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ELISA KAUARK FONTES

NOVAS PERSPECTIVAS PARA A FOTOBIOMODULAÇÃO EXTRAORAL EM PACIENTES COM CÂNCER DE BOCA E OROFARINGE

NEW PERSPECTIVES FOR EXTRAORAL PHOTOBIOMODULATION IN ORAL AND OROPHARYNGEAL CANCER PATIENTS

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

Dissertation presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of the requirements for the degree of Master in Stomatopathology, in Stomatology area.

Orientador: Prof. Dr. Alan Roger dos Santos Silva
Coorientadora: Profa. Dra. Karina Morais Faria

Este exemplar corresponde à versão final da dissertação defendida pela aluna Elisa Kauark Fontes e orientada pelo Prof. Dr. Alan Roger dos Santos Silva

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RESUMO

A mucosite oral e orofaríngea (MO) é considerada a toxicidade de maior impacto para pacientes em radioterapia de cabeça e pescoço. A incidência e gravidade da MO está associada a limitações importantes, impacto negativo na qualidade de vida e também aumento dos custos hospitalares. A fotobiomodulação (FBM) tem sido recomendada controle da MO. Embora controverso, questiona-se o impacto da FBM no tratamento oncológico, sendo crítica a confirmação de sua segurança oncológica, principalmente no contexto de tumores de cavidade oral e orofaríngea. Assim, inicialmente foi realizada uma revisão sistemática sobre o custo-efetividade da FBM para toxicidades do tratamento oncológico. Após um processo padronizado de seleção, 1.490 estudos foram avaliados, 4 artigos atenderam aos critérios de inclusão, sendo 3 para o contexto da MO e 1 para linfedema. A relação custo-efetividade incremental para MO variou de 3,050.75 USD a 5,592.10 USD. A FBM tem um custo de 21.47 USD para cada ponto percentual de redução de linfedema comparado a 80.51 USD de drenagem linfática manual. O segundo capítulo desta dissertação discute o uso da FBM extraoral como uma alternativa para o manejo MO no contexto da pandemia pelo COVID-19. Essa nova perspectiva possibilita minimizar riscos de transmissão do SARS-CoV-2 e manter assistência aos pacientes oncológicos durante radioterapia (RT) e quimioterapia. O terceiro capítulo é uma análise interina de um estudo clínico randomizado, prospectivo e duplo cego do uso profilático da FBM para MO em pacientes com carcinoma espinocelular de cavidade oral e orofaringe durante RT. Cinquenta e cinco pacientes atenderam aos critérios finais de inclusão e foram randomizados em dois grupos: FBM extraoral e placebo. Foi observado início mais tardio de MO com incidência de 100% para o grupo FBM na sexta semana de RT, em comparação com a terceira semana para o grupo placebo. Menores níveis médios de dor associados a MO, menor necessidade de analgesia e uso de anti-inflamatórios, e melhor score de qualidade de vida geral foi observado para o grupo FBM em comparação ao placebo. Não foram observados efeitos adversos da FBM, assim como nenhum impacto na sobrevida global. Apesar de evidências de custo-efetividade do uso da FBM serem limitadas, a FBM tem grande potencial no gerenciamento de toxicidades oncológicas. A FBM extraoral é simples e bem tolerada por pacientes, pode atrasar o início da MO, reduzir níveis de dor e necessidade de uso de analgésicos e anti-inflamatórios. No entanto, a otimização de protocolos se faz necessária para melhor controle de MO grave.

Palavras-chave: Carcinoma espinocelular. Câncer de boca. Fotobiomodulação. Radioterapia de cabeça e pescoço. Mucosite oral.

ABSTRACT

Oral and oropharyngeal mucositis (OM) is considered to be the most impactful toxicity for patients undergoing head and neck radiotherapy. The incidence and severity of OM is associated with important limitations, negative impact on quality of life and also an increase in hospital costs. Photobiomodulation (PBM) has been recommended for the management of OM. Although controversial, the impact of PBM in cancer treatment is questioned, and the confirmation of its oncological safety is critical, especially in the context of oral and oropharyngeal cancers. Thus, initially a systematic review was carried out about the cost-effectiveness of PBM for cancer treatment toxicities. Through a standardized selection process, 1490 studies were assessed, 4 articles met the inclusion criteria, 3 for the context of OM and 1 for lymphedema. The incremental cost-effectiveness ratio for OM ranged from 3050.75 USD to 5592.10 USD. The PBM has a cost of 21.47USD for each percentage point of lymphedema reduction compared to 80.51USD of manual lymphatic drainage. The second chapter discusses the use of extraoral PBM as an alternative for management of OM in the context of the COVID-19 pandemic. This new perspective, makes it possible to minimize the risk of transmission of SARS-CoV-2, allowing assistance to cancer patients during radiotherapy (RT) and chemotherapy. The third chapter is an interim analysis of a randomized, prospective, double-blind clinical trial of the photobiomodulation prophylactic use for OM in patients with oral cavity and oropharynx squamous cell carcinoma during RT. Fifty-five patients met the final inclusion criteria and were randomized into two groups: extraoral PBM and placebo. Later onset of OM, with 100% of incidence at sixth week for the PBM group in comparison for the third week for placebo group. Lower mean pain levels, less need for analgesics and anti-inflammatory use, and better overall quality of life results were observed for the PBM group in comparison to placebo. No adverse effects were observed from the use of PBM, as well as no impact on overall survival. Although evidence of PBM cost-effectiveness is limited, PBM has great potential on the management of oncological toxicities. The Extraoral PBM is simple and well tolerated among patients, can delay the OM onset, reduce pain levels and the need of analgesics and anti-inflammatory drugs. However, the optimization of protocols is necessary for better severe OM control.

Key-words: Squamous cell carcinoma. Oral Cancer. Photobiomodulation. Head and neck radiotherapy. Oral mucositis.

SUMÁRIO

1 INTRODUÇÃO

Para o câncer de cavidade oral e orofaringe, em 2018, estima-se uma incidência mundial de 447.751 casos (Bray et al., 2018). No cenário nacional, a estimativa para 2020 é de 15.190 novos casos, sendo 11.180 homens e 4.010 mulheres (INCA, 2020). Neste contexto, o carcinoma espinocelular (CEC) é o subtipo histopatológico mais prevalente (Montero e Patel., 2015; Gupta et al., 2016). Neste cenário, aproximadamente dois terços dos pacientes recebem o diagnóstico em estadio avançado (III/IV) da doença, o que representa importante desafio epidemiológico, com impacto significativo no tratamento e prognóstico destes pacientes (Güneri e Epstein, 2014; Montero e Patel., 2015).

O tratamento para o CEC de cavidade oral e orofaringe é considerado como multimodal, os estádios avançados (III ou IVA/B) são usualmente abordados por meio de cirurgia associada à radioterapia (RT), à quimioterapia (QT), à quimioradioterapia concomitante (QRT) ou à QT de indução (neoadjuvante) à base de derivados da platina, sobretudo a cisplatina (Marur e Forastiere, 2016). Os tumores avançados da orofaringe são, em sua grande maioria, considerados irressecáveis, sendo tratados por meio de protocolos de preservação de órgão baseados na QRT (Kowalski et al., 2005). Pacientes submetidos à RT de cabeça e pescoço podem desenvolver efeitos adversos, categorizados entre toxicidades agudas e crônicas. A intensidade desses efeitos depende de fatores como estadiamento clínico, localização do tumor primário e metástases regionais, dose total de radiação, volume irradiado, modalidade de RT utilizada e distribuição da dose de radiação (Sroussi et al., 2017; Guedes et al., 2018).

A mucosite oral e orofaríngea (MO) é considerada a toxicidade da RT de cabeça e pescoço de maior morbidade, acometendo 80 a 100% dos pacientes, principalmente nos protocolos de tratamento que combinam QRT (Scully et al., 2006; Villa e Sonis., 2015; Sroussi et al., 2017). As lesões características da MO podem limitar a fonação, deglutição e nutrição, causando impacto negativo na qualidade de vida (QoL) dos pacientes, assim como estão associadas ao risco aumentado de infecção local e bacteremia (Jadaud e Bensadoun, 2012; Lalla et al., 2014; Villa e Sonis., 2015; Sroussi et al., 2017; Guedes et al., 2018). A incidência e gravidade da MO também está associada a um aumento de custos hospitalares devido à necessidade de medicamentos de alto custo, como opióides, uso de sondas para alimentação nasogástrica, internações hospitalares não previstas e interrupções não programadas do tratamento oncológico (Gautam et al., 2013; Lalla et al., 2014; Antunes et al., 2016; Guedes et al., 2018; Martins et al., 2020).

Apesar de não existir um consenso quanto a um agente profilático ou terapêutica ideal para MO, a última atualização protocolar dirigida pela *Multinational Association of Support Care in Cancer* / *International Society of Oral Oncology* (MASCC/ISOO), recomenda a FBM intraoral para prevenção de MO em pacientes adultos submetidos a RT ou QRT de cabeça e pescoço (Zadik, et al.,2019). Entre os diversos protocolos de FBM estudados pelo consórcio de pesquisadores MASCC/ISOO, a modalidade extraoral apresenta evidências ainda limitadas e nenhum protocolo pôde ser estabelecido, especialmente para pacientes submetidos à RT de cabeça e pescoço. Quando comparada com a FBM intraoral, possui grande impacto em topografias não acessíveis por manipulação intraoral, indicado para pacientes com limitação da abertura bucal secundárias ao trismo pós-cirúrgico, induzido pela RT ou à dor intensa por MO (Hodgson et al.,2012; Treister et al., 2016).

Um fator limitante quanto ao uso dessa técnica, é a possibilidade de a FBM estimular o microambiente tumoral ou de células neoplásicas residuais adjacentes ao sítio primário do tumor, onde se questiona segurança, por meio do conhecimento do conceito de cancerização de campo, se a eficácia dos protocolos de FBM para MO não poderia resultar em um impacto negativo no tratamento oncológico por meio de fotobioestimulação de células malignas quiescentes (Sonis et al., 2016; Guedes et al., 2018; Hamblin et al., 2018; Sonis 2020;). Embora controverso, até o momento, não existe evidência clínica de efeitos adversos relevantes ou prejuízos em termos de prognóstico oncológico para pacientes com câncer em cabeça e pescoço tratados por meio da FBM (Paglioni et al., 2019a; Silveira et al., 2019). Devido ao amplo potencial de uso da FBM no mundo contemporâneo, é crítica, então, a confirmação de sua segurança oncológica por meio de ensaios clínicos randomizados duplo-cego e dos tumores de cavidade oral e orofaringe naturalmente mais próximos fisicamente da interação dos tecidos orais com a luz durante a FBM, principalmente para a FBM extraoral, ainda não explorada nesse contexto específico (Myakishev-Rempel et al., 2012; Bensadoun 2018; Bensadoun, Epstein 2020).

O estudo clínico resultante desta dissertação está disponível no Registro Brasileiro de Ensaios Clínicos (ReBEC) e na *International Clinical Trials Registry Platform* (ICTRP/WHO), com o código RBR-4w4swx. O registro garante uma visão completa, transparente e acessível a toda a população, fortalecendo a validade das evidências científicas deste estudo. Informações sobre o registro do estudo encontram-se disponíveis em http://www.ensaiosclinicos.gov.br/rg/RBR-4w4swx/. Este ensaio clínico recebeu financiamento da Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) por meio

auxílios cujos números dos processos são 2018/02233-6 e 2018/23479-3. Em suma, este estudo teve como objetivo avaliar múltiplos desfechos da FBM em pacientes com CEC de cavidade oral e orofaringe tendo em vista perspectivas futuras para a técnica extraoral em termos de custo-eficiência, performance clínica e segurança oncológica.

