeted and methodologically sound investigations in this promising field.

RECOMMENDATIONS FOR FUTURE RESEARCH

Future research on LLLT in managing osteoradionecrosis should focus on improving the understanding and application of this treatment. Firstly, it is essential to standardize LLLT protocols. This involves establishing consistent doses, durations, and session frequencies to enable comparability between studies and facilitate replication of results. Long-term studies are also crucial to evaluate the lasting preventive and therapeutic effects of LLLT, ensuring its immediate effectiveness and long-term safety. Additionally, robust randomized clinical trials (RCT) with larger sample sizes, standardized outcome measures, and controlled, randomized designs are needed to provide more reliable and generalizable evidence. The comprehension of the biological mechanisms underlying LLLT, particularly in bone healing and inflammation modulation, has the potential to discover new therapeutic proposals. It is also possible to explore the combination of LLLT with other treatment modalities to enhance its benefits. Finally, cost-benefit analyses and studies on accessibility are essential to determine the economic feasibility of LLLT. As well as its widespread dissemination in various public and private health services, ensuring that the therapy is effective and accessible to a wide range of patients.

CONCLUSION

In summary, this review suggests that low-level laser therapy is promising in stimulating bone repair and mitigating damage from ionizing radiation, which could aid in treating and preventing osteoradionecrosis. Based on the consensus document from the World Association for Laser Therapy (WALT), it is recommended to use visible red (630-680 nm) or near-infrared (800-1100 nm) lasers with a power density of 10-150 mW/cm², delivering a total dose of 2 J/cm² per field, repeated 3 to 4 times a week for 4 to 6 weeks or until clinical improvements. However, our review identified a lack of large-scale clinical trials, small patient populations, and substantial variability in treatment parameters across studies. These factors make it challenging to understand the effectiveness of the therapy and establish definitive and standardized protocols. Thus, future research should focus on standardizing LLLT protocols, conducting large-scale randomized clinical trials, and exploring the combination of LLLT with other treatment modalities to enhance its effectiveness. Given the potential impact on patients' quality of life, addressing clinical outcomes such as pain reduction, wound healing, and overall well-being is crucial.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

CRediT authorship contribution statement

Larissa Di Carvalho Melo: Investigation, Conceptualization, Methodology, Software, Data curation, Formal analysis, Writing – review & editing, Writing – original draft. Bruna Bastos Silveira: Investigation, Data curation, Formal analysis, Writing – review & editing. Mylene Martin Monteiro: Investigation, Writing – review & editing. Juliana Amorim dos Santos: Investigation, Writing – review & editing. Elaine Barros Ferreira: Investigation, Writing – review & editing. Paula Elaine Diniz Reis: Investigation, Writing – review & editing. Camila de Barros Gallo: Investigation, Writing – review & editing. Elite Neves da Silva Guerra: Supervision, Project administration, Conceptualization, Data curation, Writing – review & editing.

ACKNOWLEDGMENTS

This work has been supported by the Coordination for the Improvement of Higher Education Personnel (CAPES) and the National Council for Scientific and Technological Development (Processo 406557/2021-7, Chamada CNPq/MCTI/FNDCT N. 18/2021 - Faixa B).

REFERENCES

[1] Chronopoulos, A., Zarra, T., Ehrenfeld, M., & Otto, S. (2018). Osteoradionecrosis of the jaws: definition, epidemiology, staging and clinical and radiological findings. A concise review. *International dental journal*, 68(1), 22–30. doi:10.1111/idj.12318

[2] Frankart, A. J., Frankart, M. J., Cervenka, B., Tang, A. L., Krishnan, D. G., & Takiar, V. (2021). Osteoradionecrosis: Exposing the Evidence Not the Bone. *International journal of radiation oncology, biology, physics*, 109(5), 1206–1218. doi:10.1016/j.ijrobp.2020.12.043

[3] Costa, D. A., Costa, T. P., Netto, E. C., Joaquim, N., Ventura, I., Pratas, A. C., Winckler, P., Silva, I. P., Pinho, A. C., Sargento, I. G., Guerreiro, F. G., & Moreira, A. R. (2016). New perspectives on the conservative management of osteoradionecrosis of the mandible: A literature review. *Head & neck*, 38(11), 1708–1716. https://doi.org/10.1002/hed.24495

[4] Franco, T., Cezini, D. C., Metropolo, L., Ferreira, D. C., & Tannure, P. N. (2017). Success of preventive approach to mandibular osteoradionecrosis in an adolescent: Case report. *Oral Surgery*, 10(4), e104-e109. https://doi.org/10.1111/ors.12294

[5] Campos, L., Martins, F., Tateno, R. Y., Sendyk, W. R., & Palma, L. F. (2021). Antimicrobial photodynamic therapy using optical fiber for oral fistula resulting from mandibular osteoradionecrosis. *Photodiagnosis and photodynamic therapy*, 34, 102247. https://doi.org/10.1016/j.pdpdt.2021.102247

[6] Tateno, R. Y., Palma, L. F., Sendyk, W. R., & Campos, L. (2020). Laser and antimicrobial photodynamic therapy for the management of delayed healing following multiple dental extractions in a post-radiotherapy patient. *Photodiagnosis and photodynamic therapy*, 30, 101764. https://doi.org/10.1016/j.pdpdt.2020.101764

[7] Chrcanovic, B. R., Reher, P., Sousa, A. A., & Harris, M. (2010). Osteoradionecrosis of the jaws--a current overview--part 1: Physiopathology and risk and predisposing factors. *Oral and maxillofacial surgery*, 14(1), 3–16. https://doi.org/10.1007/s10006-009-0198-9

[8] Marcondes, C. F., Rodrigues, J. V. S., Zuza, E. C., Tanimoto, H. M., & Barroso, E. M. (2022). Risk factors associated with osteoradionecrosis of the mandible in patients with cancer of oral cavity and oropharynx. *Revista de Odontologia da UNESP*, 51, e20220037. https://doi.org/10.1590/1807-2577.03722

[9] Robijns, J., Nair, R. G., Lodewijckx, J., Arany, P., Barasch, A., Bjordal, J. M., Bossi, P., Chilles, A., Corby, P. M., Epstein, J. B., Elad, S., Fekrazad, R., Fregnani, E. R., Genot, M.-T., Ibarra, A. M. C., Hamblin, M. R., Heiskanen, V., Hu, K., Klastersky, J., Lalla, R., Latifian, S., Maiya, A., Mebis, J., Migliorati, C. A., Milstein, D. M. J., Murphy, B., Raber-Durlacher, J. E., Roseboom, H. J., Sonis, S., Treister, N., Zadik, Y., Bensadoun, R.-J., & WALT Working Group on Cancer Supportive Care. (2022). Photobiomodulation therapy in management of cancer therapy-induced side effects: WALT position paper 2022. *Frontiers in Oncology*, 12, 927685. https://doi.org/10.3389/fonc.2022.927685

[10] Shaw, R., Tesfaye, B., Bickerstaff, M., Silcocks, P., & Butterworth, C. (2017). Refining the definition of mandibular osteoradionecrosis in clinical trials: The Cancer Research UK HOPON trial (Hyperbaric Oxygen for the Prevention of

Osteoradionecrosis). *Oral Oncology, 64*, 73-77. https://doi.org/10.1016/j.oraloncology.2016.12.002

[11] Beaumont, S., et al. (2021). Timing of dental extractions in patients undergoing radiotherapy and the incidence of osteoradionecrosis: a systematic review and meta-analysis. *British Journal of Oral and Maxillofacial Surgery, 59*(5), 511-523.

[12] Kolokythas, A., Rasmussen, J. T., Reardon, J., & Feng, C. (2019). Management of osteoradionecrosis of the jaws with pentoxifylline-tocopherol: a systematic review of the literature and meta-analysis. *International Journal of Oral and Maxillofacial Surgery, 48*(2), 173-180.

[13] Nabil, S., & Samman, N. (2011). Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: a systematic review. *International Journal of Oral and Maxillofacial Surgery, 40*, 229-243.

[14] De Felice F, Tombolini V, Musio D, Polimeni A. Radiation Therapy and Mandibular Osteoradionecrosis: State of the Art. *Curr Oncol Rep*. 2020;22(9).

[15] Sonis, S. T., Hashemi, S., Epstein, J. B., Nair, R. G., & Raber-Durlacher, J. E. (2016). Could the biological robustness of low-level laser therapy (Photobiomodulation) impact its use in the management of mucositis in head and neck cancer patients. *Oral Oncology, 54*, 7-14. doi: 10.1016/j.oraloncology.2016.01.005

[16] Pellicioli, A. C., Martins, M. D., Dillenburg, C. S., Marques, M. M., Squarize, C. H., & Castilho, R. M. (2014). Laser phototherapy accelerates oral keratinocyte migration through the modulation of the mammalian target of rapamycin signaling pathway. *Journal of Biomedical Optics, 19*(2), 028002.

[17] Marques, M. M., Diniz, I. M., de Cara, S. P., Pedroni, A. C., Abe, G. L., D'Almeida-Couto, R. S., ... Moreira, M. S. (2016). Photobiomodulation of Dental Derived Mesenchymal Stem Cells: A Systematic Review. *Photomedicine and Laser Surgery, 34*(11), 500-508.

[18] Raggio, B. S., & Winters, R. (2018). Modern management of osteoradionecrosis. *Current Opinion in Otolaryngology & Head and Neck Surgery, 26*(4), 254-259.

[19] Kalhori, K. A. M., Vahdatinia, F., Jamalpour, M. R., Vescovi, P., Fornaini, C., Merigo, E., & Fekrazad, R. (2019). Photobiomodulation in Oral Medicine. Photobiomodulation, Photomedicine, and Laser Surgery, 37(12), 837-861.

[20] Bensadoun, R. J. (2018). Photobiomodulation or low-level laser therapy in the management of cancer therapy-induced mucositis, dermatitis and lymphedema. Current Opinion in Oncology, 30(4), 226-232. doi: 10.1097/CCO.0000000000000452. PMID: 29794809.

[21] Bensadoun, R. J., Nair, R. G., & Robijns, J. (2020). Photobiomodulation for Side Effects of Cancer Therapy. Photobiomodulation, Photomedicine, and Laser Surgery, 38(6), 323-325. doi: 10.1089/photob.2019.4759. Epub 2020 May 4. PMID: 32364823.

[22] Elad, S., Cheng, K. K. F., Lalla, R. V., Yarom, N., Hong, C., Logan, R. M., Bowen, J., Gibson, R., Saunders, D. P., Zadik, Y., Ariyawardana, A., Correa, M. E., Ranna, V., Bossi, P., & Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) (2020). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*, *126*(19), 4423–4431. https://doi.org/10.1002/cncr.33100

[23] Zadik, Y., Arany, P. R., Fregnani, E. R., Bossi, P., Antunes, H. S., Bensadoun, R. J., Gueiros, L. A., Majorana, A., Nair, R. G., Ranna, V., Tissing, W. J. E., Vaddi, A., Lubart, R., Migliorati, C. A., Lalla, R. V., Cheng, K. K. F., Elad, S., & Mucositis Study

Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) (2019). Systematic review of photobiomodulation for the management of oral mucositis in cancer patients and clinical practice guidelines. *Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer*, *27*(10), 3969–3983. https://doi.org/10.1007/s00520-019-04890-2

[24] Aguiar, B. R. L., Guerra, E. N. S., Normando, A. G. C., Martins, C. C., Reis, P. E. D. D., & Ferreira, E. B. (2021). Effectiveness of photobiomodulation therapy in radiation dermatitis: A systematic review and meta-analysis. Critical Reviews in Oncology/Hematology, 162, 103349. doi: 10.1016/j.critrevonc.2021.103349. Epub 2021 May 11. PMID: 33989768.

[25] Escudero, J. S. B., Perez, M. G. B., de Oliveira Rosso, M. P., Buchaim, D. V., Pomini, K. T., Campos, L. M. G., Audi, M., & Buchaim, R. L. (2019). Photobiomodulation therapy (PBMT) in bone repair: A systematic review. *Injury, 50*(11), 1853-1867. doi: 10.1016/j.injury.2019.09.031. Epub 2019 Sep 21. PMID: 31585673.

[26] Magalhães, I. A., Forte, C. P. F., Viana, T. S. A., Teófilo, C. R., Lima Verde, R. M. B., Magalhães, D. P., Praxedes Neto, R. A. L., Lima, R. A., & Dantas, T. S. (2020). Photobiomodulation and antimicrobial photodynamic therapy as adjunct in the treatment and prevention of osteoradionecrosis of the jaws: A case report. *Photodiagnosis and Photodynamic Therapy, 31*, 101959. doi: 10.1016/j.pdpdt.2020.101959. Epub 2020 Aug 18. PMID: 32818642.

[27] Pedroni, A. C. F., Miniello, T. G., Hirota, C., Carvalho, M. H., Lascala, C. A., & Marques, M. M. (2020). Successful application of antimicrobial photodynamic and photobiomodulation therapies for controlling osteoradionecrosis and xerostomia after laryngeal carcinoma treatment: A case report of full oral rehabilitation. *Photodiagnosis and Photodynamic Therapy, 31*, 101835. doi: 10.1016/j.pdpdt.2020.101835. Epub 2020 May 25. PMID: 32464267.

[28] Peters, M. D. J., Godfrey, C., McInerney, P., Munn, Z., Tricco, A. C., & Khalil, H. (2020). Chapter 11: Scoping Reviews (2020 version). In E. Aromataris & Z. Munn (Eds.), *JBI Manual for Evidence Synthesis*. JBI. Available from https://synthesismanual.jbi.global. https://doi.org/10.46658/JBIMES-20-12.

[29] Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L. A., & PRISMA-P Group (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ (Clinical research ed.), 350*, g7647. https://doi.org/10.1136/bmj.g7647

[30] Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., Lewin, S., … Straus, S. E. (2018). PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Annals of internal medicine, 169*(7), 467–473. https://doi.org/10.7326/M18-0850

[31] OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 3.01. (2013). Retrieved from https://www.openepi.com. (accessed 15 March 2024).

[32] Abramoff, M.M.F., Pereira, M. D., de Seixas Alves, M. T., Segreto, R. A., Guilherme, A., & Ferreira, L. M. (2014). Low-level laser therapy on bone repair of rat

tibiae exposed to ionizing radiation. *Photomedicine and laser surgery*, *32*(11), 618–626. https://doi.org/10.1089/pho.2013.3692

[33] Batista, J. D., Zanetta-Barbosa, D., Cardoso, S. V., Dechichi, P., Rocha, F. S., & Pagnoncelli, R. M. (2014). Effect of low-level laser therapy on repair of the bone compromised by radiotherapy. *Lasers in medical science*, *29*(6), 1913–1918. https://doi.org/10.1007/s10103-014-1602-8

[34] Bernaola-Paredes, W. E., Veronese, H. R. M., Bella Filho, V., Martins, I. S., & Pellizzon, A. C. A. (2021). Conservative management of advanced mandibular osteoradionecrosis with mild clinical presentation after 17 years of oncological treatment: A case report. *International Journal of Case Reports and Images, 12*. doi: 10.5348/101206Z01WP2021CR

[35] Camolesi, G. C., Ortega, K. L., Medina, J. B., Campos, L., Lorenzo Pouso, A. I., Gándara Vila, P., & Pérez Sayáns, M. (2021). Therapeutic alternatives in the management of osteoradionecrosis of the jaws. Systematic review. *Medicina oral, patologia oral y cirugia bucal*, *26*(2), e195–e207. https://doi.org/10.4317/medoral.24132

[36] Da Cunha, S. S., Sarmento, V., Ramalho, L. M., De Almeida, D., Veeck, E. B., Da Costa, N. P., Mattos, A., Marques, A. M., Gerbi, M., & Freitas, A. C. (2007). Effect of laser therapy on bone tissue submitted to radiotherapy: experimental study in rats. *Photomedicine and laser surgery*, *25*(3), 197–204. https://doi.org/10.1089/pho.2007.2002

[37] de Freitas, L. C., Kawamoto, E. L., Souza, A. M. A., Kawakami, P. Y., Gonçalves, A. S., & Azevedo, L. H. (2023). Use of Phototherapy and Er-YAG Laser in the Management of Mandible Osteoradionecrosis: A Case Report. *Journal of lasers in medical sciences*, *14*, e58. https://doi.org/10.34172/jlms.2023.58

[38] de Oliveira, S. V., Dos Reis, T., Amorim, J., Rocha, F. S., Marques, M. M., Guerra, E. S., Hanna, R., & Gallo, C. B. (2022). Efficacy of photobiomodulation therapy on healing of ionizing irradiated bone: a systematic review of in vivo animal studies. *Lasers in medical science*, *37*(9), 3379–3392. https://doi.org/10.1007/s10103-022-03649-2

[39] Ferreira, K. D. M., Corrêa, P. D., Balenzio, G. R., Pigatti, F. M., Ferreira, D. D. C., & Tannure, P. N. (2019). Osteoradionecrosis in a Patient Submitted to Head and Neck Radiotherapy: A Case Report. *International Journal of Odontostomatology, 13*(4), 428-432. doi: http://dx.doi.org/10.4067/S0718-381X2019000400428

[40] Freire, M. R. S., Almeida, D., Santos, J. N., & Sarmento, V. A. (2010). The photobiomodulation in the bone repair after radiotherapy: experimental study in rats. In *Proceedings of SPIE 7552, Mechanisms for Low-Light Therapy V* (p. 75520H). doi: 10.1117/12.842314

[41] Palma, L. F., Marcucci, M., Remondes, C. M., & Chambrone, L. (2021). Antibiotic therapy for the prevention of osteoradionecrosis following tooth extraction in head-and-neck cancer patients postradiotherapy: An 11-year retrospective study. *National journal of maxillofacial surgery*, *12*(3), 333–338. https://doi.org/10.4103/njms.njms_413_21

[42] Ribeiro, G. H., Minamisako, M. C., Rath, I. B. D. S., Santos, A. M. B., Simões, A., Pereira, K. C. R., & Grando, L. J. (2018). Osteoradionecrosis of the jaws: case series treated with adjuvant low-level laser therapy and antimicrobial photodynamic therapy. *Journal of applied oral science: revista FOB*, *26*, e20170172. https://doi.org/10.1590/1678-7757-2017-0172

[43] El-Maghraby, E. M., El-Rouby, D. H., & Saafan, A. M. (2013). Assessment of the effect of low-energy diode laser irradiation on gamma irradiated rats' mandibles. *Archives of oral biology*, *58*(7), 796–805. https://doi.org/10.1016/j.archoralbio.2012.10.003

[44] Korany, N. S., Mehanni, S. S., Hakam, H. M., & El-Maghraby, E. M. (2012). Evaluation of socket healing in irradiated rats after diode laser exposure (histological and morphometric studies). *Archives of oral biology*, *57*(7), 884–891. https://doi.org/10.1016/j.archoralbio.2012.01.009

[45] Moreschi, C., Capparè, P., Meleti, M., Vescovi, P., Bonanini, M., Gherlone, E. F., et al. (2016). Low level laser therapy in non-surgical management of osteoradionecrosis of the jaws. *Minerva Stomatologica, 65*.

[46] Farkas, J. P., Hoopman, J. E., & Kenkel, J. M. (2013). Five parameters you must understand to master control of your laser/light-based devices. *Aesthetic surgery journal*, *33*(7), 1059–1064. https://doi.org/10.1177/1090820X13501174

[47] Carroll, L., & Humphreys, T. R. (2006). LASER-tissue interactions. *Clinics in dermatology*, *24*(1), 2–7. https://doi.org/10.1016/j.clindermatol.2005.10.019

[48] Borsatto, M. C., Correa-Afonso, A. M., Lucisano, M. P., Bezerra da Silva, R. A., Paula-Silva, F. W., Nelson-Filho, P., & Bezerra da Silva, L. A. (2016). One-session root canal treatment with antimicrobial photodynamic therapy (aPDT): an in vivo study. *International endodontic journal*, *49*(6), 511–518. https://doi.org/10.1111/iej.12486

[49] Dharmaratne, P., Wang, B., Wong, R. C. H., Chan, B. C. L., Lau, K. M., Ke, M. R., Lau, C. B. S., Ng, D. K. P., Fung, K. P., & Ip, M. (2020). Monosubstituted tricationic Zn(II) phthalocyanine enhances antimicrobial photodynamic inactivation (aPDI) of methicillin-resistant *Staphylococcus aureus* (MRSA) and cytotoxicity evaluation for topical applications: *in vitro* and *in vivo* study. *Emerging microbes & infections*, *9*(1), 1628–1637. https://doi.org/10.1080/22221751.2020.1790305

[50] Pérez-Laguna, V., , Gilaberte, Y., , Millán-Lou, M. I., , Agut, M., , Nonell, S., , Rezusta, A., , & Hamblin, M. R., (2019). A combination of photodynamic therapy and antimicrobial compounds to treat skin and mucosal infections: a systematic review. *Photochemical & photobiological sciences: Official journal of the European Photochemistry Association and the European Society for Photobiology*, *18*(5), 1020–1029. https://doi.org/10.1039/c8pp00534f

[51] Palma, L. F., Marcucci, M., Remondes, C. M., & Chambrone, L. (2020). Leukocyte- and platelet-rich fibrin does not provide any additional benefit for tooth extraction in head and neck cancer patients post-radiotherapy: a randomized clinical trial. *Medicina oral, patologia oral y cirugia bucal*, *25*(6), e799–e804. https://doi.org/10.4317/medoral.23804

[52] Porcaro, G., Amosso, E., Mirabelli, L., Busa, A., Carini, F., & Maddalone, M. (2015). Osteoradionecrosis of the posterior maxilla: A new approach combining erbium aluminium garnet laser and Bichat bulla flap. *The Journal of Craniofacial Surgery, 26*(7). doi: 10.1097/SCS.0000000000002136

[53] Qualliotine, J. R., Yousef, A., Orosco, R. K., Fugere, M., Kolb, F. J., Kristallis, T., & Archambault, K. (2023). Carbon Dioxide Laser Sequestrectomy for Osteoradionecrosis: A Case Series. *Photobiomodulation, photomedicine, and laser surgery*, *41*(2), 73–79. https://doi.org/10.1089/photob.2022.0090

[54] Hohmann, M., Kühn, D., Ni, D., Späth, M., Ghosh, A., Rohde, M., Stelzle, F., Klämpfl, F., & Schmidt, M. (2024). Relevant parameters for laser surgery of soft tissue. *Scientific reports*, *14*(1), 1263. https://doi.org/10.1038/s41598-024-51449-1

[55] Meleca, J. B., Zhang, E., Fritz, M. A., & Ciolek, P. J. (2021). Overview and emerging trends in the treatment of osteoradionecrosis. *Current Treatment Options in Oncology, 22*(115). doi: 10.1007/s11864-021-00915-3

SUPPLEMENTARY FILES

Appendix A. Search strategies with appropriate key words and MeSH terms.

Database	Search strategy (search date: September 20nd, 2023/ updated date: January 15th, 2024)	Number of Results
MEDLINE/ PubMed	Search: ("osteoradionecrosis"[MeSH Terms] OR ("osteoradionecrosis"[MeSH Terms] OR "osteoradionecrosis"[All Fields] OR "osteoradionecroses"[All Fields]) OR "Radiation Injuries"[All Fields] OR "Osteoradionecroses" OR "Jaw osteoradionecrosis" OR "Jaws osteoradionecrosis" OR " Bone Necrosis" OR "Exposed bone" OR "ORNJ") AND ("Laser Therapy"[MeSH Terms] OR "low level light therapy"[MeSH Terms] OR "photobiomodulation"[All Fields] OR "phototherapy laser"[All Fields] OR "Laser Biostimulation"[All Fields] OR "low level light therapy"[All Fields] OR "Low-Level Light Therapies"[All Fields] OR "Low Level Laser Therapy"[All Fields] OR "LLLT"[All Fields])	358 (2024, Jan, 15)
Embase	'osteoradionecrosis'/exp OR 'osteoradionecrosis' OR 'radiation injury'/exp OR 'radiation injury' OR 'osteoradionecroses' OR 'jaw osteoradionecrosis' OR 'jaws osteoradionecrosis' OR 'bone necrosis'/exp OR 'bone necrosis' OR 'exposed bone' OR 'ornj' AND 'laser therapy'/exp OR 'laser therapy' OR 'phototherapy laser' OR 'laser biostimulation'/exp OR 'laser biostimulation' OR 'low level light therapy'/exp OR 'low level light therapy' OR 'low-level light therapies' OR 'low level laser therapy'/exp OR 'low level laser therapy' OR 'lllt'	603 (2024, Jan, 15)
Web of Science	(ALL=(("osteoradionecrosis" OR "osteoradionecrosis" OR "osteoradionecrosis" OR "Radiation Injuries" OR "osteoradionecrosis" OR "Jaw osteoradionecrosis" OR "Jaws osteoradionecrosis" OR " Bone Necrosis" OR "Exposed bone" OR "ornl"))) AND ALL=("Laser Therapy" OR "low level light therapy" OR "photobiomodulation" OR "phototherapy laser" OR "Laser Biostimulation" OR "low level light therapy" OR "Low-Level Light Therapies" OR "Low Level Laser Therapy" OR "LLLT")	33 (2024, Jan, 15)
Google Scholar	osteoradionecrosis AND Laser Therapy	100 (2024, Jan, 15)

ProQuest Dissertations & Theses	osteoradionecrosis AND Laser Therapy	7 (2024, Jan, 15)
Total		1101

Appendix B. Summary of overall descriptive characteristics of included studies

Table 1 - Summary of overall descriptive characteristics of *in vivo* included studies (n= 6)

Author, Year, Country	Laser use Indication (Therapeutic or Prevention)	Radiotherapy Dose (Gy)	Evaluation	Animals and Experimental Groups	Main Result OR Conclusions
Abramoff et al., 2014 Brazil	Therapeutic	30: gamma radiation (single session) Local of irradiation: Tibiae Surgery: 28 days after IR Bone defect surgically created: 2.5 mm	Bone neoformation assessment by histomorphometry and digital image analysis; Evaluated on days 7, 14 and 21 after surgery	Male Albino Wistar rats (*Rattus norvegicus*) (N=72) Age: Young adult (between 90 and 105 days of age) Group I: sham control (n=18); Group II: LLLT (n=18); Group III: irradiated with IR (n=18); Group IV, irradiated with IR and LLLT (n=18).	LLLT increased the newly formed bone area during the initial phase of the tibial repair process in rats exposed to IR. Results: "No significant differences were observed between Group I and Group IV" and "Significant increases in newly formed bone were noted in Group IV compared with Group III"
Batista et al., 2014 Brazil	Therapeutic	30: gamma radiation (single session) Local of irradiation: Femur and tibia Surgery: 4 weeks after surgery	Influence of LLLT on femur repair after ionizing radiation Bone neoformation assessment Morphometrically with conventional microscopy Evaluated 7 days after surgery	Healthy male Wistar rats (*Rattus novergicus*) (N=20) Age: NR Control group (GC): animals with bone defects (BDs) only	Punctual application of the laser immediately after surgery, with an interval of 48 hours for 7 days; LLLT had a local bio stimulating effect on the normal bone but could not reverse bone metabolic damage due to ionizing radiation.

		Bone defect surgically created: 2.3 mm		(n=5); Laser group (GL): animals with BD and the application of LLLT (n=5); Radiotherapy group (GR): animals previously submitted to ionizing radiation and with BD (n=5); Radiotherapy and laser group (GRL): animals previously submitted to ionizing radiation, with BD and applying LLLT (n=5).	
Da Cunha et al., 2007 Brazil	Therapeutic and Prevention	30: gamma radiation (single session) Local of irradiation: Femur Bone defect surgically created: NR	Effect of LLLT on bone tissue submitted to IR by radiographic and histological analysis Evaluated one day before radiotherapy, on the same day as radiotherapy, and at 4 weeks after radiotherapy	Male *Wistar Albinus* rats (N=22) Age: Young adult Group I: control submitted only to IR (n=4); Group II: IR D0 + PBMT laser treatment starting 1 day before radiotherapy (n=6); Group III: IR D0 + PBM D0 (n=6);	Laser therapy on bone tissue in rats presented a positive bio stimulation effect, especially when applied before or 4 weeks after radiotherapy. However, “the use of laser at the parameters described above should be handled with caution due to epithelial erosions”

				Group IV: IR D0 + PBM D28 (n=6); 6 weeks after ionizing radiation all animals from all groups were euthanized	
El-Maghraby et al., 2013 Egypt	Therapeutic and Prevention	6: gamma radiation (2 Gy every 3 sessions during 3 consecutive days) Local of irradiation: Left side of the jaw	To evaluate the bio stimulation and regenerative effects of LLLT (applied before or after initiation of radiotherapy) on gamma-irradiated rats' jaw bones by histological, histomorphometric, and scanning electron microscopic examination Evaluated on days 3, 7, 14, and 21 after IR	Male Swiss Albino rats (150–200g) (N=48) Age: NR Group 1: left side of the mandible with PBM + IR in day 7 (D7) (n=24) Group 2: left side of the mandible with IR + PBM in day 4 (D4) (n=24) Control group: the right jaw of all animals Six animals from each group were euthanized on days 3, 7, 14, and 21 after IR	LLLT seemed to attenuate the radiation-related damage in alveolar bones.
Freire et al., 2010 Brazil	Therapeutic	30: gamma radiation (single session, four days after surgery)	To evaluate the effect of the GaAlAs photobiomodulation in the healing of surgical wounds produced in Wistar rats' femurs, a few days	Male Wistar rats (*Rattus norvegicus albinus, Rodentia mammalia*) (N=16)	PBMT after surgery involving bone tissue before IR stimulates the bone and the repair of surgical wounds repair process.

		Local of irradiation: Femur Surgery: Day zero Bone defect surgically created: 1 cm	before the beginning of the radiotherapy by histological examination. Evaluated on 3 and 5 weeks	Age: Young adult Group I (blue): Surgical bone defect (femur) D0 + PBMT D0 + IR D4 (n=5) - sacrificed after three weeks; Group II (red): Surgical bone defect (femur) D0 + PBM D0 + IR D4 (n=5) - sacrificed after five weeks; Group III (black): Surgical bone defect (femur) D0 + IR D4 (n=3) - sacrificed after three weeks; Group IV (green): Surgical bone defect (femur) D0 + IR D4 (n=3) - sacrificed after five weeks.	
Korany et al., 2012 Egypt	Prevention	6: gamma radiation (single session) Local of irradiation: Whole body Surgery: 3 days	To assess the effect of LLLT in ameliorating bone repair in irradiated sockets of albino rats by histological and histomorphometry analysis Evaluated on days 3, 7, and 10 after tooth extraction.	Male Swiss Albino rats (120-150g) (N=30) Age: NR Group I: IR + tooth extraction in	LLLT with a GaAIAs diode laser in a rat model device can enhance bone healing and mineralization in sockets subjected to gamma radiation.

	post-IR. Both right and left mandibular first molars were extracted. Bone defect surgically created: First molar extraction	D3 + PBM left side in D3 (n=10); Group II: IR + tooth extraction in D3 + PBM left side in D3 (n=10); Group III: IR + tooth extraction in D3 + PBM left side in D3 (n=10); The animals were sacrificed 3 (Group I), 7 (Group II), and 10 days (Group III) after tooth extraction.	

Abbreviations: Day zero (D0); Day three (D3); Day four (D4); Day seven (D7); Gallium-aluminum-arsenide laser (GaAlAs); Grams (mg); Gray (Gy); Ionizing radiation (IR); Low-level laser therapy (LLLT); Photobiomodulation therapy (PBMT).

Table 2 - Summary of overall descriptive characteristics of Case report or Series Case Report included studies (n= 11)

Author, Year, Country	Laser use Indication (Therapeutic or Prevention)	Radiotherapy Dose (Gy)	Cancer Type	Clinical Characteristics	Associated Treatments to Low-Level Laser Therapy	Follow-up time	Main Result OR Conclusions
Bernaola-Paredes et al., 2021 Brazil	Therapeutic	54 (primary lesion) 45 (homolateral lymphatic neck drainage) associated with CMT	OSCC (left side of the floor of the mouth) - "did not involve the bone/periosteum/cortex or medullary portion of the mandible"	62-year-old Afro-descendent woman; Cancer stage: pT1N0M0; Cancer diagnosis: 2004; ORN diagnosis: 2020 - ORN classified as advanced Complaints: Toothache (tooth 47) and prosthetic rehabilitation performed with dental implants	Antibiotic therapy (Amoxicillin + Clavulanic acid 500 mg; every 8 hours for 15 days); AINE therapy (Nimesulide 100 mg; every 12 hours for 4 days) Antifibrotic therapy (PENTO protocol - 400 mg of pentoxifylline twice daily plus 500 UI tocopherol - twice daily for 7 months); aPDT: Methylene Blue dye (concentration of 0.02% for 5 minutes); Surgical treatment: extraction of tooth	12 months	PENTO protocol proved to be effective in stabilizing the lesion in an advanced stage of ORN associated with adjuvant therapies and surgical treatment.

					33 and superficial sequestrectomy.		
Campos et al., 2021 Brazil	Therapeutic	70 with CMT	OSCC (mandible)	57-year-old woman; Cancer diagnosis: 2019; ORN diagnosis: 2020 Complaint: Pain arising from the mandibular mucosa	Antibiotic therapy (Amoxicillin 500 mg – three times a day, for seven days) aPDT (every 15 days for six weeks; 0.5 mL of methylene blue at a 0.01 % concentration)	6 weeks	PBMT and aPDT with an optical fiber to deliver the laser light seem to be a suitable alternative for restricted areas such as fistula paths.
de Freitas et al., 2023 Brazil	Therapeutic	66.6	OSCC (left cervical)	59-year-old female; Cancer diagnosis: 2013; ORN diagnosis: 2021 (8 years after the cancer diagnosis) Complaints: pain in the mandibular region	Surgical treatment: Sequestromy bone aPDT (methylene blue at a 0.01 % concentration for 5 minutes)	11 months	LLLT and HLLT treatment can be an effective therapeutic alternative to resolve ORN.

				associated with the extraoral lesion sought dental care (after dental extractions and surgery installation of five morse taper implants in the mandible)			
Ferreira et al., 2019 Brazil	Therapeutic	70.2 with CMT	OSCC (floor of the mouth)	41-year-old male; chronic alcoholic and active smoker, with depression Cancer diagnosis: 2014; ORN diagnosis: 2016 Complaints: Intensive pain, trismus, and persistent infection in the left jaw region (after third molar extraction)	Surgical treatment: partial mandibulectomy with mandibular reconstruction Antibiotic therapy (Cephalexin 500 mg every 6 hours, for 7 days; Metronidazole 400 mg, every 8 hours, for 7 days; Cephalothin, 1 g, every 6 hours, for 7 days); Mouthwashes (Chlorhexidine 0.12 %, 3 times a day, for 14 days); Analgesic (dipyrone	6 months	The patient died before ORN control was achieved, due to a heart attack.

					sodium 500 mg, if pain).		
Franco et al., 2017 Brazil	Prevention	70	MEC (left parotid gland)	16-year-old female Cancer diagnosis: 2011; ORN diagnosis: NA Follow-up since the 11 years old	Antibiotic therapy (Amoxicillin + clavulanic acid 875mg, 2 times a day, for 14 days); Antifibrotic therapy (Pentoxifylline 400mg, 2 times a day, for 8 weeks) and tocopherol (1000U) once daily was started 1 week before the extractions for 8 weeks.); AINE therapy (Nimesulide 1000U, 1h before the surgery and continued for 3 days); Mouthwashes (Chlorhexidine 0.12%); Surgical treatment: extraction of elements 36, 37 e	1 year	The protocol used was efficient in preventing ORN in this adolescent. One year after the extractions, there were no clinical or radiographic signs of any pathological alteration in the region.

					38; Other treatment: Use Platelet Rich Fibrin (L-PRF)		
Magalhães et al., 2020 Brazil	Therapeutic and Prevention	70 + Surgery (for the primary tumor) and 46−60 (for high-risk areas).	OSCC (floor of the mouth)	58-years-old man, Cancer diagnosis: NR; ORN diagnosis: NR Complaints: Xerostomia and severe tooth-ache Clinical examination: "Necrotic bone in the mandibular anterior region associated with intraoral fistula and purulent exudation"	Surgical treatment: removal of necrotic bone, root remnants in proximity to the ORN area and, extraction of non-rehabilitated teeth (14 teeth); Antibiotic therapy (Amoxicillin 500 mg + metronidazole 250 mg; 7 days, every 8 hours; starting 24h before the surgery); Mouthwashes (Chlorhexidine 0.12%), aPDT (methylene blue at a 0.01 % concentration)	More than 12 months	The adjuvant therapy combining aPDT and LLLT with minimally invasive surgical procedures and antibiotic therapy was successful in the treatment and prevention of ORN in our patient after radiotherapy, without recurrence or new lesion emergence after 1-year of follow-up.
Moreschi et al., 2016	Therapeutic	NR	OSCC (oropharyngeal and tongue)	65-year-old, male	Antibiotic therapy (Amoxicillin 875 mg, Clavulanic acid	12 months	LLLT in association with systemic

Italy					Cancer diagnosis: 2005 ORN diagnosis: 2010 Complaint: Pain in the left part of his lower-jaw	125 mg: 1 tablet every 12 hours; Metronidazole 250mg, 15 days, every 6 hours); Surgical treatment: emimandibulectomy without surgical reconstruction		antibiotic therapy could represent a conservative treatment, without potential side effects, in patients with contraindication to surgery as for systemic disease, as for local-regional complications.
Palma et al., 2021 Brazil	Case 1: Prevention Case 2: Prevention	Case 1: 66 Case 2: 70	Case 1: EMC (parotid gland) Case 2: OSCC	Case 1: 53-year-old Afro-descendant man Cancer diagnosis: NR; ORN diagnosis: NR Case 2: 56-year-old Caucasian, man Cancer diagnosis: NR; ORN diagnosis: NR	Case 1: Antibiotic therapy (preoperative: Clindamycin 300 mg; 10 days, every 8 hours) Case 2: Antibiotic therapy (preoperative: Clindamycin 300 mg; 10 days, every 8 hours)	Case 1: 5 years Case 2: 3 years	Perioperative systemic antibiotic therapy protocol seems to be efficient in preventing ORN following tooth extraction in post irradiated head and neck cancer patients.

Pedroni et al., 2020 Brazil	Therapeutic	50 (bilateral lymphatic drainages) 70 (tumor and positive lymph nodes) with CMT	OSCC (laryngeal cancer)	57-year-old male Cancer diagnosis: 2015; ORN diagnosis: 2017 Complaint: "Dry mouth" and pain in the region where a tooth was extracted	Antibiotic therapy (Amoxicillin 500 mg; 7 days, every 8 hours); Analgesic (Dipyrone 500 mg; 7 days) aPDT (methylene blue at a 0.01 % concentration) Surgical treatment: tooth extractions	6 months	The combined PBMT and aPDT therapies proved to be efficient for controlling ORN clinical lesion and for the improvement of the painful symptomatology in the region.
Ribeiro et al., 2018 Brazil	Therapeutic	66 - 92	Leukoderma and melanoderma	20 patients (both men and woman, 40 to 71 years old, the mean age was of 59.1 years) Cancer diagnosis: NR; ORN diagnosis: after 24 months.	aPDT (methylene blue 0.01%)	2 years	LLLT and aPDT showed positive results as adjuvant therapy to treat ORN.
Tateno et al., 2020 Brazil	Prevention	70 + CMT	OSCC (tongue base)	62-year-old man, Cancer diagnosis: NR;	Antibiotic therapy (Clindamycin 600 mg an hour	12 months	PMBT and aPDT were essential to improve

			ORN diagnosis: time. One year after the end of the cancer treatment.	before surgery and maintained 300 mg, 4 times daily, for only 7 days) Surgical treatment: tooth extractions; aPDT (methylene blue 0.01% for 3 minutes)	delayed healing following multiple extractions in the post-IR patient, been capable to preventing ORN development.