2 ARTIGOS

ARTIGO: Cost-effectiveness of photobiomodulation therapy for the prevention and management of cancer treatment toxicities: a systematic review.

CAPÍTULO 1 – Artigo aceito para publicação no periódico *Supportive Care in Cancer. 2021* Jan 7. Doi: 10.1007/s00520-020-05949-1. Online ahead of print (Anexo 1)

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Abstract

Purpose: To identify and summarize the evidence on the cost-effectiveness of photobiomodulation (PBM) therapy for the prevention and treatment of cancer treatment-related toxicities.

Methods: This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE). Scopus, MEDLINE/PubMed, and Embase were searched electronically.

Results: A total of 1490 studies were identified, and after a two-step review, 4 articles met the inclusion criteria. The included studies analyzed the cost-effectiveness of PBM therapy used in the context of lymphedema for breast cancer and oral mucositis (OM) induced by chemotherapy and radiotherapy. Better outcomes were associated with PBM therapy. The incremental cost-effectiveness ratio ranged from 3050.75 USD to 5592.10 USD per grade 3-4 OM case prevented. PBM therapy cost 21.47 USD per percentage point reduction in lymphedema in comparison with 80.51 USD for manual lymph drainage and physical therapy.

Conclusion: There is limited evidence that PBM therapy is cost-effective in the prevention and treatment of specific cancer treatment-related toxicities, namely, OM and breast cancer-related lymphedema. Studies may have underreported the benefits due to a lack of a comprehensive cost evaluation. This suggests a wider acceptance of PBM therapy at cancer treatment centers, which has thus far been limited by the number of robust clinical studies that demonstrate cost-effectiveness for the prevention and treatment of toxicities.

Keywords: Photobiomodulation, cancer toxicities, cost, systematic review

Introduction

Economic evaluation of the management of health conditions is essential in supporting decision-making by clinicians, policymakers and planners to shape healthcare policy and health services delivery [1-4]. Cancer treatment toxicities consist of several adverse consequences that often affect quality of life and may result in increased medical consultations, emergency room visits, new or prolonged hospitalizations, the need for nutritional support, and the use of opioids for pain management, all of which are drivers of healthcare costs [4-8]. Management of these toxicities is an ongoing challenge, but therapeutic interventions can potentially improve outcomes and reduce costs [7, 9, 10]. Even though most reported cancer costs are related to direct medical expenditures for the treatment of malignant disease, it is crucial to understand the overall cost, which encompasses both the direct treatment costs and the incremental costs associated with high rates of acute and chronic treatment toxicities [1].

Photobiomodulation (PBM) therapy is used in cancer care to prevent or manage treatment-related toxicities such as oral mucositis (OM), lymphedema, peripheral neuropathy, radiodermatitis, dysphagia, radiation fibrosis, radionecrosis, bisphosphonate-related osteonecrosis of the jaw, trismus and graft-versus-host disease [11-16]. PBM includes a broad range of nonionizing light sources that lead to anti-inflammatory effects, promote wound healing and tissue repair, improve neural function and exert an analgesic effect [11, 13, 17-21]. Moreover, the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) has recommended PBM for oral mucositis (OM) [21]. Despite PBM therapy being accessible, implementation requires trained staff and specific equipment [21, 22]. To our knowledge, the present systematic review is the first to evaluate the evidence on the cost-effectiveness of PBM therapy in the prevention and treatment of complications related to cancer treatment.

Materials and Methods

A systematic literature review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) [23] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [24] guidelines. The protocol for this systematic review was registered in the International Prospective Register of Systematic Review (PROSPERO) database (registration number CRD42019133695 - https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=133695) to avoid potential duplication and to enable comparison among methods as they are reported in the review protocol.

Search strategy

A systematic electronic search for scientific studies evaluating the cost-effectiveness of PBM therapy in cancer patients for the prevention and/or treatment of toxicities induced by antineoplastic therapies was conducted without restriction on the publication year (the last search was performed on July 17th, 2020). To this end, Medline/PubMed (https://www.ncbi.nlm.nih.gov/pubmed), EMBASE (https://www.embase.com/login), and Scopus (https://www.scopus.com) were screened with the following keywords: "low-level laser therapy", "photobiomodulation", "cost-effectiveness", "oral mucositis", "lymphedema", "esophagitis", "radiodermatitis", "peripheral neuropathy", "hyposalivation", "xerostomia", "dysphagia", "radiation fibrosis", "radionecrosis", "bisphosphonate osteonecrosis of the jaw", "dysgeusia", "graft-versus-host disease", "trismus", "postsurgical wound healing", "tinnitus", "dyshidrotic eczema" and "cancer toxicities". Synonyms, abbreviations, and related keywords for each of these terms were used for the search, linked in independent strategies by the Boolean operator "AND". We retrieved all publications containing a combination of controlled, predefined medical subject headings (MeSH) and free terms related to PBM therapy using Boolean operators (OR, AND) to combine searches. The process was repeated in each database to ensure that relevant results were not missed during the identification phase, which was adapted to the syntax rules of each electronic database. Additional manual searches were conducted by reading the reference lists from all selected studies to detect other potentially eligible reports meeting the inclusion criteria. Key authors/coauthors were identified among the included studies, allowing for the verification of additional database searches filtered by author/coauthor name.

Inclusion criteria

The inclusion criteria for this systematic review were based on the PICOS approach [Population (P), Intervention (I), Comparison (C), Outcome (O), and Study design (S)]. We included (S) clinical trials, regardless of randomization, and retrospective clinical studies that evaluated (O) the cost-effectiveness of preventive and therapeutic (I) PBM therapy compared with a (C) placebo group or any other therapy for cancer treatment toxicity management in (P) cancer patients undergoing oncological treatment.

Exclusion criteria

We excluded case reports, case series, animal studies, in vitro studies, letters to editors, editorials, review articles, guidelines, study protocols, commentaries, monographs, conference

papers, unpublished data, studies published in a language other than English, and studies lacking information on the cost-effectiveness analysis of PBM therapy in the treatment of toxicities induced by antineoplastic therapies.

Study selection

The study selection was completed using Rayyan QCRI [26] reference manager software for the initial screening phase. After duplicates were excluded, a screening of titles and abstracts was independently performed by two authors (EKF, ARSS) for possible inclusion in the qualitative synthesis of this review. Subsequently, studies assessed for eligibility were reviewed independently in full-text versions by two reviewers (EKF, ARSS). A final decision was made by a third reviewer (LRO) to achieve consensus when discrepant ratings occurred between the two reviewers.

Data extraction

Study characteristics

Study characteristics extracted from the included studies were as follows: (1) first author, (2) year of publication, (3) cancer toxicity, (4) study type, (5) patient condition, (6) sample size, (7) study groups, (8) cost-effectiveness based on authors' considerations, and (9) PBM therapy parameters.

Cost-effectiveness and cost analysis

PBM therapy was defined as cost-effective when there was an improvement in the relative costs of cancer toxicity outcomes compared with the corresponding costs related to placebo or an alternative treatment. To evaluate cost-effectiveness, we extracted information on the (10) toxicity prevalence, (11) basis for the cost analysis, and (12) cost analysis procedures.

The costs reported in the systematic review were converted to 2020 US dollars (USD) by applying the gross domestic product deflator index (GDP values) and purchasing power parity conversion rates (PPP values) using the Campbell and Cochrane Economics Methods Group-the Evidence for Policy and Practice Information (CCEMG–EPPI)-Centre Cost Converter software (V1.6) [27, 28], which automatically adjusts estimates for costs and price year. This conversion methodology is meant to provide a way to compare data from articles that are written at different times and that use currencies other than USD. In situations where a

reference year was not provided, we used the last year in which patients were included, or when this was unknown, the costs were calculated based on one year before the publication year.

Risk of bias assessment

The risk of bias for selected studies was evaluated using the standardized critical appraisal instrument for risk of bias assessed by the Meta-Analysis of Statistics Assessment and Review Instrument (MAStARI) critical appraisal tool [29]. Higher scores denote a lower risk of bias. The risk of bias was categorized as high when the study scored less than 50% on the MAStARI scale, moderate when the study scored 50% to 69%, and low when the study scored 70% or higher. Both reviewers scored each item as "yes", "no", "unclear" or "not applicable" and assessed the quality of each included study independently. A third reviewer resolved disagreements.

To critically appraise the quality of studies, we completed the Consensus on Health Economic Criteria (CHEC) list for each publication that mentioned a cost evaluation [30]. The CHEC list consists of 19 yes-or-no questions, one for each category. Higher scores of "yes" denote a better methodological quality of the economic evaluation.

Data analysis

It was not possible to perform a meta-analysis of the included studies due to the lack of uniformity in the presented cost-effectiveness analysis and CHEC-list items. Therefore, this systematic review presented a detailed qualitative synthesis of the results from the included studies.

Results

Study selection and study characteristics

A flow diagram that summarizes the process of selecting studies is shown in Fig. 1. In total, 1490 studies were identified through the aforementioned search strategies. No additional studies were identified through the manual search. For the initial review process, 369 duplicates were excluded, and after a thorough evaluation of titles and abstracts, an additional 1104 articles that did not meet the inclusion criteria were excluded, resulting in 17 articles.

A full-text analysis was performed on the 17 remaining studies, and a second review process led to the further exclusion of 13 studies: 3 were conference abstracts not associated with full-text articles, 1 was excluded due to the publication language (Russian), 2 were study protocols of ongoing clinical trials, 1 full-text article was not available for evaluation, 2 were

publications using the same sample but with updated data, and 4 did not conduct a cost-effectiveness analysis. Finally, 4 studies met all inclusion criteria and were included in the systematic review. All of the included studies evaluated the cost-effectiveness of PBM for the prevention and treatment of toxicities induced by cancer treatments [22, 31, 35, 36].

Table 1 presents the main characteristics of the included studies. The cost-effectiveness of PBM therapy for OM was evaluated in 3 studies. Two studies analyzed PBM therapy for OM in head and neck cancer patients receiving radiation therapy [35, 36], and one study focused on patients undergoing hematopoietic stem cell transplantation (HSCT) [22]. No uniformity of PBM parameters was observed. The fourth study assessed the cost-effectiveness of PBM therapy for lymphedema in breast cancer patients [31], specifically among patients with chronic lymphedema, and included a small sample. All of the included studies reported the cost-effectiveness of PBM therapy for OM and lymphedema.

Cost-effectiveness of PBM therapy for OM

Table 2 presents the prevalence of cancer toxicity and the parameters for the cost-effectiveness analysis. All included studies found PBM to be a cost-effective therapy for OM. The efficacy of PBM therapy for OM was demonstrated by the presence of higher grades (grades 3-4) of OM (World Health Organization [WHO] Oral Toxicity Score scale) [37] in the control group than in the PBM group (grades 1-2) [22, 35, 36]. For all 3 studies evaluating PBM therapy for OM, the cost analysis evaluation was performed by assessing inpatient charges limited to the period of cancer treatment (HSCT and chemoradiation), costs associated with nutritional support (parenteral nutrition, nasoenteral feeding tube, gastrostomy) and those related to opioid use. For the PBM therapy group, costs related to PBM therapy (e.g., equipment and professional wages) were also added.