Abbreviations: Adenoid cystic carcinoma (ACC); Antimicrobial photodynamic therapy (aPDT); Chemotherapy (CMT); Epithelial–myoepithelial carcinoma (EMC); Gray (Gy); Ionizing radiation (IR); Low-level laser therapy (LLLT); Milligrams (mg); Mucoepidermoid Carcinoma Tumor (MEC); Not Applicable (NA); Oral squamous cell carcinoma (OSCC); Osteoradionecrosis (ORN); Photobiomodulation therapy (PBMT).

Table 3 - Summary of overall descriptive characteristics of Systematic Review included studies (n= 2)

Author, Year, Country	Number of studies included	Design of included studies	Number of laser studies	Risk of bias in laser studies	Sample size	Laser use Indication (Therapeutic or Prevention)	Analysis	Conclusions
Camolesi et al., 2021 Brazil	110	Case series, case reports, cohort studies, and case and control studies	1 (Ribeiro et al., 2018)	Medium	20 (patients)	Therapeutic associated with aPDT	The laser study was not included in the analysis	Combined surgical and/or pharmacological treatment is the indicated treatment for improve the prognosis of ORN.
de Oliveira et al., 2022 Brazil	6	Preclinical interventional studies with a control group *(in vivo*)	6 (Abramof et al., 2014, Batista et al., 2014, Da Cunha et al., 2007, El-Maghraby et al., 2013, Freire et al., 2011, Korany et al., 2012)	Low	208 (rats)	Therapeutic and Prevention	First outcome: to evaluate the effects of PBMT on the prevention of bone damage triggered by the ionizing radiation; Second outcome: to evaluate the effects of PBMT on the healing process of the irradiated bone after surgical intervention.	PBMT shows promise in improving bone healing after exposure to ionizing radiation.

Abbreviations: Antimicrobial Photodynamic Therapy (aPDT); Low-level laser therapy (LLLT); Osteoradionecrosis (ORN); Photobiomodulation therapy (PBM

Appendix C. Excluded articles and reasons for exclusion (n=36).

	Author/Year	Reason for Exclusion
1	Ajila and Hegde, 2020	1
2	Arya, Hall, and Patel, 2023	1
3	Cumbo and Scardina, 2019	4
4	de Bataille et al., 2017	1
5	de Carvalho et al., 2018	3
6	De Castro et al., 2020	3
7	de Lima Dantas and Reis, 2019	3
8	De Sousa-Neto et al., 2022	3
9	Desmons et al., 2010	1
10	Direttore, 2016	4
11	Epstein et al., 2018	3
12	Ferigatto et al., 2022	3
13	Franco et al., 2017 (b)	3
14	Gomes et al., 2022	3
15	Grando et al., 2015	3
16	Granström et al., 1992	4
17	Granström et al., 1993	4
18	Klausner et al., 2021	1
19	Kün-Darbois and Fauvel, 2021	3
20	Lima, 2022	3
21	Manné and Thevenot, 1986	4
22	Martins et al., 2021	2
23	Minamisako et al., 2014	3
24	Patel et al., 2022	4
25	Penha et al., 2017	3
26	Porcaro et al., 2015	1
27	Qualliotine et al., 2023	1
28	Rayan et al., 1992	1
29	Robijns et al., 2022	3
30	Siddiqui and Movsas, 2017	1
31	Southerland and Patton, 1993	1
32	Tomazelli et al., 2020	3
33	Urquhart et al., 2022	1
34	Vahidi et al., 2020	3
35	van Baar et al., 2021	1
36	Vescovi et al., 2023	4

1. Studies in which laser therapy, photobiomodulation and/or photodynamic therapy was not used for osteoradionecrosis (n= 10);
2. Studies that evaluated medication-related osteonecrosis (n= 1);
3. Conference abstract, letter to editor, and narrative reviews (n= 16);

4. Full paper copy not available, even after attempts to contact the corresponding authors (n= 7).

References

1. Ajila, V and S. Hegde. *Osteoradionecrosis - a Review of Clinical Features and Management.* Feb. 2020, pp. 213–3. *Gülhane Medical Journal*, https://doi.org/DOI: 10.4274/gulhane.galenos.2020.1076.

2. Arya, R., et al. *Histopathological Insight into a Healed Case of Osteoradionecrosis Treated with Triple Therapy Medical Management*. no. 1, Feb. 2023, pp. 33–37. *Oral Surgery*, https://doi.org/10.1111/ors.12839.

3. Cumbo, E.and G. A. Scardina. *Osteoradionecrosis of the jaw after head/neck radiotherapy: causes and management*. no. 4, Feb. 2019, pp. 349–56. *International Journal of Clinical Dentistry*.

4. de Bataille, C., et al. *Management of Radiation-induced Mucosal Necrosis with Photobiomodulation Therapy.* no. 8, Feb. 2017, pp. 2491–92. *Supportive Care in Cancer*, https://doi.org/10.1007/s00520-017-3899-x.

5. de Carvalho, E. L. F., et al. The *Use of Photodynamic Therapy (Pdt) in Osteoradionecrosis of the Maxilla in a Patient in Palliative Care – A Case Report in the Northeastern Countryside of Brazil*. no. 6, Feb. 2018, pp. e81–82. *Journal of Pain and Symptom Management*, https://doi.org/10.1016/j.jpainsymman.2018.10.295.

6. De Castro, F. S., et al. *Prevention protocol of osteoradionecrosis after radiotherapy of the head and neck: bimodal treatment*. no. 1, Feb. 2020, p. e46. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, https://doi.org/10.1016/j.oooo.2019.06.154.

7. de Lima Dantas, J. B.and J. V. Neri Andrade Reis. *New Therapeutic Approaches to Osteoradionecrosis: Literature Review*. no. 3, Sept. 2019, pp. 243–49. *Journal Health Science*, https://doi.org/https://doi.org/10.17921/2447-8938.2019v21n3p243-249.

8. De Sousa-Neto, S. S., et al. *Photodynamic therapy as resource to control osteoradionecrosis in alveolar bone: a case report*. no. 3, Feb. 2022, p. e158. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, https://doi.org/10.1016/j.oooo.2022.01.415.

9. Desmons, S. O., et al. *Laser Preconditioning on Cranial Bone Site: Analysis of Morphological Vascular Parameters*. Oct. 2010, pp. 631–37. *Lasers in Surgery and Medicine*, https://doi.org/DOI 10.1002/lsm.20971.

10. Direttore, E. *Low Level Laser Therapy in Nonsurgical Management of Osteoradionecrosis of the Jaws*. May 2016, pp. 186–87. *Minerva Stomatologica*.

11. Epstein, Joel B et al. Management of radiation-induced mucosal necrosis with photobiomodulation therapy. *Supportive care in cancer: official journal of the*

Multinational Association of Supportive Care in Cancer vol. 26,8 (2018): 2493. doi:10.1007/s00520-018-4228-8.

12. Ferigatto, J. L., et al. *Antimicrobial photodynamic therapy: an alternative for the treatment of osteoradionecrosis*. Feb. 2022, pp. S105–06. *Supportive Care in Cancer*.

13. FRANCO, T., et al. *Prevention of osteoradionecrosis in an adolescent: case report*. no. 2, Aug. 2017, pp. E79–80. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, https://doi.org/https://doi.org/10.1016/j.oooo.2017.05.103.

14. Gomes, M. F. C., et al. *Mandibular osteoradionecrosis in a patient subjected to oncological treatment: case report*. no. 3, Sept. 2022, p. e171. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, https://doi.org/10.1016/j.oooo.2022.01.484.

15. GRANDO, L. J., et al. *Osteoradionecrosis Handling with Low-level Laser Therapy Support*. no. 2, Aug. 2015, p. E74. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, https://doi.org/https://doi.org/10.1016/j.oooo.2015.02.324.

16. Granström, G., et al. *Aspects on the Management of Patients with Osteoradionecrosis After Therapy of Head and Neck Cancer*. no. 0, Feb. 1992, pp. 163–69.

17. Granström, G., et al. *A Prospective Study of Osteoradionecrosis Therapy*. no. 0, Feb. 1993, pp. 121–5.

18. Klausner, G et al. "État de l'art de la photobiomodulation dans la prise en charge des effets secondaires de la radiothérapie: indications et niveaux de preuve" [State of art of photobiomodulation in the management of radiotherapy adverse events: Indications and level of evidence]. *Cancer radiotherapie: journal de la Societe francaise de radiotherapie oncologique* vol. 25,6-7 (2021): 584-592. doi:10.1016/j.canrad.2021.06.025.

19. Kün-Darbois, J-D, and F Fauvel. *Medication-related osteonecrosis and osteoradionecrosis of the jaws: Update and current management*. Morphologie: bulletin de l'Association des anatomistes vol. 105,349 (2021): 170-187. doi:10.1016/j.morpho.2020.11.008

20. Lima, R. *Photobiomodulation and Antimicrobial Photodynamic Therapy as Adjunct in the Prevention and Treatment of Osteonecrosis of the Jaws*. no. 9, Feb. 2022, pp. 3767–82. *Lasers in Medical Science*, https://doi.org/10.1007/s10103-022-03623-y.

21. Manné, J and A. Thevenot. *The Fight Against Pain in Various Cases of Osteoradionecrosis in a Hospital Setting*. no. 346, Sept. 1986, pp. 49–51. *Chirurgien-Dentiste de France*.

22. Martins, Fabiana et al. "Photobiomodulation and antimicrobial photodynamic therapy for the prevention of osteonecrosis of the jaw in an oncologic patient." *Photodiagnosis and photodynamic therapy* vol. 36 (2021): 102587. doi:10.1016/j.pdpdt.2021.102587.

23. Minamisako, M. C., et al.. *Osteoradionecrosis Management with Low-level Laser Therapy Support*. Feb. 2014. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology*, https://doi.org/DOI:10.1016/J.OOOO.2013.12.168.

24. Patel, V., et al. *Osteoradionecrosis in the Current Era of Radiation Treatment*. no. 1, Jan. 2022, pp. 64–67. *Dental Update*, https://doi.org/https://doi.org/10.12968/denu.2022.49.1.64.

25. PENHA, S. S., et al. *Treatment of osteoradionecrosis of the jaw with laser therapy and surgical debridement: case report*. no. 2, Aug. 2017, p. e86. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology*, https://doi.org/10.1016/j.oooo.2017.05.136.

26. Porcaro, Gianluca et al. *Osteoradionecrosis of the Posterior Maxilla: A New Approach Combining Erbium: Yttrium Aluminium Garnet Laser and Bichat Bulla Flap*. *The Journal of craniofacial surgery* vol. 26,7 (2015): e627-9. doi:10.1097/SCS.0000000000002136

27. Qualliotine, Jesse R et al. *Carbon Dioxide Laser Sequestrectomy for Osteoradionecrosis: A Case Series*. *Photobiomodulation, photomedicine, and laser surgery* vol. 41,2 (2023): 73-79. doi:10.1089/photob.2022.0090

28. Rayan, G M et al. "Effects of rapid pulsed CO2 laser beam on cortical bone in vivo." *Lasers in surgery and medicine* vol. 12,6 (1992): 615-20. doi:10.1002/lsm.1900120608.

29. Robijns, Jolien et al. *Photobiomodulation therapy in management of cancer therapy-induced side effects: WALT position paper 2022*. *Frontiers in oncology* vol. 12 927685. 30 Aug. 2022, doi:10.3389/fonc.2022.927685.

30. Siddiqui, Farzan, and Benjamin Movsas. "Management of Radiation Toxicity in Head and Neck Cancers." *Seminars in radiation oncology* vol. 27,4 (2017): 340-349. doi:10.1016/j.semradonc.2017.04.008.

31. Southerland, J H, and L L Patton. Management of spontaneous osteoradionecrosis: a case report. *Special care in dentistry: official publication of the American Association of Hospital Dentists, the Academy of Dentistry for the Handicapped, and the American Society for Geriatric Dentistry* vol. 13,5 (1993): 200-4. doi:10.1111/j.1754-4505.1993.tb01496.x.

32. Tomazelli, K. B., et al. *OSTEORADIONECROSIS OF THE JAWS: A RETROSPECTIVE STUDY OF CASES AND TREATMENTS IN A HOSPITAL DENTISTRY SERVICE*. no. 3, Sept. 2022, p. e125. *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology*, https://doi.org/10.1016/j.oooo.2022.01.240.

33. Urquhart, Olivia et al. Effect of preradiation dental intervention on incidence of osteoradionecrosis in patients with head and neck cancer: A systematic review and meta-analysis. *Journal of the American Dental Association (1939)* vol. 153,10 (2022): 931-942.e32. doi:10.1016/j.adaj.2022.06.003.

34. Vahidi, Nima et al. *Osteoradionecrosis of the Midface and Mandible: Pathogenesis and Management. Seminars in plastic surgery* vol. 34,4 (2020): 232-244. doi:10.1055/s-0040-1721759.

35. van Baar, Gustaaf J C et al. A Novel Treatment Concept for Advanced Stage Mandibular Osteoradionecrosis Combining Isodose Curve Visualization and Nerve Preservation: A Prospective Pilot Study. *Frontiers in oncology* vol. 11 630123. 22 Feb. 2021, doi:10.3389/fonc.2021.630123.

36. Vescovi, P., et al. *Laser in Odontostomatologia: Principali Applicazioni – Modulo 2: Il Laser Nella Gestione Delle Patologie Delle Ossa Mascellari*. no. 2, Feb. 2023. *DentalCadmos*, https://doi.org/10.19256/d.cadmos.02.2023.

Appendix D. Bibliometric analysis of included studies (n = 19).

Author	Year of publication	Country (first author from)	Continent (first author from)	Journal	Impact factor (2022)	Affiliation/Institution (first author from)	Title	Keywords	Type of study	Primary focus (group of disease)
Abramoff et al	2014	Brazil	South America	Photomedicine and Laser Surgery	1.8	Division of Plastic Surgery, Department of Surgery, Universidade Federal de São Paulo, São Paulo, SP	Low-Level Laser Therapy on Bone Repair of Rat Tibiae Exposed to Ionizing Radiation	NR	In vivo	To evaluate the effects of low-level laser therapy (LLLT) on the repair of rat tibiae exposed to ionizing radiation (IR).
Batista et al	2014	Brazil	South America	Lasers in Medical Science	2.1	Department of Oral and Maxillofacial Surgery, School of Dentistry, Federal University of Uberlândia, Uberlândia, MG.	Effect of low-level laser therapy on repair of the bone compromised by radiotherapy	Bone repair; Low-level laser therapy; Radiotherapy	In vivo	Influence of LLLT on bone neoformation (femur) after ionizing radiation
Bernaola-Paredes et al	2021	Brazil	South America	International Journal of Case Reports and Images	2.6	Department of Radiation Oncology, A.C. Camargo Cancer Center, Sao Paulo, Brazil;	Conservative management of advanced mandibular osteoradionecrosis with mild clinical presentation after 17 years of oncological treatment: A case report	Alpha-tocopherol; Conservative treatment; Debridement; Osteoradionecrosis; Pentoxifylline; Photobiomodulation therapy	Case Report	To describe the conservative management of an advanced mandibular ORN by medication with PENTO and other adjuvant therapies.
Camolesi et al.	2021	Brazil	South America	Medicina Oral Patologia Oral y Cirugia Bucal	2.54	Assistant Professor of Specialization in Oral Maxillofacial Surgery at Foundation for Scientific and Technological Development of Dentistry, University of São Paulo, Brazil	Therapeutic alternatives in the management of osteoradionecrosis of the jaws. Systematic review	Osteoradionecrosis; radiotherapy bone necrosis; hyperbaric oxygen; pentoxifylline; teriparatide; low level laser therapy.	Systematic review	To systematically review the literature, comparing the healing of osteoradionecrosis (ORN) among the therapeutic alternatives: surgical, pharmacological and combined.
Campos et al	2021	Brazil	South America	Photodiagnosis and Photodynamic Therapy	3.3	Department of Post-Graduation in Implantology, School of Dentistry, University of Santo Amaro, São Paulo, SP, Brazil	Antimicrobial photodynamic therapy using optical fiber for oral fistula resulting from mandibular osteoradionecrosis	Photobiomodulation therapy; Antimicrobial photodynamic therapy; Optical fiber; Osteoradionecrosis	Case Report	To report a clinical case in which the combination of PBMT and aPDT was used to manage mandibular ORN manifested as an oral fistula.
Da Cunha et al	2007	Brazil	South America	Photomedicine and Laser Surgery	1.8	Federal University of Bahia, Salvador, Bahia, Brazil	Effect of Laser Therapy on Bone Tissue Submitted to Radiotherapy: Experimental Study in Rats	NR	In vivo	To investigate the effect of LLLT on bone tissue submitted to ionizing radiation.

de Freitas et al	2023	Brazil	South America	Journal of Lasers in Medical Sciences	2.1	School of Dentistry, University of São Paulo, São Paulo, São Paulo, Brazil	Use of Phototherapy and Er-YAG Laser in the Management of Mandible Osteoradionecrosis: A Case Report	Osteoradionecrosis of the jaws; Low-intensity light therapy; Er-YAG laser; High power laser; Drug-related osteonecrosis of the jaws; Implant Dentistry	Case Report	To report the case of a patient affected by ORN after implant placement in the mandibular region and to present the treatment proposed to resolve the condition, suggesting a care protocol with low- and high-power lasers.
de Oliveira et al	2022	Brazil	South America	Lasers in Medical Science	2.1	Department of Stomatology, School of Dentistry of the Universidade de Sao Paulo	Efficacy of photobiomodulation therapy on healing of ionizing irradiated bone: a systematic review of in vivo animal studies	Bone regeneration; Radiation; Ionizing; Low-level light therapy; Head and neck neoplasms; Osteoradionecrosis	Systematic Review	Aimed at scrutinizing the available in vivo animal studies, evaluating the effects of PBM therapy on bone healing after ionizing irradiation.
El-Maghraby et al	2013	Egypt	Africa	Archives of Oral Biology	5.1	Health Radiation Research Department, National Centre for Radiation Research and Technology (NCRRT), Cairo, Egypt	Assessment of the effect of low-energy diode laser irradiation on gamma irradiated rats' mandibles	Laser therapy; Low-level; Bone and bones; Radiotherapy; Osteoradionecrosis	In vivo	To evaluate the bio-stimulative and regenerative effects of LLLT (applied before or after initiation of radiotherapy) on gamma-irradiated rats’ jaw bones
Ferreira et al	2019	Brazil	South America	International Journal of Odontostomatology	0.1182	Oral and Maxillofacial Surgery Service, Hospital Evangélico de Cachoeiro de Itapemirim, Espírito Santo, Brazil	Osteoradionecrosis in a Patient Submitted to Head and Neck Radiotherapy: A Case Report	Osteoradionecrosis; Radiotherapy; Head and neck neoplasms; Mandibular osteotomy.	Case Report	To reports a case of ORN in the left mandibular body which resulted in a pathological fracture
Franco et al	2017	Brazil	South America	Oral Surgery	0.197	Universidade Veiga de Almeida, Rio de Janeiro, Brazil	Success of preventive approach to mandibular osteoradionecrosis in an adolescent: case report	Mandible; Osteoradionecrosis; Parotid gland; Radiotherapy	Case Report	To present a clinical case where a protocol was used to prevent the development of ORN after the extraction of lower molars in an adolescent who had undergone surgical removal and radiotherapy
Freire et al	2010	Brazil	South America	Proceedings of SPIE	NF	Federal University of Bahia	The photobiomodulation in the bone repair after radiotherapy: experimental study in rats	Radiotherapy; laser photobiomodulation; osteoradionecrosis.	In vivo	To evaluate the effect of the GaAlAs photobiomodulation in the healing of surgical wounds produced in Wistar rats’ femurs, a few days before the beginning of the radiotherapy