Bezinelli et al. [22] evaluated the total cost of HSCT in two groups, the PBM group and a control group receiving no PBM, which included patients treated in a period before the introduction of a dental team in the transplant unit. This study evaluated the costs related to daily hospitalization fees, nutritional support and opioid use, in addition to the costs of the cancer treatment itself. The results were reported as overall costs of treatment separated in coordination with the autologous or allogeneic transplant modality and subdivided into patients with and without nutritional support and opioid use. The individual cost of PBM therapy was not available.

All results from Bezinelli et al. [22] presented lower costs for the PBM group than for the control group. However, the cost of the treatment for patients submitted to autologous

transplantation without parenteral nutrition and opioid use was slightly increased for the PBM group. When comparing costs for patients who required nutritional support and opioid use, an additional cost of approximately 12,000 USD for autologous transplantation and 18,000 USD for allogenic transplantation was posed for the control group in comparison with the PBM group.

Antunes et al. [35] and Martins et al. [36] evaluated the mean cost per patient by including the costs of PBM, hospitalization, opioid use, and nutritional support in two distinct groups: PBM therapy and placebo. The cost analysis was presented in individual costs for each outcome assessed [35, 36], and the individual cost of PBM therapy was reported [35, 36]. Both studies assumed the cost of cancer treatment to be equivalent between groups and, therefore, did not assess the cost of chemoradiation in the cost analysis [35, 36].

For Antunes et al. [35], incremental costs were higher for the control group, except for the additional cost associated with PBM therapy, estimated at 1,903.70 USD. When costs related to PBM therapy were not considered, the total incremental cost per patient was 283.07 USD higher in the control group due to OM toxicity. The incremental cost-effectiveness ratio (ICER) was assessed in this study, and 5,592.10 USD was saved per grade 3-4 OM cases prevented by PBM therapy. For Martins et al. [36], all incremental costs were higher for the control group, and PBM therapy posed an additional cost per patient of 935.30 USD. The base-case ICER assessed to prevent grade 3-4 OM was 3,050.75 USD. Additionally, the ICER to prevent RT interruption due to OM was 2,864.37 USD.

Cost-effectiveness of PBM therapy for lymphedema

One study that evaluated the cost-effectiveness of PBM therapy for lymphedema was included [31]. The study demonstrated a positive impact of PBM therapy, which decreased the lymphedema severity. Piller and Thelander [31] evaluated the PBM therapy efficacy for lymphedema in breast cancer patients, and PBM was shown to decrease edema volumes by an average of 19% after 16 sessions (10 weeks). The cost-effectiveness analysis was based on the total cost of treatment and the percentage reduction in lymphedema as the health outcome. The patient's contralateral arm was used as the control group for volume comparison. Cost analysis compared the costs of PBM therapy with the costs of manual lymph drainage and complex physical therapy, which represented conventional lymphedema treatment. PBM cost 21.47 USD per percentage point reduction in edema volume, while conventional treatment cost 80.51 USD. For 10 weeks of treatment, PBM therapy cost 402.57 USD, and for the same period, conventional treatment cost 774.18 USD. In addition, the authors suggested that fewer PBM

sessions would be necessary to achieve similar results. Thus, PBM therapy can potentially be more cost-effective than reported in the present study.

Risk of bias

The selected studies were considered at low risk of bias [22] for comparable cohort/case-control studies and at low risk of bias [35, 36] and moderate risk of bias [31] for randomized control trials.

The included articles that evaluated costs were critically appraised by the CHEC-list tool. The articles evaluating OM had more transparent, informative and comparable quality assessments of economic evaluations, with higher scores: 73.68% [22] and 89.47% [35, 36] in comparison with the lymphedema study, at 52.63% [31].

Discussion

PBM is being increasingly utilized to prevent and treat a wide range of cancer treatment toxicities that pose an incremental economic cost to cancer treatment, such as OM, lymphedema, peripheral neuropathy and radiodermatitis [5, 11, 13-16, 18, 20]. Understanding and evaluating the incremental costs associated with these toxicities and the impact of PBM therapy on cost savings may help increase the acceptance of PBM therapy by health care professionals and administrators [4]. To our knowledge, this is the first systematic review to address and evaluate the cost-effectiveness of PBM therapy for the prevention and treatment of cancer-related toxicities.

Several prior studies discussed the economic benefits of integrating PBM therapy into cancer care [19, 22, 31-36], yet most studies did not conduct an economic evaluation [19, 32-34] and assumed cost-effectiveness conclusions by relying on outcomes associated with treatment time, outpatient services, pharmaceutical costs, nutritional support and hospitalization days, which are parameters associated with the per-patient costs for individual resources and cost criteria [1, 2, 39, 40]. A cost-effectiveness analysis of PBM therapy has been conducted in only a small number of studies [22, 31, 35, 36].

The prevention and effective management of cancer-related toxicities can optimize care outcomes and reduce the cost of care [11], although there are costs associated with PBM therapy (e.g., equipment, highly skilled professionals, and additional consultation costs), as reviewed by Antunes et al. [35] and Martins et al. [36], these costs are likely offset by the reduction in the costs of managing complications of cancer treatment, such as hospitalization, which is the largest driver of total costs [19, 38, 40, 41].

In terms of cancer-related toxicities, OM was the most prevalent toxicity described in the included studies [22, 35, 36]. Moreover, the costs of OM seem to be more significant than those reported for a wide range of other cancer treatment toxicities. The only toxicity that seems to be as costly as OM is neutropenia [5, 22, 35, 40]. Previous studies have shown that the presence, extension, and severity of OM are associated with incremental costs [9, 25, 37, 40, 41]. Higher costs were observed to be positively correlated with higher grades of OM, in agreement with the literature, which suggests that the presence, extension, and severity of OM are associated with an increased cost of care [5, 41]. These findings support the use of PBM as an intervention that potentially prevents or minimizes the severity of OM and leads to lower costs [9]. Interestingly, two of the included studies estimated an ICER per grade 3-4 OM case prevented by PBM therapy of 5,592.10 USD [35] and 3,050.75 USD [36]. Furthermore, Martins et al. [36] calculated the ICER to prevent RT interruption due to OM as equaling 2,864.37 USD. Unplanned treatment interruption is not only related to incremental costs but is also associated with lower survival rates [2, 9, 36].

One clinical study evaluated the cost-effectiveness of PBM therapy for lymphedema [31]. In this study, PBM decreased edema volumes by an average of 19% after only 16 sessions over 10 weeks in comparison with a slower rate using traditional manual lymphatic drainage [31]. Lymphedema outcomes may lead to out-of-pocket expenses for many patients, as it is shown to be a chronic toxicity with a high impact on patient quality of life [10, 3]. It is important to note our definition of 'systemic effects' of PBM as referring to the impact of treating one part of the body on another part through circulatory means [42]. The important implication for this study of lymphedema is that the contralateral arm used as a control may have actually been treated systemically, thereby reducing the difference in effect between the treatment and the control.

Few comprehensive evaluations of the costs of care associated with PBM therapy have been completed. Future studies should investigate the costs associated with prolonged medical visits, additional procedures and medications, and outpatient costs, including over-the-counter products and medications, as well as indirect costs, including impact on work (time off work, return to work), caregiver costs and quality of life. Such omissions to the provision of a full account of the costs of care may have led to the underreporting of potential benefits [2, 4, 6, 39].

In addition to the published studies included in this systematic review, there was a clinical trial protocol for studying radiodermatitis in breast cancer patients receiving

radiotherapy [43]. This study may strengthen the evidence in support of PBM as a potential cost-effective therapy once completed.

The clinical research community has not yet adequately characterized the protocols, costs, and benefits of PBM therapy for lymphedema, peripheral neuropathy, radiodermatitis, and other cancer toxicities [10]. The universal acceptance of PBM therapy at cancer centers has been limited to date by the paucity of data on its economic benefits. The limited number of available studies that measured the cost-effectiveness of PBM therapy was the primary limitation of this systematic review.

One underlying challenge was the limited comparability of data measures and the prevailing heterogeneity in cost comparisons and PBM protocols across studies [2]. Standard protocols for economic analysis have been designed to guide large-scale cost studies, such as the Northwestern University Costs of Cancer Program (NUCCP) [2], and guidance to evaluate specific toxicities as developed by Sonis et al. [25] for OM. Recently, new guidelines for the prevention and treatment of OM were published that suggest that future cost-effective analyses should be conducted based on the recommended PBM protocol [21, 36].

Conclusions

This systematic review found limited evidence for the cost-effectiveness of PBM therapy in the prevention and treatment of cancer treatment-related toxicities. Given the potential for PBM therapy to reduce cancer toxicities and subsequently improve health outcomes and reduce incremental costs, rigorous cost-effectiveness studies are necessary. The current review provides preliminary evidence for the use of PBM as a potentially cost-effective therapy for specific cancer therapy-related toxicities.

***Declarations**

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Consent to participate: N/A

Consent for publication: N/A

Availability of data and material: The authors confirm that the data supporting the findings of the study are available within the article and supplementary materials.

Code availability: N/A

Figure 1. Flow diagram of the literature search and selection criteria adapted from PRISMA (Moher et al., 2010)

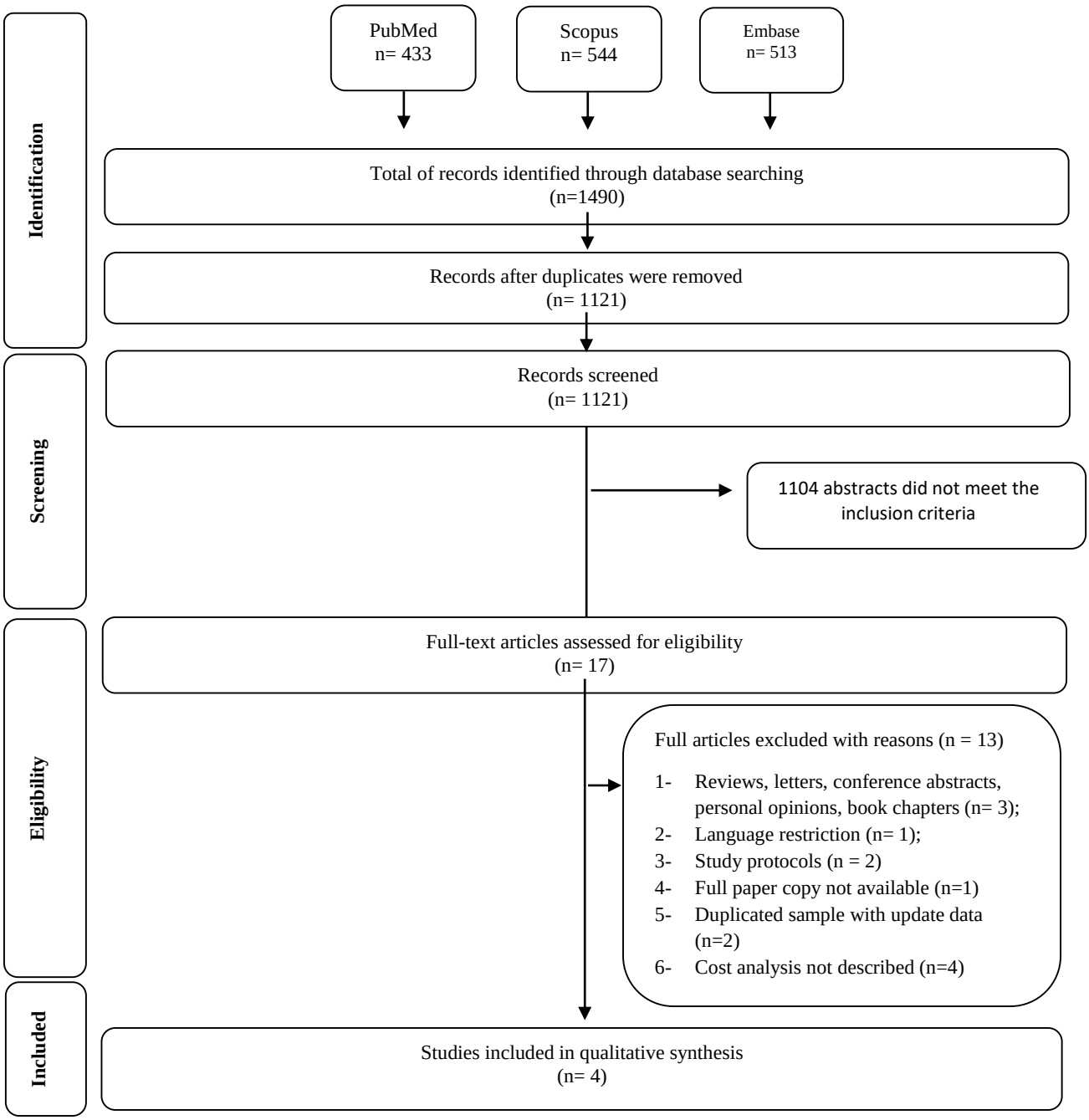

Table 1. Baseline characteristics and PBM therapy protocol of studies included in the systematic review.