Korany et al	2012	Egypt	Africa	Archives of Oral Biology	2.78	Oral Biology Department, Faculty of Oral and Dental Medicine, Cairo University, Egypt	Evaluation of socket healing in irradiated rats after diode laser exposure (histological and morphometric studies)	Preoperative irradiation; Bone repair; Low-level laser therapy (LLLT); Rats	In vivo	To evaluate the effect of low-level laser therapy (LLLT) in enhancing bone repair in irradiated sockets of albino rats.
Magalhães et al	2020	Brazil	South America	Photodiagnosis and Photodynamic Therapy	3.3	Christus University Center, Fortaleza, Brazil	Photobiomodulation and antimicrobial photodynamic therapy as adjunct in the treatment and prevention of osteoradionecrosis of the jaws: A case report	Osteonecrosis, Photodynamic therapy; Laser therapy	Case report	To report a case of mandibular ORN with multiple root remnants, treated by LLLT and aPDT for ORN treatment and prevention.
Moreschi et al	2016	Italy	Europe	Minerva Stomalogica	0.3	Unit of Dentistry and Oral and Maxillofacial Surgery Unit, San Rocco Hospital, Brescia, Italy	Low level laser therapy in non-surgical management of osteoradionecrosis of the jaws	NR	Case Report	To evaluate the use of LLLT in for the management of ORN in humans
Palma et al	2021	Brazil	South America	National Journal of Maxillofacial Surgery	0.57	Graduate Dentistry Program, Ibirapuera University	Antibiotic therapy for the prevention of osteoradionecrosis following tooth extraction in head-and-neck cancer patients postradiotherapy: An 11-year retrospective study	Head-and-neck cancer; Osteoradionecrosis; Radiotherapy; Tooth extraction	Case Report	To evaluate retrospectively a perioperative systemic antibiotic therapy protocol for the prevention of ORN following tooth extraction in head-and-neck patients post-3D conformal RT.
Pedroni et al	2020	Brazil	South America	Photodiagnosis and Photodynamic Therapy	3.3	School of Dentistry, University of Sao Paulo, Sao Paulo, Brazil	Successful application of antimicrobial photodynamic and photobiomodulation therapies for controlling osteoradionecrosis and xerostomia after laryngeal carcinoma treatment: A case report of full oral rehabilitation	Head and neck cancer; Photodynamic therapy; Photobiomodulation therapy; Osteoradionecrosis; Xerostomia	Case Report	To present a conservative treatment based on photonics (PBMT associated to aPDT) of a patient with ORN due to the radiotherapy (RT) treatment of laryngeal cancer.
Ribeiro et al.	2018	Brazil	South America	Journal of Applied Oral Science	2.71	Universidade Federal de Santa Catarina, Núcleo de Odontologia Hospitalar do Hospital Universitário, Florianópolis, SC, Brazil.	Osteoradionecrosis of the jaws: case series treated with adjuvant low-level laser therapy and antimicrobial photodynamic therapy	Osteoradionecrosis. Oral cancer. Radiotherapy. Low-level laser therapy. Antimicrobial photodynamic therapy.	Case Series	To assess the clinical effects of LLLT and aPDT to treat ORNJ in patients who underwent head and neck RT, as well as to propose an adjuvant treatment protocol to the pathology.
Tateno et al	2020	Brazil	South America	Photodiagnosis and Photodynamic Therapy	3.3	Department of Post-Graduation in Implantology, School of Dentistry, University of Santo Amaro, São Paulo, SP, Brazil	Laser and antimicrobial photodynamic therapy for the management of delayed healing following multiple dental extractions in a post-radiotherapy patient	NR	Case Report	To report a case on the use of PBMT and aPDT for the management of delayed healing following multiple dental extractions in a head and neck cancer patient post-RT.

Abbreviations: Antimicrobial Photodynamic Therapy (aPDT); Low-level laser therapy (LLLT); Ionizing Radiation (IR); NF (Not Found); Not Reported (NR); Osteoradionecrosis (ORN); Photobiomodulation therapy (PBMT).

Appendix E. Summary of laser parameters characteristics of included studies

Table 1 - Summary of laser parameters of primary *in vivo* studies included (n=6).

Author (Year)	Laser used	Photosensitizer	Wavelength (nm)	Energy per point (J)	Power (mW)	Fluence (J/cm²)	Irradiance (W/cm²)	Cross-sectional area (cm²)	Diameter of the Spot (cm²)	Duration of exposure per application (s)	Emission mode	Distance between laser and ORN	Number of points applied	Points distance	Laser application Frequency/ period
Abramoff et al., 2014 Brazil	(DMC, Brazil) LLLT (GaAlAs)	No	808	2	100	71.4	3.57	0.028	0.028	20	Continuous	Contact punctual (Perpendicular to the tissue) Transcutaneal	1	NA	3 sessions on alternative days (starting after surgery) with 48h intervals.
Batista et al., 2014 Brazil	(Flash lase III; DMC, Brazil) LLLT (GaAlAs); infrared;	No	830	6	100	210	NR	0.04	0.028	120	Continuous	Contact, punctual Transcutaneal	1	NA	4 sessions for 2 min at intervals of 48 hours for 7 days, starting immediately after the surgery (bone defect induction) with 48h intervals.
Da Cunha et al., 2007 Brazil	(Twin Laser; MM Optics, Brazil) LLLT (GaAlAs)	No	780	NR	40	4	NR	0.04	0.04	100	Continuous	Contact, punctual Transcutaneal	4	1 cm apart from each other	7 sessions with 48h intervals Group II: 1 day before IR Group III: at the same day IR Group IV: 4 weeks after IR.
El-Maghraby et al., 2013 Egypt	LLLT (Ga–As); infrared	No	904	5.4	30	NR	NR	1	1	180	Continuous	Contact (on the left side of the jaw with a rotatory scanning movement, using slight pressure)	NR	NR	3 times a week, with 48h intervals.
Freire et al., 2010 Brazil	(Twin Laser; MM Optics, Brazil) LLLT (GaAlAs); infrared;	No	780	5	40	100	NR	0.126	0.126	100	NR	Contact, punctual Transcutaneal	4	1 cm around the injured bone	7 sessions - each 48h (starting at the day of the surgery)

Korany et al., 2012 Egypt	(NR) LLLT (GaAIAs); infrared	No	830	NR	75	NR	NR	2.01	2.01	NR	Continuous	Contact, punctual	1	NR	In contact with the socket of the left side immediately after extraction (right side = control)

Abbreviations: Antimicrobial Photodynamic Therapy (aPDT); Carbon Dioxide (CO_2); Erbium-doped yttrium aluminum garnet laser (Er-YAG); Gallium-aluminum-arsenide laser (GaAlAs); Gallium arsenide laser (GaAlAs); Joules (J); Joule per square centimeter (J/cm^2); Low-level laser therapy (LLLT); Nanometer (nm); Not Reported (NR); Not Applicable (NA); Milliwatts (mW); Osteoradionecrosis (ORN); Photobiomodulation therapy (PBMT); Seconds (s); Square centimeter (cm^2); Watts per square centimeter (W/cm^2).

Table 2 - Summary of laser parameters of primary case report studies included (n=11).

Author (Year)	Laser used	Photosensitizer	Wavelength (nm)	Energy per point (J)	Power (mW)	Fluence (J/cm²)	Irradiance (W/cm²)	Cross-sectional area (cm²)	Diameter of the Spot (cm²)	Duration of exposure per application (s)	Emission mode	Distance between laser and ORN	Number of points applied	Points distance	Laser application Frequency/ period
Bernaola-Paredes et al., 2021 Brazil	(Therapy EC, DMC, Brazil) LLLT (AlGaAs) red and infrared	Yes - Methylene Blue dye (concentration of 0.02% for 5 minutes);	660	PBMT: 3 aPDT: 6	100	NR	NR	NR	NR	NR	NR	NR	PBMT: 6 aPDT: 6	NR	PBMT: Operating wound area (7 and 15 days after the surgical treatment) aPDT: NR
Campos et al., 2021 Brazil	(Twin Flex Evolution, MMOptics, Brazil) LLLT red and infrared	Yes - Methylene blue at a 0.01 % concentration	PBMT: 808 aPDT: 660	PBMT:1 aPDT: 4.8	PBMT: 70 aPDT: 40	PBMT: NR aPDT: 120	NR	PBMT: NR aPDT: 0.3	PBMT: NR aPDT: 0.3	PBMT: NR aPDT: 120	NR	Contact	NR	PBMT: intra oral: all over the buccal and lingual bone; extraoral: swollen region aPDT: injected into the fistula path	NR
de Freitas et al., 2023 Brazil	(Therapy XTR, DMC, Brazil) LLLT (Diode laser) red and infrared	Yes - Methylene blue at a 0.01 % concentration for 5 minutes	PBMT: 660 and 808 aPDT: 660	PBMT:4 aPDT: 9 (intraoral) and 4 (extraoral)	PBMT: 100 aPDT: 100	NR	NR	NR	NR	PBMT: NR aPDT: NR	Continuous	NR	NR	NR	PBMT: two months aPDT: eight mouths (once a week)
Ferreira et al., 2019 Brazil	(Therapy EC, DMC, Brazil) LLLT (Diode laser) infrared	No	660	1	100	35	NR	0.028	0.028	10	NR	NR	NR	PBMT: post-surgical, around the bone exposure	PBMT: weekly (3 months)
Franco et al., 2017 Brazil	(Therapy EC, DMC, Brazil) LLLT (Diode laser) infrared	No	808	2	100	35	NR	0.0028	0.0028	10	NR	NR	NR	On the center of each alveolus and also after suturing.	3 sessions of 4 J of energy per point around the alveolus, every 48 hours
Magalhães et al., 2020 Brazil	(Therapy XT, DMC, Brazil) LLLT (Diode laser) red and infrared	Yes - Methylene blue at a 0.01 % concentration	660	PBMT:4 aPDT: 9	100	PBMT: 35 aPDT:321.4	NR	NR	NR	PBMT: 10 aPDT: 90	NR	NR	PBMT: 6 (Three vestibular and three lingual) aPDT: 2	PBMT: one point each 1.0 cm aPDT: one point each 1.0 cm	1 month (one aPDT session and three LLLT sessions, weekly)

Moreschi et al., 2016 Italy	(Fotona, Slovenia) LLLT (Diode laser)	No	660	NR	500	NR	NR	NR	NR	60	NR	Non-contact (unfocused mode)	NR	2mm distance from the tissue.	5 times, once a week
Palma et al., 2021 Brazil	(NR) LLLT	No	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pedroni et al., 2020 Brazil	(NR) LLLT red and infrared	Yes - Methylene blue at a 0.01 % concentration	PBMT and aPDT: 660 Xerostomia: 808	PBMT: 1 aPDT: 2 Xerostomia: 2	100	71.42	3.57	NR	0.0028	PBMT: 10 aPDT: 20 Xerostomia: 20	NR	Contact, punctual	NR (enough quantity of points to cover the entire visible ORN lesion)	Approximately 1 cm distance between each point	Five days a week on alternate days (aPDT three times and PBMT twice a week)
Ribeiro et al., 2018 Brazil	(Therapy XT, DMC, Brazil) LLLT (Diode laser) red and infrared	Yes - Methylene blue at a 0.01 % concentration	PBMT: 660 and 808 aPDT: 660	PBMT: NR aPDT: NR	100	PBMT: 37.71 and 142.85 aPDT: 142.85	NR	NR	0.25	PBMT: 10 and 40 aPDT: 40	NR	NR	PBMT: 1 (Oral mucosa surrounding the bone exposure) and 6 (vestibular alveolar) aPDT: 1 (Bone exposure and/or purulent secretion)	NR	NR
Tateno et al., 2020 Brazil	(Therapy XT, DMC, Brazil) LLLT (Diode laser) red and infrared	Yes - Methylene blue at a 0.01 % concentration	PBMT: 660 and 808 aPDT: 660	PBMT: 1 aPDT: 5	100	NR	NR	NR	NR	PBMT: 10 aPDT: 50	NR	Contact, punctual	PBMT: 21 (1 point in maxilla; 3 points in mandible (Oral mucosa, surgical wound); 17 points vestibular, and 17 points lingual (right and left side in maxila and madible) aPDT: 8 (5 points in maxilla and 3 points in mandible)	PBMT: 1 point each 1 cm2 aPDT: 1 point each 1 cm2	PBMT and aPDT protocols: were performed once a week and lasted 30 days

Abbreviations: Antimicrobial Photodynamic Therapy (aPDT); Carbon Dioxide (CO_2); Erbium-doped yttrium aluminum garnet laser (Er-YAG); Gallium-aluminum-arsenide laser (GaAlAs); Gallium-arsenide laser (GaAlAs); Joules (J); Joule per square centimeter (J/cm^2); Low-level laser therapy (LLLT); Nanometer (nm); Not Reported (NR); Not Applicable (NA); Milliwatts (mW); Osteoradionecrosis (ORN); Photobiomodulation therapy (PBMT); Seconds (s); Square centimeter (cm^2); Watts per square centimeter (W/cm^2).

Appendix F. Summary of Case Report or Series Case Report Studies on Low-Level Laser Therapy for Osteoradionecrosis (n=11)

Author, Year, and Country	Patient Info	Prior Treatment	Treatment for or to prevent ORN	Laser use Indication (Therapeutic or Prevention)	Low-Level Laser Therapy Parameters	Follow-up	Side Effects	Outcome	Notes
Bernaola-Paredes et al., 2021 Brazil	62-year-old Afro-descendent woman; Cancer stage: pT1N0M0; Cancer diagnosis: 2004; ORN diagnosis: 2020 - ORN classified as advanced Complaints: Toothache (tooth 47) and prosthetic rehabilitation performed with dental implants	Radiotherapy: 54 Gy (primary lesion) and 45 Gy (homolateral lymphatic neck drainage) associated with CMT. Antifibrotic therapy (PENTO protocol - 400 mg of pentoxifylline twice daily plus 500 UI tocopherol - twice daily for 4 months); Surgical treatment: extraction of tooth 33 and superficial sequestrectomy. aPDT: Methylene Blue dye (concentration of 0.02% for 5 minutes).	Antibiotic therapy (Amoxicillin + Clavulanic acid 500 mg; every 8 hours for 15 days); AINE therapy (Nimesulide 100 mg; every 12 hours for 4 days) Antifibrotic therapy (PENTO protocol - 400 mg of pentoxifylline twice daily plus 500 UI tocopherol - twice daily for 3 months); LLLT	Therapeutic	Laser used: (Therapy EC, DMC, Brazil) LLLT (AlGaAs) red and infrared; Photosensitizer: Yes - Methylene Blue dye (concentration of 0.02% for 5 minutes); Wavelength (nm): 660; Energy per point (J): PBMT: 3 and aPDT: 6; Power (mW): 100; Fluence (J/cm²): NR; Irradiance (W/cm²): NR; Cross-sectional area (cm²): NR; Diameter of the Spot (cm²): NR; Duration of exposure per application (s): NR; Emission mode: NR; Distance between laser and ORN: NR; Number of points applied : PBMT: 6 and aPDT: 6; Points distance: NR; Laser application Frequency/ Period: PBMT: Operating wound area (7 and 15 days after the surgical treatment) and aPDT: NR	12 months	PENTO protocol: nausea or vomiting as undesirable side effects, related to the dosage of 400 mg of pentoxifylline twice daily and 1000,000 IU of tocopherol.	PENTO protocol proved to be effective in stabilizing the lesion in an advanced stage of ORN associated with adjuvant therapies and surgical treatment.	Incomplete data
Campos et al., 2021 Brazil	57-year-old woman; Cancer diagnosis: 2019; ORN diagnosis: 2020 Complaint: Pain arising from the mandibular mucosa	Radiotherapy: 70 Gy with CMT. History of radiation-induced dental caries affecting all teeth and generalized periodontitis following cancer treatment, with spontaneous loss of the mandibular anterior teeth. Repeated use of oral antibiotics as monotherapy did not lead to clinical improvement.	Antibiotic therapy (Amoxicillin 500 mg – three times a day, for seven days) aPDT (every 15 days for six weeks; 0.5 mL of methylene blue at a 0.01 % concentration)	Therapeutic	Laser used: (Twin Flex Evolution, MMOptics, Brazil) LLLT red and infrared; Photosensitizer: Yes - Methylene blue at a 0.01 % concentration; Wavelength (nm): PBMT: 808 and aPDT: 660 Energy per point (J): PBMT:1 and aPDT: 4.8; Power (mW): PBMT: 70 and aPDT: 40; Fluence (J/cm²): PBMT: NR and aPDT: 120; Irradiance (W/cm²): NR; Cross-sectional area (cm²): PBMT: NR and aPDT: 0.3;	6 weeks	No side effects were reported	PBMT and aPDT with an optical fiber to deliver the laser light seem to be a suitable alternative for restricted areas such as fistula paths.	Incomplete data

					Diameter of the Spot (cm²): PBMT: NR and aPDT: 0.3; Duration of exposure per application (s): PBMT: NR and aPDT: 120; Emission mode: NR; Distance between laser and ORN: Contact; Number of points applied : NR; Points distance: PBMT: intra oral: all over the buccal and lingual bone; extraoral: swollen region aPDT: injected into the fistula path; Laser application Frequency/ Period: NR				
de Freitas et al., 2023 Brazil	59-year-old female; Cancer diagnosis: 2013; ORN diagnosis: 2021 (8 years after the cancer diagnosis) Complaints: pain in the mandibular region associated with the extraoral lesion sought dental care (after dental extractions and surgery installation of five morse taper implants in the mandible)	Radiotherapy: 66.6 Gy. Multiple extractions were performed, followed by the placement of osseointegrated implants, resulting in extensive intraoral bone exposure and the development of an oral cutaneous fistula	LLLT; aPDT (methylene blue at a 0.01 % concentration for 5 minutes); Surgical treatment: Sequestromy bone; Er:YAG laser to remove necrotic bone (2940 nm, with energy of 150 mJ, frequency of 20 Hz and power of 3.0 W)	Therapeutic	Laser used: (Therapy XTR, DMC, Brazil) LLLT (Diode laser) red and infrared Photosensitizer: Yes - Methylene blue at a 0.01 % concentration for 5 minutes; Wavelength (nm): PBMT: 660 and 808; and aPDT: 660; Energy per point (J): PBMT:4 and aPDT: 9 (intraoral) and 4 (extraoral); Power (mW): PBMT: 100 and aPDT: 100; Fluence (J/cm²): NR; Irradiance (W/cm²): NR; Cross-sectional area (cm²): NR; Diameter of the Spot (cm²): NR; Duration of exposure per application (s): NR; Emission mode: Continuous; Distance between laser and ORN: NR; Number of points applied: NR; Points distance: NR; Laser application Frequency/ Period: PBMT: two months and aPDT: eight mouths (once a week).	11 months	The use of the Er:YAG laser presents minimal side effects due to its low thermal energy, preventing damage to surrounding tissues, unlike other lasers that cause carbonization and protein denaturation.	LLLT and HLLT treatment can be an effective therapeutic alternative to resolve ORN.	Incomplete data
Ferreira et al., 2019 Brazil	41-year-old male; chronic alcoholic and active smoker, with depression	Radiotherapy: 70.2 Gy with CMT. Third molar extraction.	Surgical treatment: partial mandibulectomy with mandibular reconstruction;	Therapeutic	Laser used: (Therapy EC, DMC, Brazil) LLLT (Diode laser) Infrared;	6 months	No side effects were reported	The patient died before ORN control was achieved, due to a heart attack.	Incomplete data