Oral mucositis

Study	Study type	Patient condition	Sample size	Experimental group	Control group	Cost-effectiveness	PBM protocol
Bezinelli et al., 2014 [22]	Retrospective, case-control	HSCT (transplantation)	167	PBM (n= 91)	No PBM (n= 76)	Yes, PBM contribute to minimize hospitalization costs during HSCT	Wavelength 660 nm, power 40 mW, energy density 8 J/cm^2. Daily, starting 1 day after the conditioning until marrow engraftment
Antunes et al., 2016 [35]	Randomized, double-blind, placebo controlled, clinical trial	Head and neck cancer (chemoradiation)	94	PBM (n= 47)	Placebo (n= 47)	Yes, PBM has important cost-impact per oral mucositis case prevented	Wavelength 660 nm, power 40 mW, energy density of 8 J/cm^2. Daily during radiotherapy treatment. 5 days/week during radiotherapy
Martins et al., 2020 [36]	Randomized, double-blind, placebo controlled, clinical trial	Head and neck cancer (chemoradiation)	48	PBM (n= 25)	Placebo (n=23)	Yes, PBM is a cost-effective option in preventing severe degrees of oral mucositis and interruption of RT	Wavelength 660 nm, power 25 mW, energy density of 6.2 J/cm^2. Daily during radiotherapy treatment. 5 days/week during radiotherapy

Lymphedema

Study	Study type	Patient condition	Sample size	Experimental group	Control group	Cost-effectiveness	PBM protocol
Piller and Thelander, 1995 [31]	Prospective, interventional, clinical trial	Breast cancer (mastectomy)	11	PBM (n=11)	Contralateral arm (n= 11)	Yes, PBM therapy is a cost effective strategy for the treatment of chronic lymphedema.	Wavelength 632 nm and 904 nm (4 semiconductors), average power 7 mW, energy density of 24 J/cm^2. Twice a week during 6 weeks, and single session for further 4 weeks.

*HSCT – hematopoietic stem cell transplantation **PBM - photobiomodulation

Table 2. Cost analysis of studies included in the systematic review.

Study	Toxicity prevalence	Basis for cost analysis	Cost analysis PBM group (2020 USD)[1]	Cost analysis control group (2020 USD)[1]
Bezinelli et al., 2014 [22].	Grades 1- 2 oral mucositis for PBM group; Grades 3- 4 oral mucositis for control group. (WHO scale)	Sum of inpatient charges, costs of parenteral nutrition, opioids use, PBM (when received) and HSCT (autologous and allogenic). Limited to impatient time.	Total cost of transplantation (mean): - Without PN/opioids: 33,484.69 USD (autologous) 49,847.48 USD (allogenic) - With PN and opioids: 41,714.84 USD (autologous) 61,614.95 USD (allogenic)	Total cost of transplantation (mean): - Without PN/opioids: 33,259.34 USD (autologous) 55,661.42 USD (allogenic) - With PN and opioids: 53,614.77 USD (autologous) 79,972.65 USD (allogenic)
Antunes et al., 2016 [35].	Grades 1- 2 oral mucositis for PBM group; Grades 3- 4 oral mucositis for control group. (WHO scale)	Individual cost of hospitalization charges, nutrition support, opioids use, and PBM (when received). Limited to time of radiation therapy. Costs associated with cancer treatment were not considered.	Incremental cost per patients: Opioids: 10.23 USD Gastrostomy: 56.92 USD Hospitalization: 0.00 USD PBMT: 2,119.64 USD ICER* to prevent oral mucositis grade 3-4 5,592.10 USD	Incremental cost per patients: Opioids: 49.89 USD Gastrostomy: 146.37 USD Hospitalization: 86.82 USD PBM therapy: 0.00 USD
Martins et al., 2020 [36]	Grades 1- 2 oral mucositis for PBM group; Grades 3- 4 oral mucositis for control group. (WHO scale)	Individual cost of hospitalization charge, nutrition support (nasoenteral tube and polyvitamins), opioids use, and PBM (when received). Limited to time of radiation therapy. Costs associated with cancer treatment were not considered.	Incremental cost per patients: Opioids: 0.25 USD Nutritional support: 40.61 USD Hospitalization: 0.00 USD PBMT: 935.30 USD ICER* to prevent oral mucositis grade 3-4 3050.75 USD ICER* to prevent RT interruption due to oral mucositis 2864.37 USD	Incremental cost per patients: Opioids: 4.61 USD Nutritional support: 53.91 USD Hospitalization: 263.39 USD PBM therapy: 0.00 USD
Piller and Thelander, 1995 [31].	PBM therapy was associated with 19% of average reduction of lymphedema in 10 weeks.	Total cost of treatment per percentage reduction of lymphedema	- PBM therapy cost 21.47 USD per percentage point reduction in lymphedema. - 16 sessions of PBM therapy (10 weeks) cost 402.57 USD	- Physical therapy of MLD cost 80.51 USD per percentage point reduction in lymphedema. - One year of treatment cost up to 4,025.74 USD, (~774.18 USD for 10 weeks)

* Incremental cost-effectiveness ratio (ICER) ** Photobiomodulation (PBM) ***Parenteral nutrition (PN) **** MLD – manual lymphatic drainage

1 - Campbell and Cochrane Economics Methods Group-the Evidence for Policy and Practice Information (CCEMG–EPPI)- Centre Cost Converter software (V1.6).

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SUPPLEMENTARY MATERIAL

Appendix 1: Search strategy in the databases.

Database	Search
PubMed July, 17, 2020	#1 "Cost-Benefit Analysis"[Mesh] OR cost OR costs OR "Cost-effectiveness" OR "Cost-Benefit Analyses" OR "Cost Benefit Analysis" OR "Cost Benefit Analyses" OR "Cost Effectiveness" OR "Cost-Benefit Data" OR "Cost Benefit Data" OR "Cost Benefit" OR "Costs and Benefits" OR "Benefits and Costs" OR "Cost-Effectiveness Analysis" OR "Cost Effectiveness Analysis" OR "Cost of Illness"[Mesh] OR "economic burden" OR burden #2 "Lasers"[Mesh] OR laser OR "Low-Level Light Therapy"[Mesh] OR "low-level-laser-therapy" OR photobiomodulation OR "Low Level Light Therapy" OR "Low-Level Light Therapies" OR "Photobiomodulation Therapy" OR "Photobiomodulation Therapies" OR LLLT OR "Low-Level Laser Therapies" OR "Low-Power Laser Therapy" OR "Low Power Laser Therapy" OR "Low-Power Laser Therapies" OR "Low-Level Laser Therapy" OR "Low Level Laser Therapy" OR "Low-Power Laser Irradiation" OR "Low Power Laser Irradiation" OR "Laser Biostimulation" OR "Laser Phototherapy" OR "bioregulating laser" OR "biostimulating laser" OR "broad band radiation therapy" OR "cold laser" OR "cold light laser" OR "high energy laser therapy" OR "high intensity laser therapy" OR "infrared led illumination" OR "infrared light emitting diode" OR "infrared light emitting diodes" OR "intensity laser therapy" OR "laser acupuncture" OR "laser biomodulation" OR "laser biostimulation" OR "laser electrophoresis" OR "laser irradiation" OR "laser therapy" OR "lasotherapy" OR "lazer therapy" OR "LED Therapy" OR "light therapy" OR "low energy laser" OR "low energy photon therapy" OR "low intensity laser" OR "low level diode laser therapy" OR "low level infrared radiation" OR "low level laser" OR "low level light" OR "low light laser therapy" OR "low light therapy" OR "low output helium neon laser" OR "low power laser" OR "low reactive level laser" OR "mid laser therapy" OR "monochromatic infra red energy" OR "monochromatic light therapy" OR "near infrared laser stimulation" OR "near infrared light stimulates" OR "non ablative co2 laser therapy" OR "photo irradiation" OR "photon therapy" OR "physiotherapy laser" OR "polarised polychromatic light" OR "polarised radiation" OR "red light emitting diode" OR "red light emitting diodes" OR "soft laser" OR "CLILT" OR "Combined Low Intensity Laser therapy/Phototherapy" OR "Red Light Therapy" OR "Transcranial infrared laser stimulation" OR "therapeutic laser" OR biophoton OR biophotons OR CHELT OR HILT OR lasotherapy OR LEDT OR LLDLT OR LLLS OR LLLT OR LLRL OR LPRLL OR MIRE OR NACLT OR photobioactivation OR photobiostimulation OR photomedicine OR photomodulation OR photostimulation OR phototherapy OR PLLL OR PWLLLT OR SLLLT #3 "Mucositis"[Mesh] OR "oral mucositis" OR "Stomatitis"[Mesh] OR Esophagitis OR Aphthous OR "Radiodermatitis"[Mesh] OR "Radiation-Induced Dermatitis" OR "Radiation Induced Dermatitis" OR "Radiation Fibrosis" OR "Radiation-induced fibrosis" OR "peripheral neuropathy" OR "Lymphedema"[Mesh] OR Lymphoedema OR "Trismus"[Mesh] OR "Osteonecrosis of the jaw" OR "Osteoradionecrosis"[Mesh] OR "Bisphosphonate-Associated Osteonecrosis of the Jaw"[Mesh] OR BRONJ OR "Graft vs Host Disease"[Mesh] OR GVHD OR