	Cancer diagnosis: 2014; ORN diagnosis: 2016 Complaints: Intensive pain, trismus, and persistent infection in the left jaw region (after third molar extraction)		Antibiotic therapy (Cephalexin 500 mg every 6 hours, for 7 days; Metronidazole 400 mg, every 8 hours, for 7 days; Cephalothin, 1 g, every 6 hours, for 7 days); Mouthwashes (Chlorhexidine 0.12 %, 3 times a day, for 14 days); Analgesic (dipyrone sodium 500 mg, if pain).		Photosensitizer: No; Wavelength (nm): 660; Energy per point (J): 1; Power (mW): 100; Fluence (J/cm²): 35; Irradiance (W/cm²): NR; Cross-sectional area (cm²): 0.028; Diameter of the Spot (cm²): 0.028; Duration of exposure per application (s): 10; Emission mode: NR; Distance between laser and ORN: NR; Number of points applied: 10 Points distance: PBMT: post-surgical, around the bone exposure; Laser application Frequency/ Period: PBMT: weekly (3 months)				
Franco et al., 2017 Brazil	16-year-old female Cancer diagnosis: 2011; ORN diagnosis: NA Follow-up since the 11 years old	Radiotherapy: 70 Gy. Dental extractions (37 and 38 elements).	LLLT; Antibiotic therapy (Amoxicillin + clavulanic acid 875mg, 2 times a day, for 14 days); Antifibrotic therapy (Pentoxifylline 400mg, 2 times a day, for 8 weeks) and tocopherol (1000U) once daily was started 1 week before the extractions for 8 weeks.); AINE therapy (Nimesulide 1000U, 1h before the surgery and continued for 3 days); Mouthwashes (Chlorhexidine 0.12%); Surgical treatment: extraction of elements 36, 37 e 38; Other treatment: Use Platelet Rich Fibrin (L-PRF)	Prevention	Laser used: (Therapy EC, DMC, Brazil) LLLT (Diode laser) Infrared; Photosensitizer: No; Wavelength (nm): 808; Energy per point (J): 2; Power (mW): 100; Fluence (J/cm²): 35; Irradiance (W/cm²): NR; Cross-sectional area (cm²): 0.0028; Diameter of the Spot (cm²): 0.0028; Duration of exposure per application (s): 10; Emission mode: NR; Distance between laser and ORN: NR; Number of points applied: NR; Points distance: On the center of each alveolus and also after suturing;	1 year	No side effects were reported	The protocol used was efficient in preventing ORN in this adolescent. One year after the extractions, there were no clinical or radiographic signs of any pathological alteration in the region.	Incomplete data

					Laser application Frequency/ Period: 3 sessions of 4 J of energy per point around the alveolus, every 48 hours.				
Magalhães et al., 2020 Brazil	58-years-old man, Cancer diagnosis: NR; ORN diagnosis: NR Complaints: Xerostomia and severe tooth-ache Clinical examination: “Necrotic bone in the mandibular anterior region associated with intraoral fistula and purulent exudation”	Radiotherapy: 70 Gy + Surgery (for the primary tumor) and 46−60 Gy (for high-risk areas). The initial treatment included antibiotic coverage with amoxicillin and metronidazole, followed by surgical removal of necrotic bone and root remnants.	Surgical treatment: removal of necrotic bone, root remnants in proximity to the ORN area and, extraction of non-rehabilitated teeth (14 teeth); Antibiotic therapy (Amoxicillin 500 mg + metronidazole 250 mg; 7 days, every 8 hours; starting 24h before the surgery); Mouthwashes (Chlorhexidine 0.12%), aPDT (methylene blue at a 0.01 % concentration)	Therapeutic and Prevention	Laser used: (Therapy XT, DMC, Brazil) LLLT (Diode laser) red and infrared; Photosensitizer: Yes - Methylene blue at a 0.01 % concentration; Wavelength (nm): 660; Energy per point (J): PBMT:4 and aPDT: 9 Power (mW): 100; Fluence (J/cm²): PBMT: 35 and aPDT:321.4; Irradiance (W/cm²): NR; Cross-sectional area (cm²): NR; Diameter of the Spot (cm²): NR; Duration of exposure per application (s): PBMT: 10 and aPDT: 90; Emission mode: NR; Distance between laser and ORN: NR; Number of points applied: PBMT: 6 (Three vestibular and three lingual) and aPDT: 2; Points distance: PBMT: one point each 1.0 cm, and aPDT: one point each 1.0 cm; Laser application Frequency/ Period: 1 month (one aPDT session and three LLLT sessions, weekly).	More than 12 months	No side effects were reported	The adjuvant therapy combining aPDT and LLLT with minimally invasive surgical procedures and antibiotic therapy was successful in the treatment and prevention of ORN in our patient after radiotherapy, without recurrence or new lesion emergence after 1-year of follow-up.	Incomplete data
Moreschi et al., 2016 Italy	65-year-old, male Cancer diagnosis: 2005 ORN diagnosis: 2010 Complaint: Pain in the left part of his lower-jaw	Radiotherapy: NR Gy	LLLT; Antibiotic therapy (Amoxicillin 875 mg, Clavulanic acid 125 mg: 1 tablet every 12 hours; Metronidazole 250mg, 15 days, every 6 hours); Surgical treatment: emimandibulectomy without surgical reconstruction	Therapeutic	Laser used: (Fotona, Slovenia) LLLT (Diode laser); Photosensitizer:No; Wavelength (nm): 660; Energy per point (J): NR; Power (mW): 500; Fluence (J/cm²): NR; Irradiance (W/cm²): NR; Cross-sectional area (cm²): NR;	12 months	No side effects were reported	LLLT in association with systemic antibiotic therapy could represent a conservative treatment, without potential side effects, in patients with contraindication to surgery as for systemic disease, as for local-regional complications.	Incomplete data

					Diameter of the Spot (cm²): NR; Duration of exposure per application (s): 60; Emission mode: NR; Distance between laser and ORN: Non-contact (unfocused mode); Number of points applied: NR; Points distance: 2mm distance from the tissue; Laser application Frequency/ Period: 5 times, once a week.				
Palma et al., 2021 Brazil	Case 1: 53-year-old Afro-descendant man Cancer diagnosis: NR; ORN diagnosis: NR Case 2: 56-year-old Caucasian, man Cancer diagnosis: NR; ORN diagnosis: NR	Radiotherapy: 66 Gy (case 1) and 70 Gy (case 2). Case 1 and Case 2: Antibiotic therapy (preoperative: Clindamycin 300 mg; 3 days, every 8 hours) Tooth extraction	Case 1 and Case 2: LLLT; Case 1: Antibiotic therapy (preoperative: Clindamycin 300 mg; 7 days, every 8 hours) Case 2: Antibiotic therapy (preoperative: Clindamycin 300 mg; 7 days, every 8 hours) Surgical treatment: hemimandibulectomy	Case 1: Prevention Case 2: Prevention	Laser used: (NR) LLLT; Photosensitizer: No; Wavelength (nm): NR; Energy per point (J): NR; Power (mW): NR; Fluence (J/cm²): NR; Irradiance (W/cm²): NR; Cross-sectional area (cm²): NR; Diameter of the Spot (cm²): NR; Duration of exposure per application (s): NR; Emission mode: Distance between laser and ORN: NR; Number of points applied: NR; Points distance: NR; Laser application Frequency/ Period: NR	Case 1: 5 years Case 2: 3 years	Case 1: No side effects were reported Case 2: pathological mandibular fracture after tooth extractions and treatments, equiring hemimandibulectomy	Perioperative systemic antibiotic therapy protocol seems to be efficient in preventing ORN following tooth extraction in post irradiated head and neck cancer patients.	Incomplete data
Pedroni et al., 2020 Brazil	57-year-old male Cancer diagnosis: 2015; ORN diagnosis: 2017 Complaint: “Dry mouth” and pain in the region where a tooth was extracted	Radiotherapy: 50 Gy (bilateral lymphatic drainages), and 70 Gy (tumor and positive lymph nodes) with CMT. Surgical treatment: tooth extractions	LLLT; aPDT (methylene blue at a 0.01 % concentration) Antibiotic therapy (Amoxicillin 500 mg; 7 days, every 8 hours);	Therapeutic	Laser used: (NR) LLLT red and infrared; Photosensitizer: Yes - Methylene blue at a 0.01 % concentration; Wavelength (nm): PBMT and aPDT: 660; and Xerostomia: 808; Energy per point (J): PBMT: 1, aPDT: 2, and Xerostomia: 2; Power (mW): 100;	6 months	No side effects were reported, and the patient was in functional/aesthetic rehabilitation with a total prosthesis.	The combined PBMT and aPDT therapies proved to be efficient for controlling ORN clinical lesion and for the improvement of the painful symptomatology in the region.	Incomplete data

				Analgesic (Dipyrone 500 mg; 7 days). Surgical treatment: tooth extractions.	Fluence (J/cm²): 71.42; Irradiance (W/cm²): 3.57 Cross-sectional area (cm²): NR; Diameter of the Spot (cm²): 0.0028; Duration of exposure per application (s): PBMT: 10, aPDT: 20, and Xerostomia: 20; Emission mode: NR; Distance between laser and ORN: Contact, punctual; Number of points applied: NR (enough quantity of points to cover the entire visible ORN lesion) Points distance: Approximately 1 cm distance between each point Laser application Frequency/ Period: Five days a week on alternate days (aPDT three times and PBMT twice a week)			
Ribeiro et al., 2018 Brazil	20 patients (both men and woman, 40 to 71 years old, the mean age was of 59.1 years) Cancer diagnosis: NR; ORN diagnosis: after 24 months.	Radiotherapy: 66 – 92 Gy.	LLLT; aPDT (methylene blue 0.01%)	Therapeutic	Laser used: (Therapy XT, DMC, Brazil) LLLT (Diode laser) red and infrared; Photosensitizer: Yes - Methylene blue at a 0.01 % concentration; Wavelength (nm): PBMT: 660 and 808; and aPDT: 660; Energy per point (J): NR; Power (mW): 100; Fluence (J/cm²): PBMT: 37.71 and 142.85; and aPDT: 142.85; Irradiance (W/cm²): NR; Cross-sectional area (cm²): NR; Diameter of the Spot (cm²): 0.25; Duration of exposure per application (s): PBMT: 10 and 40; and aPDT: 40; Emission mode: NR; Distance between laser and ORN: NR; Number of points applied: PBMT: 1 (Oral mucosa surrounding the bone exposure) and 6 (vestibular alveolar), and aPDT: 1 (Bone exposure and/or purulent secretion) Points distance: NR;	2 years	No side effects were reported	LLLT and aPDT showed positive results as adjuvant therapy to treat ORN.	Incomplete data

					Laser application Frequency/ Period: NR.				
Tateno et al., 2020 Brazil	62-year-old man, Cancer diagnosis: NR; ORN diagnosis: time. One year after the end of the cancer treatment.	Radiotherapy: 70 Gy + CMT	LLLT; aPDT (methylene blue 0.01% for 3 minutes); Antibiotic therapy (Clindamycin 600 mg an hour before surgery and maintained 300 mg, 4 times daily, for only 7 days); Surgical treatment: tooth extractions.	Prevention	Laser used: (Therapy XT, DMC, Brazil) LLLT (Diode laser) red and infrared; Photosensitizer: Yes - Methylene blue at a 0.01 % concentration; Wavelength (nm): PBMT: 660 and 808; and aPDT: 660; Energy per point (J): PBMT: 1 and aPDT: 5; Power (mW): 100; Fluence (J/cm²): NR; Irradiance (W/cm²): NR; Cross-sectional area (cm²): NR; Diameter of the Spot (cm²): NR; Duration of exposure per application (s): PBMT: 10 and aPDT: 50; Emission mode: NR; Distance between laser and ORN: Contact, punctual; Number of points applied: PBMT: 21 (1 point in maxilla; 3 points in mandible (Oral mucosa, surgical wound); 17 points vestibular, and 17 points lingual (right and left side in maxilla and mandible); and aPDT: 8 (5 points in maxilla and 3 points in mandible); Points distance: PBMT: 1 point each 1 cm2 and aPDT: 1 point each 1 cm2; Laser application Frequency/ Period: PBMT and aPDT protocols: were performed once a week and lasted 30 days.	12 months	No side effects were reported, and the patient was in functional/aesthetic rehabilitation with a total prosthesis.	PMBT and aPDT were essential to improve delayed healing following multiple extractions in the post-IR patient, been capable to preventing ORN development.	Incomplete data

Abbreviations: Antimicrobial Photodynamic Therapy (aPDT); Carbon Dioxide (CO_2); Chemotherapy (CMT); Erbium-doped yttrium aluminum garnet laser (Er-YAG); Gallium-aluminum-arsenide laser (GaAlAs); Gallium-arsenide laser (GaAlAs); Gray (Gy); Joules (J); Joule per square centimeter (J/cm²); Low-level laser therapy (LLLT); Nanometer (nm); Not Reported (NR); Not Applicable (NA); Milligrams (mg); Milliwatts (mW); Osteoradionecrosis (ORN); Photobiomodulation therapy (PBMT); Seconds (s); Square centimeter (cm²); Watts per square centimeter (W/cm²).

5. CONSIDERAÇÕES FINAIS

Uma das principais dificuldades encontradas na avaliação da eficácia do laser de baixa intensidade no tratamento da osteorradionecrose (ORN) está relacionada à ausência de padronização dos parâmetros de tratamento. Estudos existentes utilizam uma ampla gama de parâmetros, como diferentes comprimentos de onda, densidade de energia, tempo de exposição, número de sessões e técnicas de aplicação, o que gera resultados difíceis de comparar ou consolidar. Essa falta de uniformidade impede que os pesquisadores formem uma base de dados sólida para uma análise quantitativa ou meta-análise que possa fornecer evidências robustas e confiáveis. Além disso, a metodologia empregada nos estudos incluídos também apresenta uma grande variação, não apenas nos parâmetros de tratamento, mas também na seleção de pacientes, nos critérios de inclusão e exclusão, no desenho dos estudos, e até na definição dos desfechos de sucesso ou fracasso do tratamento. Essa heterogeneidade metodológica intensifica o desafio, pois impede a reprodução dos resultados em diferentes contextos clínicos e limita a possibilidade de generalização dos achados. Dessa forma, mesmo que alguns estudos relatem benefícios promissores das terapias baseadas em laser, a falta de padronização entre os estudos compromete a criação de diretrizes clínicas consistentes, o que restringe a adoção generalizada dessas terapias na prática clínica ou ainda a formulação de recomendações definitivas.

Outro desafio significativo que prejudica a consolidação do laser de baixa intensidade como tratamentos preferenciais para ORN é a escassez de ensaios clínicos de alta qualidade. A maioria dos estudos clínicos disponíveis na literatura apresenta tamanhos de amostra relativamente pequenos, o que limita o poder estatístico das análises e aumenta o risco de resultados viesados. Além disso, muitos desses estudos são conduzidos com períodos de seguimento curtos, o que dificulta a avaliação dos efeitos a longo prazo das terapias, especialmente no que diz respeito à prevenção de recidivas e à sustentabilidade dos resultados. Essa falta de estudos longitudinais compromete a capacidade dos pesquisadores de avaliar adequadamente os benefícios terapêuticos em uma escala temporal mais longa, que é fundamental para condições crônicas e complexas como a ORN. A ausência de ensaios clínicos multicêntricos, randomizados e controlados agrava ainda mais essa situação, uma vez que estudos conduzidos em centros únicos tendem a sofrer de limitações regionais, tanto em termos de variabilidade populacional quanto de recursos clínicos. Essa limitação torna difícil extrapolar os resultados para populações maiores e mais diversas, o que seria necessário para

que as terapias fossem aceitas em uma escala global e amplamente recomendadas em diretrizes clínicas.

Diante dessas limitações, torna-se evidente que o progresso no tratamento da ORN com PBMT e aPDT depende de um esforço coordenado para a realização de ensaios clínicos robustos, bem delineados e conduzidos ao longo de períodos extensos. É essencial que futuros estudos sejam desenhados de forma a incluir amostras maiores, diversificadas e representativas, que permitam avaliar a eficácia das terapias em diferentes subgrupos de pacientes, levando em consideração variáveis como idade, sexo, comorbidades, e estágio da doença. Além disso, é crucial que esses estudos sejam multicêntricos, envolvendo a colaboração de diferentes instituições e profissionais de saúde de diversas regiões, o que ajudaria a mitigar as limitações regionais e aumentar a validade externa dos achados. Igualmente importante é a necessidade de padronizar os protocolos de tratamento, definindo com clareza os parâmetros ideais de aplicação do laser, tais como o comprimento de onda, a densidade de energia, o número de sessões e a duração do tratamento. Isso permitiria uma comparação mais direta dos resultados e ajudaria a estabelecer diretrizes práticas baseadas em evidências sólidas. Ao adotar esses protocolos padronizados e garantir o acompanhamento de longo prazo dos pacientes, espera-se que futuras pesquisas possam fornecer evidências mais definitivas sobre a eficácia da fotobiomodulação e da aPDT no manejo da ORN, permitindo, finalmente, a criação de diretrizes clínicas amplamente aceitas e aplicáveis na prática clínica diária. Além dessas considerações, um aspecto importante a ser destacado é a escassez de estudos que explorem os efeitos a longo prazo dessas terapias, especialmente no contexto da prevenção de complicações crônicas associadas à osteorradionecrose. O impacto dessas intervenções não se limita apenas à fase de tratamento agudo, mas também à capacidade de prevenir recidivas e manter a qualidade de vida dos pacientes em longo prazo. Há, portanto, uma necessidade crescente de pesquisas longitudinais e estudos multicêntricos que possam oferecer dados mais completos e generalizáveis. Tais estudos devem incluir amostras diversificadas e de maior tamanho, bem como parâmetros padronizados, de forma a gerar um conjunto de evidências mais sólido. Dessa maneira, será possível avançar na criação de diretrizes clínicas embasadas em resultados robustos e, finalmente, integrar o uso dessas terapias de forma mais consistente e eficaz no manejo clínico da osteorradionecrose.

O principal objetivo das revisões de escopo, de um modo geral, é mapear a literatura disponível a respeito de um determinado tema, oferecendo uma visão abrangente das evidências existentes, identificando lacunas no conhecimento e apontando áreas que necessitam de

investigação adicional. Diferentemente das revisões sistemáticas, que buscam fornecer respostas precisas a questões focadas, as revisões de escopo possuem uma abordagem mais exploratória, ideal para tópicos emergentes ou complexos em que há grande heterogeneidade nos métodos e nos resultados dos estudos. No caso da presente revisão, o objetivo consiste precisamente em mapear as tendências e as evidências disponíveis sobre o uso da terapia com laser de baixa intensidade e da aPDT no tratamento e na prevenção da ORN, destacando as lacunas na padronização dos parâmetros de tratamento e a heterogeneidade metodológica que permeiam os estudos atuais. Assim, a revisão buscou fornecer um panorama do estado da pesquisa nessa área, sublinhando a necessidade de ensaios clínicos robustos e padronizados que possam, no futuro, fundamentar diretrizes clínicas consistentes e de ampla aplicabilidade.

Com base nos resultados obtidos até o momento e no progresso significativo em termos de avaliação do potencial terapêutico da fotobiomodulação e da terapia fotodinâmica no manejo da osteorradionecrose, o próximo passo da minha trajetória acadêmica será o desenvolvimento de uma pesquisa aprofundada no contexto do doutorado. O foco principal do doutorado será a continuação das investigações com um estudo experimental *in vitro*, que visa explorar os mecanismos envolvidos na formação de matriz mineral em um modelo de ORN utilizando células *osteoblast-like* (SaOS-2). Este estudo permitirá uma compreensão mais detalhada do impacto da radiação ionizante na fisiologia celular e como as terapias baseadas em laser podem modular o processo de reparo celular.

No doutorado, a pesquisa será ampliada com a análise das melhores doses de laser para a fotobiomodulação, cujas doses em J/cm² ainda serão testadas e definidas, além da avaliação dos efeitos dessas terapias no processo de mineralização óssea em condições osteogênicas. A metodologia empregada incluirá técnicas como a coloração de Alizarina S e a quantificação da formação de matriz mineral por leitura de microplaca, permitindo gerar dados consistentes sobre o potencial terapêutico do laser de baixa intensidade em modelos de ORN induzidos por radiação. Espera-se que esses dados possam contribuir para um melhor entendimento da aplicação clínica dessas terapias no manejo da osteorradionecrose.

Outro aspecto relevante do doutorado será a realização de um doutorado sanduíche, cujo destino será definido em um momento futuro. Durante esse período, terei a oportunidade de colaborar com instituições internacionais de excelência, o que ampliará a rede de cooperação científica e contribuirá para o aprimoramento de abordagens terapêuticas e de protocolos

padronizados no campo das terapias a laser aplicadas à ORN. Essa experiência internacional enriquecerá a qualidade do projeto e trará uma perspectiva global às minhas investigações.

Além da continuidade dos experimentos *in vitro*, o doutorado incluirá a implementação de um projeto educacional com foco na disseminação do conhecimento sobre revisões de escopo. Com base nos resultados da pesquisa conduzida durante o mestrado, será desenvolvido um *e-book* em língua portuguesa, voltado para a comunidade acadêmica. Esse *e-book* será um recurso didático inovador, oferecendo um guia prático e acessível que orientará pesquisadores em todas as etapas da condução de revisões de escopo, desde a formulação da pergunta de pesquisa até a análise e interpretação dos dados coletados. O conteúdo abordará a metodologia e a importância da padronização de protocolos e do rigor científico, garantindo que as revisões sejam conduzidas de maneira sistemática e replicável. Serão incluídos exemplos práticos, exercícios de aplicação e discussões sobre os principais desafios enfrentados pelos pesquisadores, com sugestões de como superá-los. O material também discutirá como as revisões de escopo podem contribuir para o avanço de diferentes campos do conhecimento, destacando sua relevância no planejamento de pesquisas futuras e na identificação de lacunas na literatura. Esse projeto educacional busca expandir o acesso a metodologias robustas e promover a adoção de práticas científicas de alta qualidade, incentivando a produção de revisões de escopo metodologicamente consistentes e transparentes. Com a crescente demanda por revisões de escopo na pesquisa científica, espera-se que este *e-book* se torne uma ferramenta valiosa, especialmente para pesquisadores e grupos de pesquisa no Brasil e em outros países de língua portuguesa. Dessa forma, o doutorado não apenas dará continuidade à pesquisa experimental, mas também terá um impacto significativo no desenvolvimento da pesquisa acadêmica em um nível mais amplo.

O impacto esperado dessa etapa da minha formação acadêmica será duplo: por um lado, contribuir para o avanço nas terapias de prevenção e tratamento da ORN, fundamentadas em abordagens personalizadas; por outro, fomentar uma cultura de pesquisa científica mais robusta e bem estruturada no Brasil, por meio da educação e da disseminação de boas práticas científicas.

6. REFERÊNCIAS

1. Aguiar, B. R. L., Guerra, E. N. S., Normando, A. G. C., Martins, C. C., Reis, P. E. D. D., & Ferreira, E. B. (2021). Effectiveness of photobiomodulation therapy in radiation dermatitis: A systematic review and meta-analysis. Critical Reviews in Oncology/Hematology, 162, 103349. doi: 10.1016/j.critrevonc.2021.103349. Epub 2021 May 11. PMID: 33989768
2. Bautista-Carbajal, A., Villanueva-Arriaga, R. E., Páez-Arenas, A., Massó-Rojas, F., Frechero Molina, N., & García-López, S. (2023). Nitrogen-Containing Bisphosphonates Downregulate Cathepsin K and Upregulate Annexin V in Osteoclasts Cultured *In Vitro*. *International journal of dentistry*, *2023*, 2960941. https://doi.org/10.1155/2023/2960941Beaumont, S., et al. (2021). Timing of dental extractions in patients undergoing radiotherapy and the incidence of osteoradionecrosis: a systematic review and meta-analysis. *British Journal of Oral and Maxillofacial Surgery, 59*(5), 511-523
3. Bensadoun, R. J. (2018). Photobiomodulation or low-level laser therapy in the management of cancer therapy-induced mucositis, dermatitis and lymphedema. Current Opinion in Oncology, 30(4), 226-232. doi: 10.1097/CCO.0000000000000452. PMID: 29794809
4. Bensadoun, R. J., Nair, R. G., & Robijns, J. (2020). Photobiomodulation for Side Effects of Cancer Therapy. Photobiomodulation, Photomedicine, and Laser Surgery, 38(6), 323-325. doi: 10.1089/photob.2019.4759. Epub 2020 May 4. PMID: 32364823.
5. Camolesi, G. C., Ortega, K. L., Medina, J. B., Campos, L., Lorenzo Pouso, A. I., Gándara Vila, P., & Pérez Sayáns, M. (2021). Therapeutic alternatives in the management of osteoradionecrosis of the jaws. Systematic review. *Medicina oral, patologia oral y cirugia bucal*, *26*(2), e195–e207. https://doi.org/10.4317/medoral.24132
6. Campos, L., Martins, F., Tateno, R. Y., Sendyk, W. R., & Palma, L. F. (2021). Antimicrobial photodynamic therapy using optical fiber for oral fistula resulting from mandibular osteoradionecrosis. *Photodiagnosis and photodynamic therapy*, 34, 102247. https://doi.org/10.1016/j.pdpdt.2021.102247
7. Carroll, L., & Humphreys, T. R. (2006). LASER-tissue interactions. *Clinics in dermatology*, *24*(1), 2–7. https://doi.org/10.1016/j.clindermatol.2005.10.019
8. Chronopoulos, A., Zarra, T., Ehrenfeld, M., & Otto, S. (2018). Osteoradionecrosis of the jaws: definition, epidemiology, staging and clinical and radiological findings. A concise review. *International dental journal*, 68(1), 22–30. doi:10.1111/idj.12318
9. Costa, D. A., Costa, T. P., Netto, E. C., Joaquim, N., Ventura, I., Pratas, A. C., Winckler, P., Silva, I. P., Pinho, A. C., Sargento, I. G., Guerreiro, F. G., & Moreira, A. R. (2016). New perspectives on the conservative management of osteoradionecrosis of the mandible: A literature review. *Head & neck*, 38(11), 1708–1716. https://doi.org/10.1002/hed.24495
10. De Felice F, Tombolini V, Musio D, Polimeni A. Radiation Therapy and Mandibular Osteoradionecrosis: State of the Art. *Curr Oncol Rep*. 2020;22(9)
11. de Freitas, L. C., Kawamoto, E. L., Souza, A. M. A., Kawakami, P. Y., Gonçalves, A. S., & Azevedo, L. H. (2023). Use of Phototherapy and Er-YAG Laser in the Management of Mandible Osteoradionecrosis: A Case Report. *Journal of lasers in medical sciences*, *14*, e58. https://doi.org/10.34172/jlms.2023.58
12. DELANIAN, S.; LEFAIX, J.-L. The radiation-induced fibroatrophic process: therapeutic perspective via the antioxidant pathway. Radiotherapy and oncology:

journal of the European Society for Therapeutic Radiology and Oncology, v. 73, n. 2, p. 119–131, 2004

13. Elad, S., Cheng, K. K. F., Lalla, R. V., Yarom, N., Hong, C., Logan, R. M., Bowen, J., Gibson, R., Saunders, D. P., Zadik, Y., Ariyawardana, A., Correa, M. E., Ranna, V., Bossi, P., & Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) (2020). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*, *126*(19), 4423–4431. https://doi.org/10.1002/cncr.33100
14. Escudero, J. S. B., Perez, M. G. B., de Oliveira Rosso, M. P., Buchaim, D. V., Pomini, K. T., Campos, L. M. G., Audi, M., & Buchaim, R. L. (2019). Photobiomodulation therapy (PBMT) in bone repair: A systematic review. *Injury, 50*(11), 1853-1867. doi: 10.1016/j.injury.2019.09.031. Epub 2019 Sep 21. PMID: 31585673.
15. Esteves-Pereira, T. C., Rawat, N., Bensadoun, R. J., Arany, P. R., & Santos-Silva, A. R. (2024). How do clinicians prescribe photobiomodulation therapy (PBMT)? Harmonizing PBMT dosing with photonic fluence and Einstein. *Oral surgery, oral medicine, oral pathology and oral radiology*, S2212-4403(24)00371-7. Advance online publication. https://doi.org/10.1016/j.oooo.2024.06.017.
16. Farkas, J. P., Hoopman, J. E., & Kenkel, J. M. (2013). Five parameters you must understand to master control of your laser/light-based devices. *Aesthetic surgery journal*, *33*(7), 1059–1064. https://doi.org/10.1177/1090820X13501174
17. Ferlay, J., Colombet, M., Soerjomataram, I., Parkin, D. M., Piñeros, M., Znaor, A., & Bray, F. (2021). Cancer statistics for the year 2020: An overview. *International journal of cancer*, 10.1002/ijc.33588. Advance online publication. https://doi.org/10.1002/ijc.33588
18. Ferreira, K. D. M., Corrêa, P. D., Balenzio, G. R., Pigatti, F. M., Ferreira, D. D. C., & Tannure, P. N. (2019). Osteoradionecrosis in a Patient Submitted to Head and Neck Radiotherapy: A Case Report. *International Journal of Odontostomatology, 13*(4), 428-432. doi: http://dx.doi.org/10.4067/S0718-381X2019000400428
19. Franco, T., Cezini, D. C., Metropolo, L., Ferreira, D. C., & Tannure, P. N. (2017). Success of preventive approach to mandibular osteoradionecrosis in an adolescent: Case report. *Oral Surgery*, 10(4), e104-e109. https://doi.org/10.1111/ors.12294
20. Frankart, A. J., Frankart, M. J., Cervenka, B., Tang, A. L., Krishnan, D. G., & Takiar, V. (2021). Osteoradionecrosis: Exposing the Evidence Not the Bone. *International journal of radiation oncology, biology, physics*, 109(5), 1206–1218. doi:10.1016/j.ijrobp.2020.12.043
21. Hadis, M. A., Zainal, S. A., Holder, M. J., Carroll, J. D., Cooper, P. R., Milward, M. R., & Palin, W. M. (2016). The dark art of light measurement: accurate radiometry for low-level light therapy. *Lasers in medical science, 31*(4), 789–809. https://doi.org/10.1007/s10103-016-1914-y
22. Kalhori, K. A. M., Vahdatinia, F., Jamalpour, M. R., Vescovi, P., Fornaini, C., Merigo, E., & Fekrazad, R. (2019). Photobiomodulation in Oral Medicine. Photobiomodulation, Photomedicine, and Laser Surgery, 37(12), 837-861
23. Kolokythas, A., Rasmussen, J. T., Reardon, J., & Feng, C. (2019). Management of osteoradionecrosis of the jaws with pentoxifylline-tocopherol: a systematic review of the literature and meta-analysis. *International Journal of Oral and Maxillofacial Surgery, 48*(2), 173-180
24. Leonetti, J. P., Weishaar, J. R., Gannon, D., Harmon, G. A., Block, A., & Anderson, D. E. (2020). Osteoradionecrosis of the skull base. *Journal of neuro-oncology*, *150*(3), 477–482. https://doi.org/10.1007/s11060-020-03462-3

25. Liu, W., Qdaisat, A., Zhou, S., Fuller, C. D., Ferrarotto, R., Guo, M., Lai, S. Y., Cardoso, R., Mohamed, A. S. R., Lopez, G., Narayanan, S., van Dijk, L. V., Cohen, L., Bruera, E., Yeung, S. J., & Hanna, E. Y. (2021). Hypomagnesemia and incidence of osteoradionecrosis in patients with head and neck cancers. *Head & neck*, *43*(2), 613–621. https://doi.org/10.1002/hed.26510
26. Magalhães, I. A., Forte, C. P. F., Viana, T. S. A., Teófilo, C. R., Lima Verde, R. M. B., Magalhães, D. P., Praxedes Neto, R. A. L., Lima, R. A., & Dantas, T. S. (2020). Photobiomodulation and antimicrobial photodynamic therapy as adjunct in the treatment and prevention of osteoradionecrosis of the jaws: A case report. *Photodiagnosis and Photodynamic Therapy, 31*, 101959. doi: 10.1016/j.pdpdt.2020.101959. Epub 2020 Aug 18. PMID: 32818642
27. Marcondes, C. F., Rodrigues, J. V. S., Zuza, E. C., Tanimoto, H. M., & Barroso, E. M. (2022). Risk factors associated with osteoradionecrosis of the mandible in patients with cancer of oral cavity and oropharynx. *Revista de Odontologia da UNESP*, 51, e20220037. https://doi.org/10.1590/1807-2577.03722
28. Marques, M. M., Diniz, I. M., de Cara, S. P., Pedroni, A. C., Abe, G. L., D'Almeida-Couto, R. S., ... Moreira, M. S. (2016). Photobiomodulation of Dental Derived Mesenchymal Stem Cells: A Systematic Review. *Photomedicine and Laser Surgery, 34*(11), 500-508
29. Moreschi, C., Capparè, P., Meleti, M., Vescovi, P., Bonanini, M., Gherlone, E. F., et al. (2016). Low level laser therapy in non-surgical management of osteoradionecrosis of the jaws. *Minerva Stomatologica, 65*
30. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 3.01. (2013). Retrieved from https://www.openepi.com. (accessed 15 March 2024).
31. Otto, S., Shreeja, S., Kakoschke, S. C., Albittar, M. M., Widenhorn, A., & Kakoschke, T. K. (2024). Pre- and post-operative quality of life in patients with osteoradionecrosis of the jaw. *Cancers, 16*, 2256. https://doi.org/10.3390/cancers16122256
32. Owosho, A. A., Tsai, C. J., Lee, R. S., Freymiller, H., Kadempour, A., Varthis, S., Sax, A. Z., Rosen, E. B., Yom, S. K., Randazzo, J., Drill, E., Riedel, E., Patel, S., Lee, N. Y., Huryn, J. M., & Estilo, C. L. (2017). The prevalence and risk factors associated with osteoradionecrosis of the jaw in oral and oropharyngeal cancer patients treated with intensity-modulated radiation therapy (IMRT): The Memorial Sloan Kettering Cancer Center experience. *Oral oncology*, *64*, 44–51. https://doi.org/10.1016/j.oraloncology.2016.11.015
33. Pedroni, A. C. F., Miniello, T. G., Hirota, C., Carvalho, M. H., Lascala, C. A., & Marques, M. M. (2020). Successful application of antimicrobial photodynamic and photobiomodulation therapies for controlling osteoradionecrosis and xerostomia after laryngeal carcinoma treatment: A case report of full oral rehabilitation. *Photodiagnosis and Photodynamic Therapy, 31*, 101835. doi: 10.1016/j.pdpdt.2020.101835. Epub 2020 May 25. PMID: 32464267
34. Pellicioli, A. C., Martins, M. D., Dillenburg, C. S., Marques, M. M., Squarize, C. H., & Castilho, R. M. (2014). Laser phototherapy accelerates oral keratinocyte migration through the modulation of the mammalian target of rapamycin signaling pathway. *Journal of Biomedical Optics, 19*(2), 028002
35. Peters, M. D. J., Godfrey, C., McInerney, P., Munn, Z., Tricco, A. C., & Khalil, H. (2020). Chapter 11: Scoping Reviews (2020 version). In E. Aromataris & Z. Munn (Eds.), *JBI Manual for Evidence Synthesis*. JBI. Available from https://synthesismanual.jbi.global. https://doi.org/10.46658/JBIMES-20-12
36. Peterson, D. E., Doerr, W., Hovan, A., Pinto, A., Saunders, D., Elting, L. S., Spijkervet, F. K., & Brennan, M. T. (2010). Osteoradionecrosis in cancer patients: the evidence base

for treatment-dependent frequency, current management strategies, and future studies. *Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer*, *18*(8), 1089–1098. https://doi.org/10.1007/s00520-010-0898-6

37. Porcaro, G., Amosso, E., Mirabelli, L., Busa, A., Carini, F., & Maddalone, M. (2015). Osteoradionecrosis of the posterior maxilla: A new approach combining erbium aluminium garnet laser and Bichat bulla flap. *The Journal of Craniofacial Surgery, 26*(7). doi: 10.1097/SCS.0000000000002136
38. Prado, T. P., Zanchetta, F. C., Barbieri, B., Aparecido, C., Melo Lima, M. H., & Araujo, E. P. (2023). Photobiomodulation with Blue Light on Wound Healing: A Scoping Review. *Life (Basel, Switzerland)*, *13*(2), 575. https://doi.org/10.3390/life13020575
39. Qualliotine, J. R., Yousef, A., Orosco, R. K., Fugere, M., Kolb, F. J., Kristallis, T., & Archambault, K. (2023). Carbon Dioxide Laser Sequestrectomy for Osteoradionecrosis: A Case Series. *Photobiomodulation, photomedicine, and laser surgery*, *41*(2), 73–79. https://doi.org/10.1089/photob.2022.0090
40. Raggio, B. S., & Winters, R. (2018). Modern management of osteoradionecrosis. *Current Opinion in Otolaryngology & Head and Neck Surgery*, *26*(4), 254-259
41. Rech, C. A., Pansani, T. N., Cardoso, L. M., Ribeiro, I. M., Silva-Sousa, Y. T. C., de Souza Costa, C. A., & Basso, F. G. (2022). Photobiomodulation using LLLT and LED of cells involved in osseointegration and peri-implant soft tissue healing. *Lasers in medical science*, *37*(1), 573–580. https://doi.org/10.1007/s10103-021-03299-w
42. Ribeiro, G. H., Minamisako, M. C., Rath, I. B. D. S., Santos, A. M. B., Simões, A., Pereira, K. C. R., & Grando, L. J. (2018). Osteoradionecrosis of the jaws: case series treated with adjuvant low-level laser therapy and antimicrobial photodynamic therapy. *Journal of applied oral science: revista FOB*, *26*, e20170172. https://doi.org/10.1590/1678-7757-2017-0172
43. Robijns, J., Nair, R. G., Lodewijckx, J., Arany, P., Barasch, A., Bjordal, J. M., Bossi, P., Chilles, A., Corby, P. M., Epstein, J. B., Elad, S., Fekrazad, R., Fregnani, E. R., Genot, M.-T., Ibarra, A. M. C., Hamblin, M. R., Heiskanen, V., Hu, K., Klastersky, J., Lalla, R., Latifian, S., Maiya, A., Mebis, J., Migliorati, C. A., Milstein, D. M. J., Murphy, B., Raber-Durlacher, J. E., Roseboom, H. J., Sonis, S., Treister, N., Zadik, Y., Bensadoun, R.-J., & WALT Working Group on Cancer Supportive Care. (2022). Photobiomodulation therapy in management of cancer therapy-induced side effects: WALT position paper 2022. *Frontiers in Oncology*, 12, 927685. https://doi.org/10.3389/fonc.2022.927685
44. Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L. A., & PRISMA-P Group (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ (Clinical research ed.)*, *350*, g7647. https://doi.org/10.1136/bmj.g7647
45. Shaw, R., Tesfaye, B., Bickerstaff, M., Silcocks, P., & Butterworth, C. (2017). Refining the definition of mandibular osteoradionecrosis in clinical trials: The Cancer Research UK HOPON trial (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis). *Oral Oncology, 64*, 73-77. https://doi.org/10.1016/j.oraloncology.2016.12.002
46. Sonis, S. T., Hashemi, S., Epstein, J. B., Nair, R. G., & Raber-Durlacher, J. E. (2016). Could the biological robustness of low-level laser therapy (Photobiomodulation) impact its use in the management of mucositis in head and neck cancer patients. *Oral Oncology, 54*, 7-14. doi: 10.1016/j.oraloncology.2016.01.005
47. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and

Mortality Worldwide for 36 Cancers in 185 Countries. *CA: a cancer journal for clinicians*, *71*(3), 209–249. https://doi.org/10.3322/caac.21660

48. Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., Lewin, S., … Straus, S. E. (2018). PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Annals of internal medicine*, *169*(7), 467–473. https://doi.org/10.7326/M18-0850
49. Zadik, Y., Arany, P. R., Fregnani, E. R., Bossi, P., Antunes, H. S., Bensadoun, R. J., Gueiros, L. A., Majorana, A., Nair, R. G., Ranna, V., Tissing, W. J. E., Vaddi, A., Lubart, R., Migliorati, C. A., Lalla, R. V., Cheng, K. K. F., Elad, S., & Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) (2019). Systematic review of photobiomodulation for the management of oral mucositis in cancer patients and clinical practice guidelines. *Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer*, *27*(10), 3969–3983. https://doi.org/10.1007/s00520-019-04890-2