	Hyposalivation OR “Xerostomia”[Mesh] OR dysgeusia OR “Taste loss” OR Tinnitus OR “Dyspepsia”[Mesh] OR Dysphasia OR “Post Surgical wound healing” OR balance OR “Neck pain” OR “hand and foot dermatitis” OR “dyshidrotic eczema” OR “cancer toxicities” #1 AND #2 AND #3
EMBASE July, 17, 2020	#1"Cost-Benefit Analysis" OR cost OR costs OR “Cost-effectiveness” OR “Cost-Benefit Analyses” OR “Cost Benefit Analysis” OR “Cost Benefit Analyses” OR “Cost Effectiveness” OR “Cost-Benefit Data” OR “Cost Benefit Data” OR “Cost Benefit” OR “Costs and Benefits” OR “Benefits and Costs” OR “Cost-Effectiveness Analysis” OR “Cost Effectiveness Analysis” OR "Cost of Illness" OR “economic burden” OR burden #2 "Lasers" OR laser OR "Low-Level Light Therapy" OR "low-level-laser-therapy" OR photobiomodulation OR "Low Level Light Therapy" OR "Low-Level Light Therapies" OR "Photobiomodulation Therapy" OR "Photobiomodulation Therapies" OR LLLT OR "Low-Level Laser Therapies" OR "Low-Power Laser Therapy" OR "Low Power Laser Therapy" OR "Low-Power Laser Therapies" OR "Low-Level Laser Therapy" OR "Low Level Laser Therapy" OR "Low-Power Laser Irradiation" OR "Low Power Laser Irradiation" OR "Laser Biostimulation" OR "Laser Phototherapy" OR "bioregulating laser" OR "biostimulating laser” OR "broad band radiation therapy" OR "cold laser" OR "cold light laser" OR "high energy laser therapy" OR "high intensity laser therapy" OR "infrared led illumination" OR "infrared light emitting diode" OR "infrared light emitting diodes" OR "intensity laser therapy" OR "laser acupuncture" OR "laser biomodulation" OR "laser biostimulation" OR "laser electrophoresis" OR "laser irradiation" OR "laser therapy" OR "lasotherapy" OR "lazer therapy" OR "LED Therapy” OR "light therapy" OR "low energy laser" OR "low energy photon therapy" OR "low intensity laser" OR "low level diode laser therapy" OR "low level infrared radiation" OR "low level laser" OR "low level light" OR "low light laser therapy" OR "low light therapy" OR "low output helium neon laser" OR "low power laser" OR "low reactive level laser" OR "mid laser therapy" OR "monochromatic infra red energy" OR "monochromatic light therapy" OR "near infrared laser stimulation” OR "near infrared light stimulates” OR "non ablative co2 laser therapy" OR "photo irradiation” OR "photon therapy” OR "physiotherapy laser" OR "polarised polychromatic light" OR "polarised radiation" OR "red light emitting diode” OR "red light emitting diodes" OR "soft laser" OR “CLILT” OR “Combined Low Intensity Laser Therapy/Phototherapy” OR “Red Light Therapy” OR “Transcranial infrared laser stimulation” OR ”therapeutic laser” OR biophoton OR biophotons OR CHELT OR HILT OR lasotherapy OR LEDT OR LLDLT OR LLLS OR LLLT OR LLRL OR LPRLL OR MIRE OR NACLT OR photobioactivation OR photobiostimulation OR photomedicine OR photomodulation OR photostimulation OR phototherapy OR PLLL OR PWLLLT OR SLLLT #3 "Mucositis" OR “oral mucositis” OR "Stomatitis" OR Esophagitis OR Aphthous OR “Radiodermatitis" OR "Radiation-Induced Dermatitis" OR "Radiation Induced Dermatitis" OR “Radiation Fibrosis” OR “Radiation-induced fibrosis” OR “peripheral neuropathy” OR "Lymphedema" OR Lymphoedema OR “Trismus” OR “Osteonecrosis of the jaw” OR “Osteoradionecrosis” OR “Bisphosphonate-Associated Osteonecrosis of the Jaw” OR BRONJ OR “Graft vs Host Disease” OR GVHD OR Hyposalivation OR “Xerostomia” OR dysgeusia OR “Taste loss” OR Tinnitus OR

	"Dyspepsia" OR Dysphasia OR "Post Surgical wound healing" OR balance OR "Neck pain" OR "hand and foot dermatitis" OR "dyshidrotic eczema" OR "cancer toxicities" #1 AND #2 AND #3
SCOPUS July, 17, 2020	#1"Cost-Benefit Analysis" OR cost OR costs OR "Cost-effectiveness" OR "Cost-Benefit Analyses" OR "Cost Benefit Analysis" OR "Cost Benefit Analyses" OR "Cost Effectiveness" OR "Cost-Benefit Data" OR "Cost Benefit Data" OR "Cost Benefit" OR "Costs and Benefits" OR "Benefits and Costs" OR "Cost-Effectiveness Analysis" OR "Cost Effectiveness Analysis" OR "Cost of Illness" OR "economic burden" OR burden #2 "Lasers" OR laser OR "Low-Level Light Therapy" OR "low-level-laser-therapy" OR photobiomodulation OR "Low Level Light Therapy" OR "Low-Level Light Therapies" OR "Photobiomodulation Therapy" OR "Photobiomodulation Therapies" OR LLLT OR "Low-Level Laser Therapies" OR "Low-Power Laser Therapy" OR "Low Power Laser Therapy" OR "Low-Power Laser Therapies" OR "Low-Level Laser Therapy" OR "Low Level Laser Therapy" OR "Low-Power Laser Irradiation" OR "Low Power Laser Irradiation" OR "Laser Biostimulation" OR "Laser Phototherapy" OR "bioregulating laser" OR "biostimulating laser" OR "broad band radiation therapy" OR "cold laser" OR "cold light laser" OR "high energy laser therapy" OR "high intensity laser therapy" OR "infrared led illumination" OR "infrared light emitting diode" OR "infrared light emitting diodes" OR "intensity laser therapy" OR "laser acupuncture" OR "laser biomodulation" OR "laser biostimulation" OR "laser electrophoresis" OR "laser irradiation" OR "laser therapy" OR "lasotherapy" OR "lazer therapy" OR "LED Therapy" OR "light therapy" OR "low energy laser" OR "low energy photon therapy" OR "low intensity laser" OR "low level diode laser therapy" OR "low level infrared radiation" OR "low level laser" OR "low level light" OR "low light laser therapy" OR "low light therapy" OR "low output helium neon laser" OR "low power laser" OR "low reactive level laser" OR "mid laser therapy" OR "monochromatic infra red energy" OR "monochromatic light therapy" OR "near infrared laser stimulation" OR "near infrared light stimulates" OR "non ablative co2 laser therapy" OR "photo irradiation" OR "photon therapy" OR "physiotherapy laser" OR "polarised polychromatic light" OR "polarised radiation" OR "red light emitting diode" OR "red light emitting diodes" OR "soft laser" OR "CLILT" OR "Combined Low Intensity Laser Therapy/Phototherapy" OR "Red Light Therapy" OR "Transcranial infrared laser stimulation" OR "therapeutic laser" OR biophoton OR biophotons OR CHELT OR HILT OR lasotherapy OR LEDT OR LLDLT OR LLLS OR LLLT OR LLRL OR LPRLL OR MIRE OR NACLT OR photobioactivation OR photobiostimulation OR photomedicine OR photomodulation OR photostimulation OR phototherapy OR PLLL OR PWLLLT OR SLLLT #3 "Mucositis" OR "oral mucositis" OR "Stomatitis" OR Esophagitis OR Aphthous OR "Radiodermatitis" OR "Radiation-Induced Dermatitis" OR "Radiation Induced Dermatitis" OR "Radiation Fibrosis" OR "Radiation-induced fibrosis" OR "peripheral neuropathy" OR "Lymphedema" OR Lymphoedema OR "Trismus" OR "Osteonecrosis of the jaw" OR "Osteoradionecrosis" OR "Bisphosphonate-Associated Osteonecrosis of the Jaw" OR BRONJ OR "Graft vs Host Disease" OR GVHD OR Hyposalivation OR "Xerostomia" OR dysgeusia OR "Taste loss" OR Tinnitus OR "Dyspepsia" OR Dysphasia OR "Post Surgical wound healing" OR

	balance OR “Neck pain” OR “hand and foot dermatitis” OR “dyshidrotic eczema” OR “cancer toxicities” #1 AND #2 AND #3

Appendix 2. Risk of bias assessed by Meta-Analysis of Statistics Assessment and Review Instrument (MAStARI)[1] critical appraisal tools. Risk of bias was categorized as **High** when the study reached up to 49% score "yes", **Moderate** when the study reached 50% to 69% score "yes", and **Low** when the study reached more than 70% score "yes".

MAStARI critical appraisal tools for Comparable Cohort / Case Control Studies.

Question	Answer*
	Bezinelle et al., 2014
1. Is the sample representative of patients in the population as a whole?	Y
2. Are the patients at a similar point in the course of their condition/illness?	Y
3. Has bias been minimized in relation to selection of cases and of controls?	Y
4. Are confounding factors identified and strategies to deal with them stated?	U
5. Are the outcomes assessed using objective criteria? (costs)	Y
6. Is follow-up carried out over a sufficient time period?	Y
7. Are the outcomes of people who withdrew described and included in the analysis?	N
8. Are outcomes measured in a reliable way?	Y
9. Is appropriate statistical analysis used?	Y
% yes/risk	77%/ Low

*Y=Yes, N=No, U=Unclear, NA=Not applicable.

Appendix 3. Assessment of the study quality based on a tool from the Consensus on Health Economic Criteria (CHEC). Each question of CHEC-list was answered with "yes" or "no".

Question	Answer*			
	Martins et al. 2020	Bezinelli et al. 2014	Antunes et al. 2016	Piller and Thelander, 1995
1. Is the study population clearly described?	Y	Y	Y	Y
2. Are competing alternatives clearly described?	Y	Y	Y	Y
3. Is a well-defined research question posed in answerable form?	Y	Y	Y	Y
4. Is the economic study design appropriate to the stated objective?	Y	Y	Y	Y
5. Is the chosen time horizon appropriate to include relevant costs and consequences?	Y	Y	Y	Y
6. Is the actual perspective chosen appropriate?	Y	Y	Y	Y
7. Are all important and relevant costs for each alternative identified?	Y	Y	Y	N
8. Are all costs measured appropriately in physical units?	Y	Y	Y	Y
9. Are costs valued appropriately?	Y	N	Y	N
10. Are all important and relevant outcomes for each alternative identified?	Y	Y	Y	Y
11. Are all outcomes measured appropriately?	Y	Y	Y	Y
12. Are outcomes valued appropriately?	Y	N	Y	N
13. Is an incremental analysis of costs and outcomes of alternatives performed?	Y	Y	Y	N

14. Are all future costs and outcomes discounted appropriately?	Y	N	Y	N
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Y	N	Y	N
16. Do the conclusions follow from the data reported?	Y	Y	Y	Y
17. Does the study discuss the generalizability of the results to other settings and patient/client groups?	N	N	N	N
18. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Y	Y	Y	N
19. Are ethical and distributional issues discussed appropriately?	N	Y	N	N
% yes	89,47%	73.68%	89.47%	52.63%

*Y=Yes, N=No

1 Criteria list for assessment of methodological quality of economic evaluations: consensus on health economic criteria (CHEC), 2005.

ARTIGO: Impact of pandemic COVID-19 outbreak on oral mucositis management protocols: perspectives for extraoral photobiomodulation therapy.

Capítulo 2 - Artigo publicado no periódico *Supportive Care in Cancer. 2020. Oct28(10):* 4545-4548. Doi: 10.1007/s00520-020-05636-1 (Anexo 2)

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Abstract

This communication discusses the current challenges of oral mucositis (OM) management during the pandemic COVID-19 outbreak and reflects about an extraoral photobiomodulation protocol as an optimal alternative for preventing and treating OM in advanced cancer patients while minimizing the risk of infection by avoiding intraoral manipulation.

Keywords: COVID-19, Oral mucositis, Cancer, Photobiomodulation therapy, Laser therapy

Introduction

The recent 2019 novel coronavirus disease (COVID-19) pandemic has dramatically changed several aspects of worldwide communities, evoking many changes in the routine activities of populations as well as impacting economic burden and functioning capacity of the healthcare system [1]. Since December 2019, when the first cases emerged in Wuhan (Hubei Province of China) [2, 3], an exponential number of infected patients with the SARS coronavirus 2 (SARS-CoV-2), the known etiologic agent of the COVID-19, has spread across multiple countries with rapid community dissipation of the virus [4, 5]. Acute inflammatory distress syndrome is one of the most life-threatening complications of COVID-19 and usually requires intensive care and mechanical ventilation [1], most frequently in more vulnerable patients, which include patients undergoing anticancer treatment or diagnosed with malignancies associated with an immunosuppressive state. Cumulative evidence suggests that cancer patients are at increased risk of COVID-19 infection [6], and early published reports estimated a significant higher risk of mortality over 3.5 times on cancer patients [7].

The person-to-person spread of COVID-19 disease seems to be rapid and may quickly overwhelm the care settings from primary to tertiary levels. In this scenario, oncologic care facilities have faced the dilemma of how to maintain cancer treatment in the pandemic era, reaching appropriate treatment outcomes either for ongoing patient's therapies or therapies that will initiate during the growing phase of the outbreak, meanwhile promoting safety for both patients and healthcare professionals [8].

Discussion

Managing oral health before or during cancer treatment includes not only dental workup but also intraoral photobiomodulation therapy (PBMT)-validated protocols [9, 10] for prevention or treating oral mucositis (OM), which may place dentists and patients at a particularly high risk to COVID-19 transmission.

Therefore, it is paramount to rethink recommendations to oral care staff inserted in the oncologic setting with emphasis to PBMT protocols attempting to reduce risks of SARS-CoV-2 transmission without restricting the markedly benefits of light-based protocols for OM management during radiation therapy and chemotherapy course [10]. In this sense, Professor Holden Thorp, the Editor-in-chief of Science, was very fortunate

in saying that “The success of the world’s scientists — along with strong political and social leadership — will determine which scenarios unfold, so it is time to focus on what we can all do to help” [11]. Thus, our group reports herein the use of the so-called closed-mouth extraoral PBMT protocol based on the available body of evidence [12] of this approach against intraoral devices during the pandemic COVID-19 outbreak as an additional intention to control the contact with the saliva of potentially contaminated cancer patients.

This international challenging scenario brought new perspectives for our ongoing randomized controlled clinical trial [13] originally designed to characterize the impact of extraoral and intraoral PBMT protocols on OM and survival outcomes of patients with oral cavity and oropharynx squamous cell carcinoma. Due to the above-mentioned impact of pandemic COVID-19 outbreak on OM managing protocols, our group decided to focus exclusively on the PBMT delivery by using a large light-emitting diode (LED) probe. This technique permits the treatment within a reasonable time of tissues from an extraoral approach, enabling light delivery to the oral and oropharyngeal mucosa while avoiding intraoral manipulation as described by Treister et al. (2016) [12] and adapted for our clinical trial [13]. Moreover, it seems to be safe and effective to manage OM as well as associated pain with minimal discomfort for patients and less professional exposure to saliva [13–16].

We could eventually wait for several months to finish our ongoing trial [13] and publish more clear evidence about this strategy. However, since fast dissemination of COVID-19 viruses can be lethal to health professionals and global society, we decided to share such new insights with international supportive care in cancer multidisciplinary teams, in order to disseminate our transformed clinical practice to cope with COVID-19, as illustrated on Fig. 1. The extraoral prophylactic and therapeutic PBMT parameters are based on a Class 2M LED Thor LX2 (Thor Photomedicine Ltd., Chesham, London, UK) operating with a 69 diode LED cluster probe (1390mW). The probe contains the following specifications: 34 × 660-nm central wavelength LED, with spectral width of 20 nm at 50% intensity, average power of 10 mW, active area of 0.2cm^2; power density (irradiance) of 51 mW/cm^2; and beam divergence of 20° half angle; associated with 35 × 850-nm wavelength LED, with spectral width of 45 nm at 50% intensity, average power of 30 mW, active area of 0.2cm^2; power density (irradiance) of 150 mW/cm^2; and beam divergence of 22° half angle leading to 1390 mW of total power, an outer diameter probe

of 70 mm, 63 mm of diameter of active area, and an average power density of 44.6 mW/cm^2 [12].

The LED device is being applied flat against the face and neck of the patients (Fig. 2) at five treatment sites: face (right, center and left sides) and neck (right and left sides) [13]. The device is applied for 60 s per location (50 mW/cm2 × 60 s = 3.0 J/cm2 for five locations) [12]. No safety goggles are required for the patients because it is a LED probe, which in the current context may also avoid cross contamination among patients.

Despite the use of the closed-mouth extraoral PBMT technique, a systematic disinfectant routine of the equipment and work environment is indispensable. This includes the disinfection of all surfaces in patient-care areas and PBMT probes/equipment with hospital standardized disinfectants, such as 70% ethylic alcohol and quaternary ammonium compounds [17]. After disinfection, the probe is protected with plastic film before clinical use and is immediately disposed after the procedure. Proper COVID-19 professional protective equipment use (disposable working cap, disposable doctor cap, goggles or face shield, disposable surgical mask, and disposable gloves, among others) must be consistent with the World Health Organization protocols designed for health workers [17], local institutional guidelines, and also with the regional government recommendations.

The use of extraoral PBMT for oral mucositis is not fully novel; however, current treatment protocols often focus on intraoral PBMT. Hence, considering the current situation with COVID-19, we believe our experience may guide novel treatment protocols to protect cancer patients and providers. The main limitation of this report is that it does not support with details the grade of the OM outcomes or the results of the treatment due to the fact that an interim analysis of clinical data would take several weeks to be collected in the current panorama of the pandemic.

Conclusion

The pandemic COVID-19 outbreak brought new perspectives for the development of extraoral PBMT protocols designed to reduce risks of SARS-CoV-2 transmission without limiting its benefits on OM management during radiotherapy and chemotherapy for advanced cancer patients.

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Compliance with ethical standards

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

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

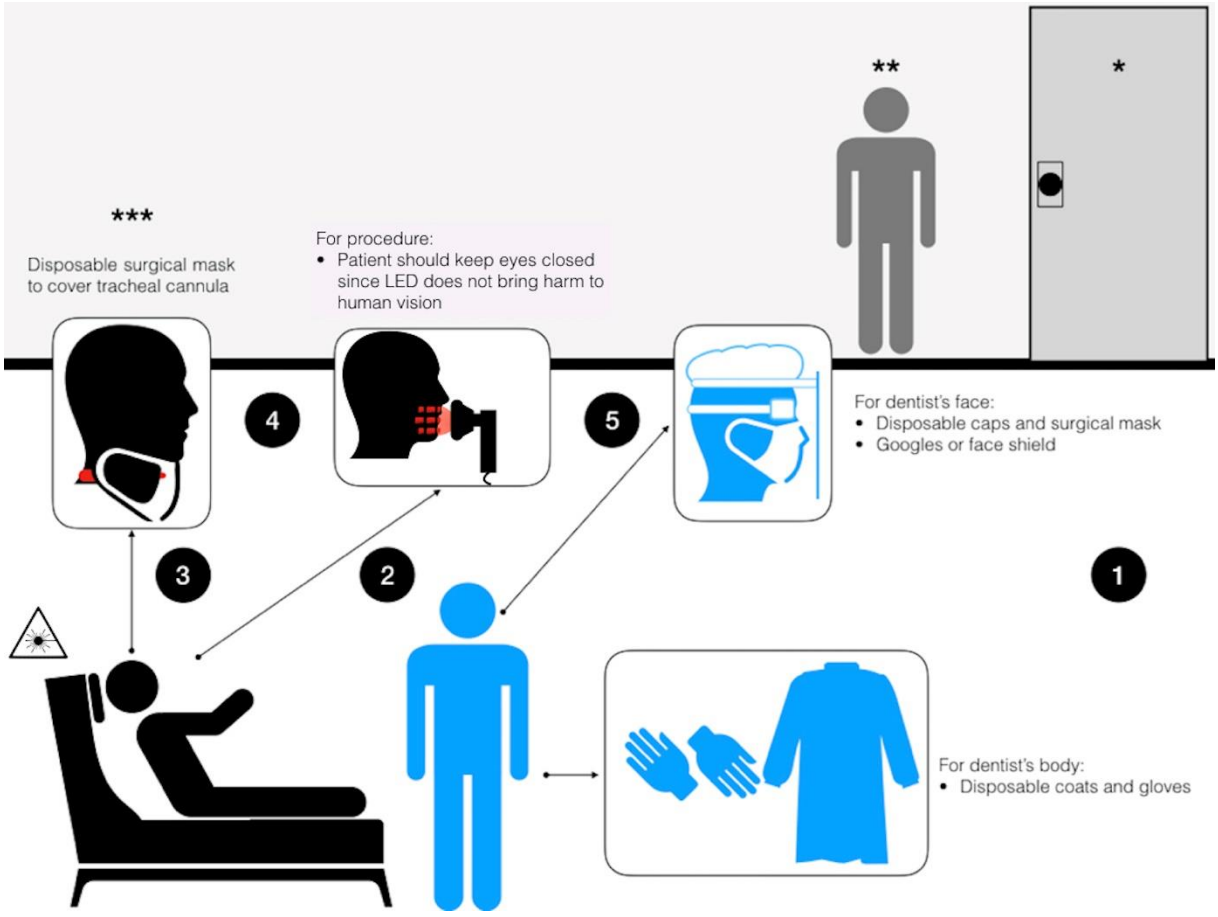

Figure 1. Scheme summarizing all information necessary for a safe PBMT appointment. *Door of the hospital room should be closed with low-pressure inside in cases of COVID-19 suspicion or confirmation or the door or window should be opened to provide airflow, minding to not put other individuals in risk of infection.** Patient's family member or carer should wait outside the hospital room. *** Patients with advanced tumors may be subjected to neck dissection with protective tracheostomy in complementation to solid tumor removal — especially for those individuals with adjuvant or exclusive radiotherapy. Cough and secretive fluids are common and persistent during radiation treatment, representing an important infection source. Therefore, their tracheal cannula should be covered with a disposable surgical mask. Also important, professionals should sanitize their hands with water and soup or alcohol gel (1) before patient examination, (2) before dental procedures, (3) after touching the patient, (4) after touching equipment without disinfection, and (5) after touching the oral mucosa or body fluids. [20] Laser flag was positioned in the back of the patient because we suggest that professionals keep PBM equipment behind working chair to avoid contamination in case of infected droplets.

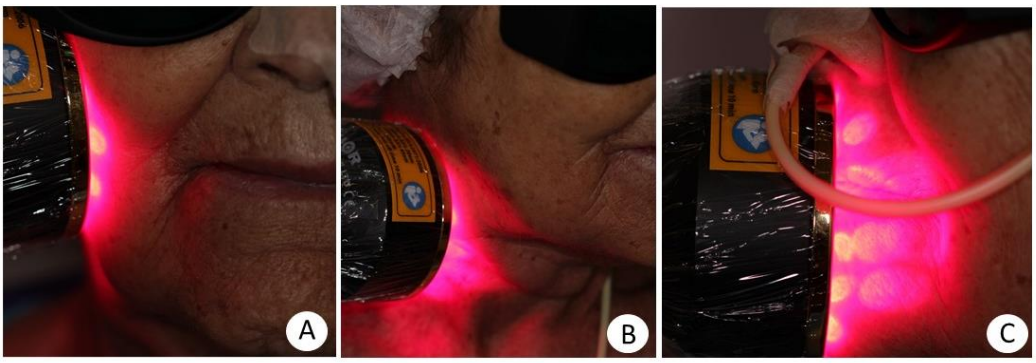

Figure 2. Extraoral PBMT protocol with 69 diodes LED cluster probe (1390mW) being applied for the prevention of chemoradiation-induced oral mucositis in an oral squamous cell patient. As demonstrated in these images, PBMT should be applied at the right side of the face (A), right side of the neck (B), center face (C), and then repeated for the left side of the patient's face and neck.