7. APÊNDICE

7.1.Apêndice 1. Protocolo da revisão de escopo

SCOPING REVIEW PROTOCOL

Laboratório de Histopatologia Bucal

SCOPING REVIEW PROTOCOL

1| REVIEW TITLE AND ADMNISTRATIVE INFORMATION

☐ **Review title** - *Give the working title of the review in English.*

Laser therapy in the management of osteoradionecrosis: A scoping review

☐ **Original language title** - *For reviews in languages other than English, this field should be used to enter the title in the language of the review. It is not necessary to fill in if the original language is English.*

☐ **Keywords** - *Give at least 6 keywords that best describe the review. If possible, use MeSH terms.*

Osteoradionecrosis; Laser therapy; Photobiomodulation therapy; Low-Level Light Therapy; Scoping review

☐ **Anticipated or actual start date** | **Anticipated completion date**

September 2023 and January, 2024 | April 2024

☐ **Registration** - *Intended registration institutions and platforms.*

☐ Joanna Briggs Institute - University of Adelaide
https://jbi.global/systematic-review-register
☐ Campbell Collaboration – Campbell National and Regional Centers (NRCs)
https://www.campbellcollaboration.org/
☒ Open Science Framework - Center for Open Science
https://osf.io/dashboard
☐ ResearchGate
https://www.researchgate.net/
☐ Preprint database: _____
☐ Other Scientific Journal: _____

UnB

This protocol was developed based on Moher D et al. (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement; Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews checklist (PRISMA-ScR) (Tricco et al. 2018); And adapted according to PROSPERO items (http://www.crd.york.ac.uk/PROSPERO/)

SCOPING REVIEW PROTOCOL

2| REVIEW TEAM AND INSTITUTINAL AFFILIATION - *Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author.*

Named contact - *The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.*

Eliete Neves Silva Guerra

Named contact address

elieteneves@unb.br

Named contact phone number

+55 (61) 99668-4988

Organizational affiliation of the review / website address

University of Brasília/ http://www.unb.br

Review team members and their organizational affiliation - *Describe contributions of protocol authors of the review*

TITLE (Professor, Dr, Mr, Ms, Miss, Mrs)	NAME (Completed name)	AFFILIATION (Organizational affiliations)	CONTACT (Contact email of the authors)	CONTRIBUTIONS (Contributions of the authors)
Dr	Larissa Di Carvalho Melo	University of Brasilia	larissa.dicarvalhom@gmail.com	1 Reviewer
Dr	Bruna Bastos Silveira	University of Brasilia	brunabastosodt@gmail.com	2 Reviewer
Dr	Mylene Martins Monteiro	University of Brasilia	mylenemonteiro7@gmail.com	3 Reviewer
Dr	Juliana Amorim dos Santos	University of Brasilia	juliana@zamorim.com	4 Reviewer
Dr	Elaine Barros Ferreira	University of Brasilia	Elaine.barrosf@gmail.com	Expert
Dr	Paula Elaine Diniz dos Reis	University of Brasilia	pauladiniz@unb.br	Expert
Dr	Camila de Barros Gallo	University of São Paulo	camilagallo@usp.br	Expert
Professor	Eliete Neves Silva Guerra	University of Brasilia	elieteneves@unb.br	Coordinator

SCOPING REVIEW PROTOCOL

Funding sources/sponsors - *Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review, as well as the grant or award number and the date of award.*

This project was funded by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) through the Edital Universal (Process: 406557/2021-7; CNPq/MCTI/FNDCT Nº 18/2021 - Faixa B - Grupos Consolidados)

Conflicts of interest - *List actual or perceived conflicts of interest (financial or academic).*

The authors have no conflicts of interest to declare

Collaborators - *Give the name and affiliation of any individuals or organizations who are working on the review but who are not listed as review team members.*

3| INTRODUCTION AND REVIEW QUESTION

Condition or domain being studied - *Describe the rationale for the review in the context of what is already known, giving a short description of the disease, condition or healthcare domain being studied.*

Osteoradionecrosis (ORN) of the maxillofacial complex is a complication resulting from radiotherapy in head and neck tumors. It is characterized by the non-healing of irradiated bone over three to six months, with no evidence of persistent or recurrent tumors at the site.
Photobiomodulation therapy is considered an effective non-invasive treatment for many oral disorders, including mucositis, xerostomia, altered taste, and dysphagia. In irradiated bone, photobiomodulation has been observed to accelerate bone regeneration, increase the number of osteocytes, regulate the inflammatory response, and enhance tissue vascularization. Moreover, studies suggest that both photobiomodulation and antimicrobial photodynamic therapy have been employed as adjuncts to surgical procedures in treating ORN, without recurrence observed after a one-year follow-up. Antimicrobial photodynamic therapy has also proven effective in lesion control. Therefore, low-level light therapies can be an effective agent to prevent and treat ORN.
It is expected to investigate the effects of modulators on the repair process and map how photobiomodulation and photodynamic therapy can contribute to a better understanding of physiological functions and therapeutic effects in osteoradionecrosis.

SCOPING REVIEW PROTOCOL

☐ **Review question(s)** - *Provide an explicit statement of the question(s) the review will address with reference to participants, interventions/exposure, comparators, outcomes, and study design.*

REVIEW QUESTION: **What are the effects of laser therapy in the management of osteoradionecrosis?**

P – Population: Animal or human with osteoradionecrosis

C – Concept: Effects of laser therapies in the management of osteoradionecrosis

C – Context: Treatment or prevention of osteoradionecrosis

Types of evidence sources (Studies): Reviews, observational studies and interventional studies

4| INCLUSION AND EXCLUSION CRITERIA DETAILS

☐ **Context** - *Provide relevant details about the review and characteristics to help identify inclusion and exclusion criteria.*

Inclusion criteria

1. Studies in animals and/or humans evaluated the effect of laser therapy in preventing osteoradionecrosis;
2. Studies in animals and humans evaluated the effect of laser therapy in treating osteoradionecrosis;
3. Reviews that evaluated the effect of laser therapy in the prevention or treatment of osteoradionecrosis after radiotherapy.

Exclusion criteria

1. Studies that did not meet the inclusion criteria (laser therapy (photobiomodulation and/or photodynamic therapy) was not used for osteoradionecrosis management);
2. Studies that evaluated medication-related osteonecrosis;
3. Conference abstract or letter to the editor;
4. Studies in humans that not receive head and neck radiotherapy.

UnB

This protocol was developed based on Moher D et al. (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement; Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews checklist (PRISMA-ScR) (Tricco et al. 2018); And adapted according to PROSPERO items (http://www.crd.york.ac.uk/PROSPERO/)

SCOPING REVIEW PROTOCOL

5| OUTCOMES AND ANALYSIS

☐ **Main outcome(s)** - *List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale.*

The main outcome is to map the effects of laser therapy in the treatment and/or prevention of osteoradionecrosis due to radiotherapy. This includes examining the specific type of laser therapy used and the associated parameters. As potential secondary outcomes, it is expected to map factors such as the affected region, sex, age, related risk factors, dose of radiation used in radiotherapy, and chemoradiotherapy.

☐ **Data extraction (selection and coding)** - *State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis). Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators.*

Two independent reviewers (LDCM and BBSS) will collect the information from the selected articles. After that, a third reviewer (MMM) will crosscheck the collected data and confirm its accuracy. If there is any disagreement in any of the phases, they will be resolved by discussion for mutual agreement between the reviewers. Besides that, the expert reviewer (ENSG) will be involved as required to enable the formulation of the final decision.

☐ **Critical appraisal of individual sources of evidence** - *If planned (non-mandatory item), describe anticipated methods for assessing risk of bias or methodology quality of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis.*

Although the risk of bias assessment is not mandatory (Tricco et al., 2018), the lack of critical appraisal has been identified as the limitation of scoping reviews. We will conduct a critical appraisal of included studies based on the JBI (https://jbi.global/critical-appraisal-tools) to identify gaps in literature related to the risk of bias of published research.

SCOPING REVIEW PROTOCOL

Strategy for data synthesis - *Describe criteria under which study data will be quantitatively synthesized. If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency. If quantitative synthesis is not appropriate, describe the type of summary planned.*

The qualitative synthesis will be performed by grouping and comparing the data described in the included studies. Summary statistics, frequencies, tables and a narrative summary will be used to describe study characteristics. If the quantitative synthesis is not appropriate, it will be conducted by grouping and comparing data reported in the included studies with GraphPad Prism software version 10 (GraphPad Software, La Jolla California, USA) will be used to compile and express the results. Also, bibliometric data may be presented through visual maps, using the VOSviewer bibliometric software to analyze and visualize publication trends, largest contributors, and scientific research mapping regarding the use of laser therapy in osteoradionecrosis.

Analysis of subgroups or subsets - *State any planned investigation of subgroups. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.*

Not applicable

SCOPING REVIEW PROTOCOL

6| SEARCHES AND DATA MANAGEMENT

☐ **Searches** - *State the sources that will be searched. Give the search dates, and any restrictions (e.g. Language or publication period).*

There will be no language limitation or publication date of the studies. In addition, there will be no restrictions on the type of light protocol used or the technique for applying laser therapy.

☐ **Search strategy**

SEARCH	QUERY – (SEPTEMBER, 20 TH, 2023)	ITEMS FOUND
#1 AND #2	Search: ("osteoradionecrosis"[MeSH Terms] OR ("osteoradionecrosis"[MeSH Terms] OR "osteoradionecrosis"[All Fields] OR "osteoradionecroses"[All Fields]) OR "Radiation Injuries"[All Fields] OR "Osteoradionecroses" OR "Jaw osteoradionecrosis" OR "Jaws osteoradionecrosis" OR "Bone Necrosis" OR "Exposed bone" OR "ORNJ") AND ("Laser Therapy"[MeSH Terms] OR "low level light therapy"[MeSH Terms] OR "photobiomodulation"[All Fields] OR "phototherapy laser"[All Fields] OR "Laser Biostimulation"[All Fields] OR "low level light therapy"[All Fields] OR "Low-Level Light Therapies"[All Fields] OR "Low Level Laser Therapy"[All Fields] OR "LLLT"[All Fields])	355
#2	Search: ("osteoradionecrosis"[MeSH Terms] OR ("osteoradionecrosis"[MeSH Terms] OR "osteoradionecrosis"[All Fields] OR "osteoradionecroses"[All Fields]) OR "Radiation Injuries"[All Fields] OR "Osteoradionecroses" OR "Jaw osteoradionecrosis" OR "Jaws osteoradionecrosis" OR " Bone Necrosis" OR "Exposed bone" OR "ORNJ")	51,379
#1	Search: ("Laser Therapy"[MeSH Terms] OR "low level light therapy"[MeSH Terms] OR "photobiomodulation"[All Fields] OR "phototherapy laser"[All Fields] OR "Laser Biostimulation"[All Fields] OR "low level light therapy"[All Fields] OR "Low-Level Light Therapies"[All Fields] OR "Low Level Laser Therapy"[All Fields] OR "LLLT"[All Fields])	69,113
TOTAL		355

SCOPING REVIEW PROTOCOL

Databases	Additional literature (grey literature)
☒ PubMed ☒ EMBASE ☐ Cochrane ☐ LILACS ☒ Web of Science Core Collection ☐ Science Direct ☐ CINAHL ☐ Livivo ☐ Scopus ☐ Other:	☒ Google Scholar web search (specify if limitations applied) ☒ Hand searches of bibliographies from included studies ☒ Bibliometric Analysis ☒ Proquest (Dissertation and Theses)

Data management

☒ Endnote	☐ Zotero
☐ Refworks	☐ Covidence
☐ Mendeley	☐ Other: _____
☒ Rayyan	

7| GENERAL INFORMATION ON THE REVIEW SUBJECT

Subject of the scoping review - *Explain the type of review and the health area(s) of interest for your review.*

Any additional information

SCOPING REVIEW PROTOCOL

Dissemination plans - *Do you intend to publish the review on completion in a scientific journal?*

☐ **Yes**

Suggest 3 journals in which this research could be published and their Impact factor:

1 Photodiagnosis and Photodynamic Therapy	IF: 3.3
2 Lasers in Medical Science	IF: 2.1
3 Photobiomodulation Photomedicine Laser Surgery	IF: 2.744
4 Oral Diseases	IF: 4.068

☐ **No**

Specify other communication vehicles that you intend to share your review study

_____

SCOPING REVIEW PROTOCOL

8| STAGE OF REVIEW AT TIME OF THIS SUBMISSION - *Provide information regarding the stage of review at protocol submission. Note that is important to submit before completion of preliminary searches, which means this review has not yet started.*

REVIEW STAGE	STARTED	COMPLETED
This review has not yet started	☒	☐
Preliminary searches	☒	☐
Piloting of the study selection process	☒	☐
Formal screening of search results against eligibility criteria	☒	☐
Data extraction	☐	☐
Risk of bias (quality) assessment	☐	☐
Data analysis	☐	☐

Provide relevant information about the stage of the review, if necessary.

9| REVIEW SUBJECT RELEVANCE

Reviews about the same subject - *Is there any previous systematic review about the same subject?*

☒ **Yes**

Please, cite the previous systematic review:

de Oliveira SV, Dos Reis T, Amorim J, Rocha FS, Marques MM, Guerra ES, Hanna R, Gallo CB. Efficacy of photobiomodulation therapy on healing of ionizing irradiated bone: a systematic review of in vivo animal studies. Lasers Med Sci. 2022 Dec;37(9):3379-3392. doi: 10.1007/s10103-022-03649-2. Epub 2022 Oct 4. PMID:36194304.

_____

Why perform another one? Specify the differences and relevance of the systematic review being planned.

A scoping review will be conducted instead of a systematic review. The research question for the scoping review is broader and aims to cover not only in vivo studies but also other study designs that evaluate the use of laser therapy in osteoradionecrosis.

_____

☐ **No, it is an inedited subject.**

SCOPING REVIEW PROTOCOL

☐ **Cite 3 sentinel studies that will probably be included in this systematic review**

1. Moreschi, C., CAPPARè, P., Meleti, M., Vescovi, P., Bonanini, M., Gherlone, E. F., & Gastaldi, G. (2016). Low level laser therapy in non-surgical management of osteoradionecrosis of the jaws. *Minerva stomatologica*, *65*(3), 185–187.

2. Camolesi, G. C., Ortega, K. L., Medina, J. B., Campos, L., Lorenzo Pouso, A. I., Gándara Vila, P., & Pérez Sayáns, M. (2021). Therapeutic alternatives in the management of osteoradionecrosis of the jaws. Systematic review. *Medicina oral, patologia oral y cirugia bucal*, *26*(2), e195–e207. https://doi-org.ez54.periodicos.capes.gov.br/10.4317/medoral.24132

3. Magalhães, I. A., Forte, C., Viana, T., Teófilo, C. R., Lima Verde, R., Magalhães, D. P., Praxedes Neto, R., Lima, R. A., & Dantas, T. S. (2020). Photobiomodulation and antimicrobial photodynamic therapy as adjunct in the treatment and prevention of osteoradionecrosis of the jaws: A case report. *Photodiagnosis and photodynamic therapy*, *31*, 101959. https://doi-org.ez54.periodicos.capes.gov.br/10.1016/j.pdpdt.2020.101959

8. ANEXOS

Anexo 1. Artigos como autora e coautora

Artigo publicado

1. Oral manifestations in pediatric patients with leukemia: A systematic review and meta-analysis

   Journal: *The Journal of the American Dental Association – JADA* (Quallis A1; IF= 3.4)

Gmail — Larissa Di Carvalho <larissa.carmelo5@gmail.com>

Share your article [ADAJ_2659] published in The Journal of the American Dental Association
1 mensagem

Elsevier - article status <noreplyrs@elsevier.com> 9 de setembro de 2024 às 00:40
Para: larissa.carmelo5@gmail.com

ELSEVIER

Share your article!

Dear Dr Di Carvalho Melo,

As co-author of the article *Oral Manifestations in Leukemia Pediatric Patients: A Systematic Review and Meta-analysis*, we are pleased to let you know that your article is now available online with author corrections incorporated. Full citation details, e.g. volume and/or issue number, publication year and page numbers, will be added when the final version becomes available.

To help you and the other authors access and share this work, we have created a Share Link – a personalized URL providing **50 days' free access** to the article. Anyone clicking on this link before October 29, 2024 will be taken directly to the latest version of your article on ScienceDirect, which they are welcome to read or download. No sign up, registration or fees are required.

Your personalized Share Link:
https://authors.elsevier.com/c/1jkWYf0DS3Pr

We encourage you to use this Share Link to download a copy of the article for your own archive. The URL is also a quick and easy way to share your work with colleagues, co-authors and friends. And you are welcome to add the Share Link to your homepage or social media profiles, such as Facebook and Twitter.

You can find out more about Share Links on Elsevier.com.

Did you know, as an author, you can use your article for a wide range of scholarly, non-commercial purposes, and share and post your article online in a variety of ways? For more information visit www.elsevier.com/sharing-articles.

Kind regards,
Elsevier Researcher Support

Increase your article's impact
Our Get Noticed guide contains a range of practical tips and advice to help you maximize visibility of your

Artigos submetidos em processo de revisão

1. Current trends and available evidence on low-level laser therapy for osteoradionecrosis: A scoping review

   Journal: *Photodiagnosis and Photodynamic Therapy* (Qualis A1, IF=3.1)

Gmail Larissa Di Carvalho Melo <larissa.dicarvalhom@gmail.com>

Confirm co-authorship of submission to Photodiagnosis and Photodynamic Therapy
1 mensagem

Photodiagnosis and Photodynamic Therapy <em@editorialmanager.com> 9 de julho de 2024 às 17:34
Responder a: Photodiagnosis and Photodynamic Therapy <support@elsevier.com>
Para: Larissa Di Carvalho Melo <larissa.dicarvalhom@gmail.com>

This is an automated message.

Journal: Photodiagnosis and Photodynamic Therapy
Title: Current trends and available evidence on low-level laser therapy for osteoradionecrosis: A scoping review
Corresponding Author: Prof Eliete Neves Silva Guerra
Co-Authors: Larissa Di Carvalho Melo; Bruna Bastos Silveira; Mylene Martins Monteiro; Juliana Amorim dos Santos; Elaine Barros Ferreira; Paula Elaine Diniz Reis; Camila de Barros Gallo
Manuscript Number: **PDPDT-D-24-00410**

Dear Larissa Di Carvalho Melo,

The corresponding author Prof Eliete Neves Silva Guerra has listed you as a contributing author of the following submission via Elsevier's online submission system for Photodiagnosis and Photodynamic Therapy.

Submission Title: Current trends and available evidence on low-level laser therapy for osteoradionecrosis: A scoping review

Elsevier asks all authors to verify their co-authorship by confirming agreement to publish this article if it is accepted for publication.

Please read the following statement and confirm your agreement by clicking on this link: Yes, I am affiliated.

I irrevocably authorize and grant my full consent to the corresponding author of the manuscript to: (1) enter into an exclusive publishing agreement with Elsevier on my behalf (or, if the article is to be published under a CC BY license, a non-exclusive publishing agreement), in the relevant form set out at www.elsevier.com/copyright ; and (2) unless I am a US government employee, to transfer my copyright or grant an exclusive license of rights (or for CC BY articles a non-exclusive license of rights) to Elsevier as part of that publishing agreement , effective on acceptance of the article for publication. If the article is a work made for hire, I am authorized to confirm this on behalf of my employer. I agree that the copyright status selected by the corresponding author for the article if it is accepted for publication shall apply and that this agreement is subject to the governing law of the country in which the journal owner is located.

If you did not co-author this submission, please contact the corresponding author directly at elieteneves.unb@gmail.com.

Thank you,
Photodiagnosis and Photodynamic Therapy

More information and support
FAQ: What is copyright co-author verification?
https://service.elsevier.com/app/answers/detail/a_id/28460/supporthub/publishing/
FAQ: How can I reset a forgotten password?
https://service.elsevier.com/app/answers/detail/a_id/28452/supporthub/publishing/
For further assistance, please visit our customer service site: https://service.elsevier.com/app/home/supporthub/publishing/
Here you can search for solutions on a range of topics, find answers to frequently asked questions, and learn more about Editorial Manager via interactive tutorials. You can also talk 24/7 to our customer support team by phone and 24/7 by live chat and email

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Remove my information/details). Please contact the publication office if you have any questions.