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ARTIGO: Extraoral photobiomodulation therapy for oral and oropharyngeal mucositis in head and neck cancer patients: interim analysis of a randomized, double-blind, clinical trial

CAPÍTULO 3 – Artigo será submetido ao periódico Oral Oncology.

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Keywords: Photobiomodulation, oral mucositis, radiotherapy, quality of life, survival analysis

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Abstract

Aim: To assess the impact of prophylactic extraoral photobiomodulation (PBM) therapy for oral and oropharyngeal mucositis (OM) on clinical outcomes and survival in patients with oral cavity and oropharyngeal squamous cell carcinoma (OSCC).

Methods: OSCC patients who received radiotherapy (RT) or chemoradiotherapy with curative intent were prospectively assessed. Patients were randomized to two groups. One received prophylactic extraoral PBM (LED 69 diode, 34x660 nm (10 mW) and 35x850 nm (30 mW), 1390 mW, energy density 50 mW /cm2, 3.0J of energy/cm2, 60s/spot, spot size (6 cm^2) and the other placebo sham LED. OM grade (NCI, *Version* 4.0, 2010), pain (VAS), analgesia, and anti-inflammatory prescriptions were assessed weekly. Quality of life evaluations were performed at the first and last day of RT. The impact of the PBM upon cancer treatment outcomes were evaluated quarterly during cancer follow-up visits following RT.

Results: A total of 67 patients were randomized and 55 completed RT within the inclusion criteria. Randomization and population characteristics were comparable between groups. Later OM onset, lower median pain score, less analgesic and less anti-inflammatory prescription were observed for the PBM group. No difference in severe OM incidence was observed. Better quality of life (QoL) scores were observed for the PBM group. There was no significant adverse side effects or impact on the overall survival. Extraoral PBM was well tolerated.

Conclusion: Prophylactic extraoral PBM during RT for OSCC can delay OM onset, reduce pain, as well as require reduced analgesic and anti-inflammatory prescription requirements. Extraoral PBM has potential to maintain better QoL scores. There was no evidence of PBM impact on cancer treatment outcomes.

Keywords: Photobiomodulation, oral mucositis, radiotherapy, quality of life, overall survival.

Introduction

Oral mucositis (OM) is an acute side effect of the cytotoxic cancer treatment that is particularly severe in patients undergoing radiotherapy (RT) and chemotherapy (CT) regimens as part of head and neck cancer (HNC) treatment protocols. OM often leads to debilitation due to painful oral mucosa erythema and ulcers [1, 2]. The incidence and severity of OM depend upon several risk factors associated with the medical treatment and patient characteristics, such as concomitant chemoradiation (CRT), RT dose, tumor site and stage, and patient's status performance [3, 4].

The dysfunction and debilitating distress linked with OM are associated with impairment in eating, swallowing and speech functions. This morbidity, in turn, can lead to increased treatment costs due to the need of hospitalization, nutritional support, opioids use, antimicrobials and anti-inflammatory drugs [5-7]. Also, OM is associated with a negative impact on patient's quality of life and if severe may lead to worse prognoses due to dose treatment reduction and non-planned treatment interruptions [8-11].

In this context, photobiomodulation (PBM) therapy has been used as an important intervention to support cancer patients to prevent and manage severe OM outcomes [11-14]. With level I scientific evidence, the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) recommends the use of PBM as an adjuvant intervention for OM (15) in the HNC setting. PBM consists of a wide range of non-ionizing lights with cell photochemical effect on wound healing, anti-inflammatory response and pain control [16,17].

Although PBM is well established and accessible, there is great variability in PBM parameters, protocols and equipment, which hampers consistent evaluation [18]. Another challenge to the large acceptance of PBM relies on the possibility that it may stimulate the growth of residual tumor cells or impact the field of cancerization in HNC leading to an increased risk for tumor recurrence, second primary tumors, metastasis or cancer treatment resistance [11, 19-21]. It is paramount that interventions used to mitigate OM do so without negatively impacting the effectiveness of the tumor treatment, especially in cases where the PBM application is anatomically adjacent to the tumor field, such as in HNC [16].

The present preplanned interim analysis of a randomized, double-blind clinical trial, aimed to evaluate the prophylactic delivery of extraoral PBM effect on OM, pain, quality of

life and cancer safety outcomes in oral and oropharyngeal squamous cell carcinoma (OSCC) patients during CRT.

Methods

This double-blind (patients and investigators), prospective clinical trial was conducted at Instituto do Cancer do Estado de São Paulo (ICESP) in São Paulo, Brazil. Ethical approval for this study was obtained from the National Human Research Ethics Committee (CAAE: 21648819.9.0000.5418). All participants signed the consent form. The study was conducted in accordance with the Declaration of Helsinki and reported according to the Consolidated Standards of Reporting Trials guidelines (CONSORT) [22]. This clinical trial was registered in the International Clinical Trials Registry Platform (ICTRP-WHO) and Brazilian Registry of Clinical Trials (ReBec) with the registration number: RBR-4w4swx [23]. This interim analysis was performed to evaluate the study results of at least 50 participants during the first year of follow up.

Patients

We included patients diagnosed with OSCC in stage III or IV (*International Union Against Cancer, 8th edition*) [24], over the age of 18, treated with curative RT protocols (60-70Gy - 2.0Gy/day, 5 sessions/week) as a single modality or in association with surgery and CT. All included patients were submitted to the institutional standard-of-care dental treatment protocol before RT, designed to identify potential source of infection and maintain maximum oral health like complete prophylaxis, restorations, dental scaling/polishing, endodontic therapy and tooth extraction if necessary [19]. Demographics and clinicopathological information of all patients was available in the electronic medical record system (Tasy, Java version; product #NOCTN306, Koninklijke Philips N.V., 2004–2017).

Patients were excluded if they had distant metastasis, with previous RT history, those scheduled to receive palliative RT and those not able to understand the applied questionnaires with a stable self-awareness.

Patients were blinded and randomly allocated into two groups: extraoral PBM and placebo. Two randomization lists, on blocks of 4 patients, were performed according to a 1:1 ratio. The lists were generated by SAS program (version 8.02). All patients received verbal and

written instructions about oral hygiene, abstinence of tobacco, alcohol and oral toxicities related to cancer treatment [25].

PBM protocol

Patients in the extraoral PBM group received daily prophylactic PBM for 5 consecutive days/week, from the first to the last day of RT, (Monday to Friday). Two trained dentists administered the PBM. PBM was performed with the red and near-infrared LED probe, with a total power of 1390mW (THOR Photomedicine Ltd - THOR LX2 with 69 diode LED cluster probe 1390 mW - 63 mm of diameter of active area and an average power density of 44.6 mW/cm^2. The LED probe was applied flat against the patient's face and neck for 60 seconds, at five treatment sites: right face side, center face, left face side, left neck and right neck (50 mW/cm2 x 60 s = 3.0 J/cm2 per location) [26] (**Fig 1**). Patients recruited to the placebo/control PBM group underwent LED sham sessions with an inactivated extraoral probe, following the same model and daily applications as extraoral PBM group (**Fig 2**). To ensure the blinding of participants, the extraoral sham sessions were performed with the same device, the activation button was pressed twice to simulate the application and activation sound (beep), and the patients were instructed to use a dark safety google.

Oral mucositis

A calibrated dentist, blinded to the allocation group completed the clinical outcomes assessment, and after the physical examination, left the room during the PBM session. The researcher responsible for applying the PBM did not perform any patient evaluations. All patients were evaluated weekly for the presence and severity of OM following the *Common Terminology Criteria for Adverse Events* (NCI, v*ersion* 4.0, 2010), graded 0-4. The extraoral PBM effectiveness was analyzed by incidence, site and severity of OM, following the recent published paper of de Pauli Paglioni et al., 2020 [27]. Effectiveness was defined as the simple proportion of 30% less severe OM in the PBM group in comparison to placebo, as proposed by the hypothesis of Legouté et al., 2019 [14].

Pain and analgesia

Pain was evaluated using a visual analogue scale (VAS) graded 0-10. Medication used for OM analgesia was recorded weekly and classified by levels based on the pain scale and the WHO Analgesic Ladder: no analgesics, patients without pain related to OM; level 1, low level pain (VAS 1-3; paracetamol or dipyrone and/or ketoprofen or celecoxib); level 2, moderate pain (VAS 4-6; codeine or tramadol or dipyrone and/or ketoprofen); and level 3, severe pain (VAS 7-10; morphine or oxycodone + paracetamol or dipyrone and/or ketoprofen) [27,28].

Anti-inflammatory prescription

The prescription of anti-inflammatory drugs for OM was also recorded weekly. All prescriptions were made by the medical team or dentists, blinded to the study group allocation at any time of the RT treatment.

Feasibility study

To evaluate the acceptance and suitability of the extraoral PBM technic, the treatment compliance, tolerance and discomfort, adverse events and failures from the device were evaluated. Data for the feasibility endpoints and preliminary results from patients' response to the extraoral PBM intervention were obtained based on guiding questions for feasibility study [29].

Quality of life (QoL)

The University of Washington Quality of Life Questionnaire *(UW-QOL v4)* validated for the Portuguese version [30], was completed by all included patients. Patients were surveyed before the first day of RT (D-1) and at the last day session of RT (D30). The UW-QoL is composed of 12 objective questions of specific variables, ranging 0 to 100, whereas 100 is the best possible answer. The analysis is divided into two domains: physical and social-emotional function.

Oncological safety outcomes

After RT, patients were evaluated every 3 months for a total of 18 months. Evaluations were based on clinical examinations and medical information available in the electronic medical record. For cancer surveillance, overall survival (OS) rate, disease-free survival (DFS), the incidence of recurrences (local-regional and distant relapse rates) or new (second) primary tumors were used as primary outcome measures [19].

Statistical analysis

Results of this interim analysis were expressed as mean values and percentages. Statistical significance rate of 5% ($p \leq 0.05$) was considered. Statistical analysis of the data obtained from the present study, including Kaplan-Meier curve for 12 months period analysis of OS, was performed with GraphPad Prism 9.0. The Mann-Whitney test was used to analyze the OM overall incidence, pain and analgesia results, and QoL scores for group comparison. The chi-square test was used to compare incidence of severe OM, anti-inflammatory prescription, OM distribution and OS. Finally, Wilcoxon signed-rank test was used to time comparison between single group QoL scores.

Research funding

This trial had the financial support of the São Paulo Research Foundation (FAPESP) processes numbers 2018/02233-6 and 2018/23479-3, and the National Council for Scientific and Technological Development (CNPq).

Results

A total of 67 patients were randomized, from June 2019 until November 2020. Twelve patients were excluded during RT, due to noncompliance with RT (n=1), RT interruption due to SARS-CoV-2 infection (n=3), death before RT completed (n=7), OM grade 4 with medical request to discontinue the trial to receive institutional PBM of OM treatment protocol (n=1/placebo group). Finally, 55 patients completed the planned RT treatment within the inclusion criteria and were included in the clinical follow-up. The flow-chart and exclusion reasons are presented in **Fig 3.** The clinical trial is programmed to be concluded 18 months after the last patient inclusion.