2. Oral manifestations of COVID-19 vaccinated, post-illness and different variants: study of Brazilian population

   Journal: *Brazilian Oral Research* (Qualis A2; IF=1.5)

Gmail Larissa Di Carvalho Melo <larissa.dicarvalhom@gmail.com>

Brazilian Oral Research - Manuscript ID BOR-2023-0662.R1
6 mensagens

Cristina Leitão <onbehalfof@manuscriptcentral.com> 13 de maio de 2024 às 21:27
Responder a: office.bor@ingroup.srv.br
Para: elieteneves@unb.br
Cc: larissa.dicarvalhom@gmail.com, juliana@zamorim.com, brunabastosodt@gmail.com, castrovitoriat@gmail.com, gabinormando@gmail.com, carol_pr@yahoo.com.br, alan@unicamp.br, fabivfer@gmail.com, elieteneves@unb.br

13-May-2024

Dear Dr. Guerra:

Your manuscript entitled "Oral manifestations of COVID-19 vaccinated, post-illness and different variants: study of Brazilian population" has been successfully submitted online and is presently being given full consideration for publication in the Brazilian Oral Research.

Your manuscript ID is BOR-2023-0662.R1.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to ScholarOne Manuscripts at https://mc04.manuscriptcentral.com/bor-scielo and edit your user information as appropriate.

You can also view the status of your manuscript at any time by checking your Author Center after logging in to https://mc04.manuscriptcentral.com/bor-scielo.

Thank you for submitting your manuscript to the Brazilian Oral Research.

Sincerely,
Brazilian Oral Research Editorial Office

Eliete Neves Da Silva Guerra <elieteneves@unb.br> 13 de maio de 2024 às 21:31
Para: "elieteneves.unb" <elieteneves.unb@gmail.com>
Cc: "larissa.dicarvalhom@gmail.com" <larissa.dicarvalhom@gmail.com>, Juliana Amorim <juliana@zamorim.com>, "brunabastosodt@gmail.com" <brunabastosodt@gmail.com>, "castrovitoriat@gmail.com" <castrovitoriat@gmail.com>, gabinormando <gabinormando@gmail.com>, "carol_pr@yahoo.com.br" <carol_pr@yahoo.com.br>, "alan@unicamp.br" <alan@unicamp.br>, "fabivfer@gmail.com" <fabivfer@gmail.com>

Prezados, realizamos a revisão do artigo conforme sugerido pelos revisores.
Estamos confiantes na publicação.
Abraço e manterei todos informados.
Eliete

--
Eliete N. S. Guerra

Professor of the University of Brasilia.

Laboratory of Oral Histopathology, Department of Dentistry, Faculty of Health Sciences, University of Brasilia, Campus Darcy Ribeiro, Asa Norte, Brazil. Zip Code: 70910-900.

Email: elieteneves@unb.br; elieteneves.unb@gmail.com

Phone: +55-61-996684988

http://lattes.cnpq.br/7525934473290213

3. Effects of ionizing radiation in osteoblastic cells: in vitro insights into the etiopathogenesis of osteoradionecrosis

   Journal: *Archives of Oral Biology* (Qualis A1, IF=2.2)

Gmail — Larissa Di Carvalho <larissa.carmelo5@gmail.com>

Confirm co-authorship of submission to Archives of Oral Biology
1 mensagem

Archives of Oral Biology <em@editorialmanager.com> 25 de agosto de 2024 às 19:16
Responder a: Archives of Oral Biology <support@elsevier.com>
Para: Larissa Di Carvalho Melo <larissa.carmelo5@gmail.com>

This is an automated message.

Journal: Archives of Oral Biology
Title: Effects of ionizing radiation in osteoblastic cells: in vitro insights into the etiopathogenesis of osteoradionecrosis
Corresponding Author: Prof Eliete Neves Silva Guerra
Co-Authors: Bruna Bastos Silveira; Larissa Di Carvalho Melo; Mylene Martins Monteiro; Juliana Amorim dos Santos; Paula Elaine Diniz Reis; Angelica Amorim Amato; Taia Maria Berto Rezende
Manuscript Number: **AOB-D-24-01015**

Dear Larissa Di Carvalho Melo,

The corresponding author Prof Eliete Neves Silva Guerra has listed you as a contributing author of the following submission via Elsevier's online submission system for Archives of Oral Biology.

Submission Title: Effects of ionizing radiation in osteoblastic cells: in vitro insights into the etiopathogenesis of osteoradionecrosis

Elsevier asks all authors to verify their co-authorship by confirming agreement to publish this article if it is accepted for publication.

Please read the following statement and confirm your agreement by clicking on this link: Yes, I am affiliated.

I irrevocably authorize and grant my full consent to the corresponding author of the manuscript to: (1) enter into an exclusive publishing agreement with Elsevier on my behalf (or, if the article is to be published under a CC BY license, a non-exclusive publishing agreement), in the relevant form set out at www.elsevier.com/copyright ; and (2) unless I am a US government employee, to transfer my copyright or grant an exclusive license of rights (or for CC BY articles a non-exclusive license of rights) to Elsevier as part of that publishing agreement , effective on acceptance of the article for publication. If the article is a work made for hire, I am authorized to confirm this on behalf of my employer. I agree that the copyright status selected by the corresponding author for the article if it is accepted for publication shall apply and that this agreement is subject to the governing law of the country in which the journal owner is located.

If you did not co-author this submission, please contact the corresponding author directly at elieteneves.unb@gmail.com.

Thank you,
Archives of Oral Biology

More information and support
FAQ: What is copyright co-author verification?
https://service.elsevier.com/app/answers/detail/a_id/28460/supporthub/publishing/

Have questions or need assistance?
For further assistance, please visit Elsevier Support Center for Author Support. Here you can search for solutions on a range of topics, find answers to frequently asked questions, and learn more about Editorial Manager via interactive tutorials.
You can also talk to our customer support team 24/7 by live chat, email and phone.

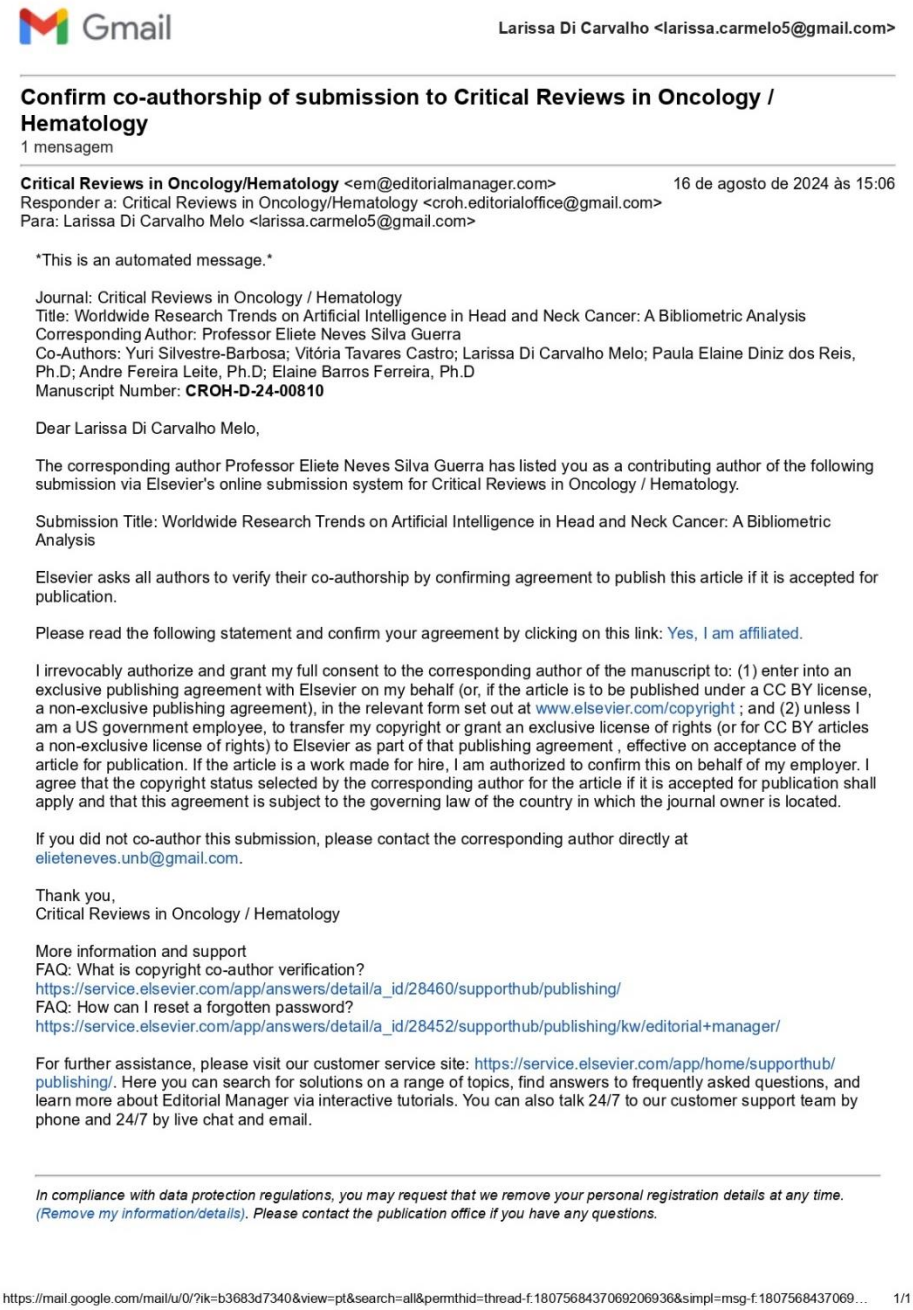
#AU_AOB#

To ensure this email reaches the intended recipient, please do not delete the above code

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Remove my information/details). Please contact the publication office if you have any questions.

4. Worldwide Research Trends on Artificial Intelligence in Head and Neck Cancer: A Bibliometric Analysis

Journal*: Critical Reviews in Oncology/Hematology* (Qualis A1, IF=5.5).



Gmail — Larissa Di Carvalho <larissa.carmelo5@gmail.com>

Confirm co-authorship of submission to Critical Reviews in Oncology / Hematology
1 mensagem

Critical Reviews in Oncology/Hematology <em@editorialmanager.com> 16 de agosto de 2024 às 15:06
Responder a: Critical Reviews in Oncology/Hematology <croh.editorialoffice@gmail.com>
Para: Larissa Di Carvalho Melo <larissa.carmelo5@gmail.com>

This is an automated message.

Journal: Critical Reviews in Oncology / Hematology
Title: Worldwide Research Trends on Artificial Intelligence in Head and Neck Cancer: A Bibliometric Analysis
Corresponding Author: Professor Eliete Neves Silva Guerra
Co-Authors: Yuri Silvestre-Barbosa; Vitória Tavares Castro; Larissa Di Carvalho Melo; Paula Elaine Diniz dos Reis, Ph.D; Andre Fereira Leite, Ph.D; Elaine Barros Ferreira, Ph.D
Manuscript Number: **CROH-D-24-00810**

Dear Larissa Di Carvalho Melo,

The corresponding author Professor Eliete Neves Silva Guerra has listed you as a contributing author of the following submission via Elsevier's online submission system for Critical Reviews in Oncology / Hematology.

Submission Title: Worldwide Research Trends on Artificial Intelligence in Head and Neck Cancer: A Bibliometric Analysis

Elsevier asks all authors to verify their co-authorship by confirming agreement to publish this article if it is accepted for publication.

Please read the following statement and confirm your agreement by clicking on this link: Yes, I am affiliated.

I irrevocably authorize and grant my full consent to the corresponding author of the manuscript to: (1) enter into an exclusive publishing agreement with Elsevier on my behalf (or, if the article is to be published under a CC BY license, a non-exclusive publishing agreement), in the relevant form set out at www.elsevier.com/copyright ; and (2) unless I am a US government employee, to transfer my copyright or grant an exclusive license of rights (or for CC BY articles a non-exclusive license of rights) to Elsevier as part of that publishing agreement , effective on acceptance of the article for publication. If the article is a work made for hire, I am authorized to confirm this on behalf of my employer. I agree that the copyright status selected by the corresponding author for the article if it is accepted for publication shall apply and that this agreement is subject to the governing law of the country in which the journal owner is located.

If you did not co-author this submission, please contact the corresponding author directly at elieteneves.unb@gmail.com.

Thank you,
Critical Reviews in Oncology / Hematology

More information and support
FAQ: What is copyright co-author verification?
https://service.elsevier.com/app/answers/detail/a_id/28460/supporthub/publishing/
FAQ: How can I reset a forgotten password?
https://service.elsevier.com/app/answers/detail/a_id/28452/supporthub/publishing/kw/editorial+manager/

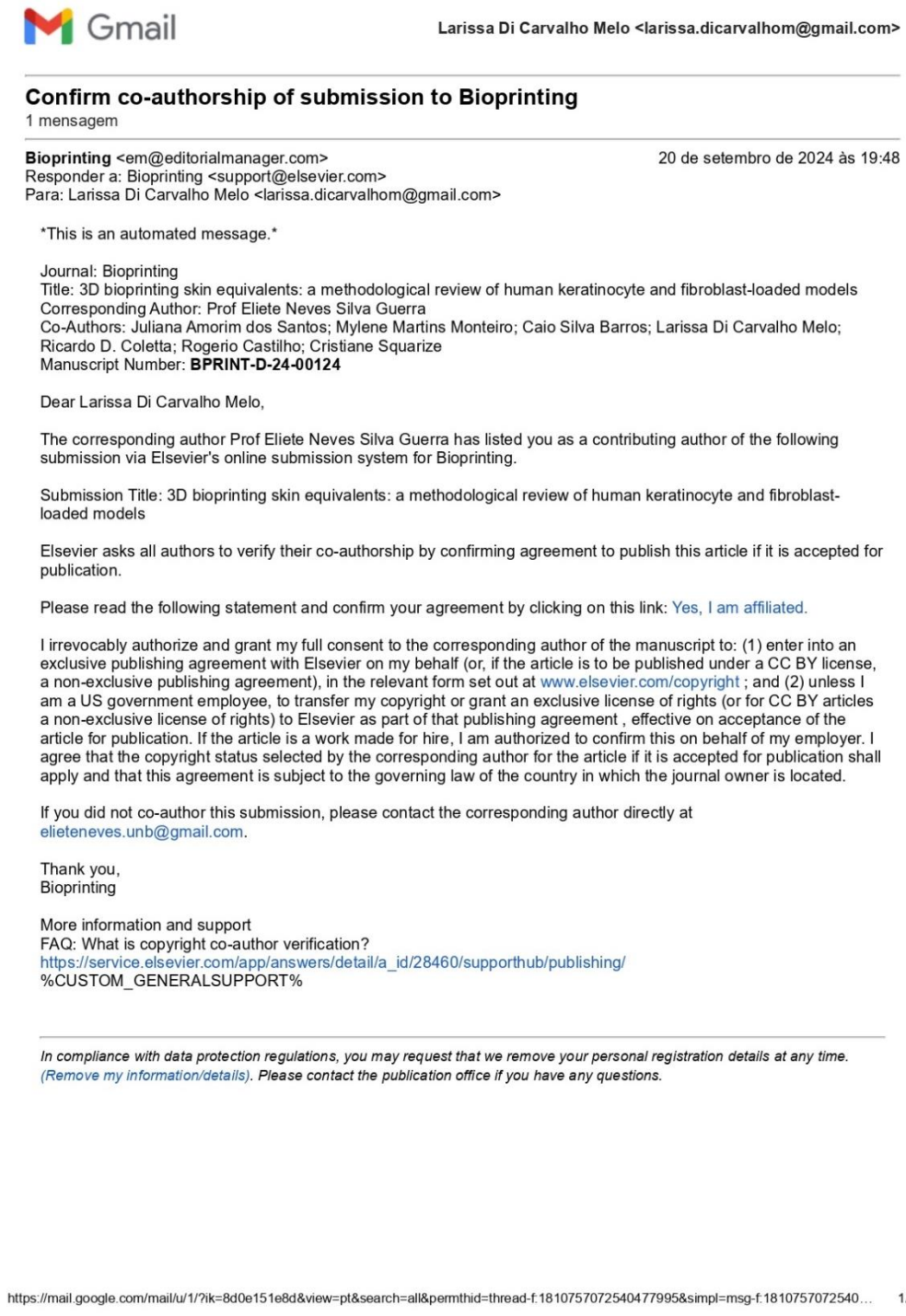
For further assistance, please visit our customer service site: https://service.elsevier.com/app/home/supporthub/publishing/. Here you can search for solutions on a range of topics, find answers to frequently asked questions, and learn more about Editorial Manager via interactive tutorials. You can also talk 24/7 to our customer support team by phone and 24/7 by live chat and email.

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Remove my information/details). Please contact the publication office if you have any questions.

https://mail.google.com/mail/u/0/?ik=b3683d7340&view=pt&search=all&permthid=thread-f:1807568437069206936&simpl=msg-f:1807568437069… 1/1

5. 3D bioprinting skin equivalents: a methodological review of human keratinocyte and fibroblast-loaded models

   Journal: *Bioprinting* (Qualis A1, IF=11.5)



Gmail — Larissa Di Carvalho Melo <larissa.dicarvalhom@gmail.com>

Confirm co-authorship of submission to Bioprinting
1 mensagem

Bioprinting <em@editorialmanager.com> 20 de setembro de 2024 às 19:48
Responder a: Bioprinting <support@elsevier.com>
Para: Larissa Di Carvalho Melo <larissa.dicarvalhom@gmail.com>

This is an automated message.

Journal: Bioprinting
Title: 3D bioprinting skin equivalents: a methodological review of human keratinocyte and fibroblast-loaded models
Corresponding Author: Prof Eliete Neves Silva Guerra
Co-Authors: Juliana Amorim dos Santos; Mylene Martins Monteiro; Caio Silva Barros; Larissa Di Carvalho Melo; Ricardo D. Coletta; Rogerio Castilho; Cristiane Squarize
Manuscript Number: **BPRINT-D-24-00124**

Dear Larissa Di Carvalho Melo,

The corresponding author Prof Eliete Neves Silva Guerra has listed you as a contributing author of the following submission via Elsevier's online submission system for Bioprinting.

Submission Title: 3D bioprinting skin equivalents: a methodological review of human keratinocyte and fibroblast-loaded models

Elsevier asks all authors to verify their co-authorship by confirming agreement to publish this article if it is accepted for publication.

Please read the following statement and confirm your agreement by clicking on this link: Yes, I am affiliated.

I irrevocably authorize and grant my full consent to the corresponding author of the manuscript to: (1) enter into an exclusive publishing agreement with Elsevier on my behalf (or, if the article is to be published under a CC BY license, a non-exclusive publishing agreement), in the relevant form set out at www.elsevier.com/copyright ; and (2) unless I am a US government employee, to transfer my copyright or grant an exclusive license of rights (or for CC BY articles a non-exclusive license of rights) to Elsevier as part of that publishing agreement , effective on acceptance of the article for publication. If the article is a work made for hire, I am authorized to confirm this on behalf of my employer. I agree that the copyright status selected by the corresponding author for the article if it is accepted for publication shall apply and that this agreement is subject to the governing law of the country in which the journal owner is located.

If you did not co-author this submission, please contact the corresponding author directly at elieteneves.unb@gmail.com.

Thank you,
Bioprinting

More information and support
FAQ: What is copyright co-author verification?
https://service.elsevier.com/app/answers/detail/a_id/28460/supporthub/publishing/
%CUSTOM_GENERALSUPPORT%

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Remove my information/details). Please contact the publication office if you have any questions.

https://mail.google.com/mail/u/1/?ik=8d0e151e8d&view=pt&search=all&permthid=thread-f:1810757072540477995&simpl=msg-f:1810757072540… 1/1