Clinicopathological characteristics of the included patients are summarized in **Table 1**. Patients from extraoral PBM and placebo groups had similar clinicopathological features, most

of the patients were male (79.3% vs. 84.6%), with a history of tobacco and alcohol use. The oropharynx was the most frequent primary tumor site for both groups, and CRT was the most common cancer treatment. There were no statistically significant differences in the clinicopathological characteristics between the groups.

Oral Mucositis

Results of OM assessment are presented in **Fig 4.** All patients experienced some grade of OM patients during RT. The first occurrence of OM was observed earlier in the placebo group (week 1) than the PBM group (week 2). Comparison over the time of RT showed a late OM onset in the PBM group. During week 3, 100% of the placebo group experienced some grade of OM, and the same results were observed at week 6 for the PBM group. Differences in the OM grade was observed during weeks 1 ($p=0.014$) and 2 ($p=0.009$), with better results in the PBM group.

Incidence of severe OM (grade ≥3) was higher in the placebo group during all study periods evaluated, with the exception of the last week of RT, where PBM showed 52% of grade 3 OM versus 41% at the placebo group ($p=0.469$). There was no difference in terms of percentage (≥30% ratio of grade ≥3) for severe OM incidence between groups in any period of evaluation, including the last week of treatment ($p=0.447$).

Pain and analgesia

Pain evaluation was variable over treatment time for both groups (**table 2**). During most of the periods of assessment, lower mean pain scores were observed for the PBM group. Moderate pain score (VAS: 3-7) was only observed at the placebo group during week 6 with 3.3 (±2.82) and week 7 with 4.5 (±3.42), which was the highest mean level of pain observed in the placebo group. In the PBM group, the highest mean level of pain was 2.8 (±2.52) during week 5 of RT. Significant statistical difference in mean pain score was observed at week 7 ($p=0.019$), associated with the highest mean pain score observed in the study.

Analgesia use is summarized in **table 2.** During all periods of evaluation, the PBM group had a higher percentage of patients that did not require analgesics use. An important difference was observed during week 7 of treatment, where 52% of PBM patients vs. 13.6% of placebo were not using any analgesic for pain relief related to OM, and also the higher prevalence of

level 3 analgesia was observed, where 27.3% of placebo patients vs. 4.0% of PBM patients where in use of opioids, a statistically significant difference was observed (p=0.02). During week 3, a statistically significant difference in analgesia evaluation was also observed (p=0.09).

Anti-inflammatory prescription

The number of anti-inflammatory prescriptions were higher for the placebo group **Fig 5**. At the week 4 of RT, the maximum number of prescriptions of anti-inflammatory drugs was observed for both groups, with a higher percentage for placebo (34.6%) in comparison with the PBM group (20.7%) (p=0.5879). At week 5 an important difference of anti-inflammatory prescription between groups was noticed, with 30.8% for the placebo whereas 6.9% for the PBM group and a statistically significant difference was observed (p=0.0346).

Quality of Life (QoL)

The QoL assessments are presented in **Fig 6**. The general UW-QoL score at the first (D1) and final RT sessions (D35) for the PBM group were 910 and 687, respectively, while for the placebo group were 868 and 607, respectively. Statistically significant results were found in D35 for general QoL for between groups (p=0.0390), with better scores in the PBM group.

Assessing functional outcomes, at D35, the physical QoL had lower scores in the placebo group, with mean score of 258 vs. 279 for the PBM group (p=0.1330). Lower mean scores for social-emotional QoL outcomes were observed at D35 for the placebo group, with scores of 348 vs. 408 for the PBM group and a statistically significant result (p=0.0034).

In terms of treatment period (D1 vs. D35), the negative impact of RT on QoL was observed by decreased scores at D35, and statistically significant results in general and physical outcomes for both placebo and PBM groups and social-emotional outcomes for the placebo group (p>0.0001). The social-emotional QoL outcomes for PBM group was an exception, although, at D35, patients presented lower scores than at D1 (p=0.1553).

Feasibility study

A total of 918 PBM therapy sessions were performed for the PBM group and of 832 sham sessions were performed for the placebo group. There was no difference in the mean number of sessions for both groups (32 sessions) and areas of treatment (p=0.38). Excellent tolerance level to the PBM was reported by 54 (98.1%) patients, while 1 (1.9%) patient reported moderate tolerance due to discomfort caused by nausea associated to the smell of the plastic film that covered the probe (for infection control purposes). No pain or other adverse events were reported.

For the PBM group, the OM analysis showed a pattern of OM incidence associated with oral mucosal sites distant from the direct contact with the extraoral probe. The OM site distribution can be observed in **Fig 7**. At the last week of treatment, oropharynx (16%), border of the tongue (14%) and retromolar trigone (14%) were the most affected sites. The results for the placebo group where more heterogeneous with severe OM incidence in the border of the tongue (15%), oropharynx (14%), and buccal mucosa (14%), this last one is an area with direct contact with the extraoral probe. A tendency of non-proportional distribution of OM on the mucosa sites for the PBM group (p=0.02) was seen in comparison with the placebo group (p=0.64).

Oncological safety outcomes

No local or systemic adverse events due to the PBM therapy were observed. Tumor response to RT, early recurrences or new second primary tumors were not observed. One local recurrence was recorded 6 months after RT in the placebo group. An interim analysis of the OS with the follow-up period of 12 months was possible, and a slight tendency for better overall survival was observed in the PBM than in placebo groups (74.0% vs. 68.7%; p=0.889; HR: 0.88; CI 95%: 0.21–3.65) (**Fig 8)**. This survival data of the ongoing clinical trial will be updated after a total follow-up period of 18 months of the last patient inclusion, with the final evaluations of oncological safety outcomes.

Discussion

We evaluated the effects of a prophylactic extraoral PBM in the outcomes of RT-induced OM and its clinical and oncological outcomes. The demographic characteristics of the included patients in this interim analysis were very similar to those presented in the literature,

patients with advanced OSCC, mostly males, with history of tobacco and alcohol use [10, 14, 20, 31]. Additionally, the oncological treatment reflected the standard of care from international cancer centers, based on a multimodal approach, including surgery, RT and CT. The combination of CRT is associated with better prognosis, but also with a substantial increase of acute side effects, particularly OM [9, 10, 32, 33].

There is robust evidence demonstrating the effectiveness of PBM for OM. The MASCC/ISOO guidelines recommend its use for OM prevention in HNC patients [15]. In our study, it was observed early onset of OM in the placebo group comparted to the PBM group, which reinforces the prophylactic effect of PBM. However, there was a high incidence of grade 3 OM for both groups during the last week of treatment. Different PBM effectiveness results can be attributed to many factors related to PBM therapy parameters, oncological treatment regimen, and patient's characteristics [14, 18, 34]. Also, it is important to mention that this is an interim analysis of the present ongoing clinical trial and that results could change at completion of the trial.

One of the main disadvantages when comparing PBM results between studies is the heterogeneity of protocols and PBM parameters used [19, 20, 34-37]. The MASCC/ISOO guidelines recommend as prophylactic PBM parameters, red and infrared wavelengths and energy density between 2-3 J per cm^2 [15]. There are no specific parameters in terms of scientifically validated protocols for extraoral PBM for OM. Thus, this study protocol was based on results from Treister et al., 2016 [26], that used extraoral PBM for the prevention of OM during hematopoietic stem cell transplantation.

Despite the prophylactic intent of our study, although delay in development of mucositis was seen, we failed to demonstrate significant differences in severe OM control by PBM therapy. We observed incidence of severe OM mainly in the oropharynx, and bilateral border of the tongue, areas distant from the extraoral light surface. The literature shows that light delivery to target tissue is affected by distance from the light source and in extraoral PBM tissue in closer contact with the probe surface will have greater energy delivered. This may include the buccal mucosa, the vestibule, and the oral surfaces of the lips [34, 36]. The specific OM incidence per oral site found on our study may be due to the different light dose distribution in superficial non-target tissues than in deeper tissues, more distant from the light source. Preliminary data on light penetration on the human buccal mucosa published by Hodgson et al., 2012 [38], measured 85.5% reduction in the power of the LED light device when 2 cm distant from the light source.

In our study, patients from the PBM group experienced less severe pain associated with OM, lower mean pain score during RT with reduced opioid use. Important differences in pain assessment and analgesics between PBM and placebo were observed to be greatest during the last week of RT. The PBM is known to be associated with pain reduction and thus may lead to reduced use of opioid analgesics [35, 38, 39, 40]. Similar studies, Antunes et al., 2013[40] and Gautam et al., 2015 [41] reported significantly less severe oral pain scores for PBM treated patients compared to placebo, in addition to reduced number of opioids during RT. The systematic review from Paglioni et al., 2019, suggest intraoral PBM as a safe method for pain reduction and control, as this therapy can reduce pain scores and the need for analgesics during RT for HNC patients [17]

Although PBM delayed onset of OM, it was not associated with prevention of grade 3 OM. This may be due to the PBM dose used, the use of extraoral PBM and less impact upon deeper mucosal tissues and also could be associated with higher prescriptions of anti-inflammatory agents in the placebo group. All prescriptions were made by the medical team or dentists, blinded to the study groups allocation. Although no guideline supports the use of systemic anti-inflammatory agents to manage OM, inflammation is considered to be an important major effect of RT-induced OM and anti-inflammatory inhibition is a potential treatment strategy in this context [42, 43].

Few studies have evaluated the effectiveness of extraoral PBM for OM. One study by Arora et al., 2008 [44], associated extraoral and intraoral PBM for managing RT-induced OM. Patients were asked to keep their mouth wide open during the extraoral therapy. Results were statistically significant in terms of OM severity and pain control, with better results for the PBM group. A study by Hodgson et al., 2012 [38], used exclusive extraoral PBM with 4 J/cm^2 to prevent OM associated with hematopoietic cells transplantation chemotherapy and reported a statistically significant reduction in pain but failed to show any significant results on OM control. In the study by Treister et al., 2016 [26], of 13 pediatric patients undergoing hematopoietic cells transplantation, 77% experienced OM grade 3 and the most affected site was the floor of the mouth. Our study applied exclusive extraoral PBM and also failed to demonstrate significant results on severe OM control, however, we showed delay in progression to Grade 3 and recorded reduced OM-related pain in the PBM group.

Oral and oropharyngeal cancer is associated to reduced QoL due to the effects of primary tumor and treatment side effects impairing patient's daily functional and self-image [20, 33, 45]. Worsening levels of general QoL were observed at the end of the treatment, as reported in previously-published studies [39, 40, 45-47]. The variability of QoL is directly

associated with cancer treatment toxicities alterations in swallowing, chewing, saliva changes, taste and especially OM-related pain [45]. Our study shows better QoL in those treated with PBM, which could be explained by the positive impact in OM symptoms attenuation specifically decreased pain levels [40, 47, 48].

It is essential that an intervention used to support cancer patients during therapy does not adversely affect tumor risk, tumor behavior, or tumor response to treatment [36, 12, 14, 16, 21, 36, 49]. Data about PBM impact on tumor activity and oncological treatment response based on *in vitro* studies are conflicting. Contradictory results may be correlated to the variation of PBM parameters, tumor cell lines, and tumor genomic heterogeneity between studies [11, 16, 49, 50]. Current literature indicates that any *in vitro* experiment assessing the effect of PBM should not be considered representative of what happens in the clinical care. Based on the existing data, confirmation of the safety of PBM in the management of OM is important.to be examined in prospective randomized controlled clinical trials in oral and oropharyngeal tumors [4, 19, 49, 51].

No significant adverse side effects were noted in the present study, in the setting of oral and oropharyngel cancer patients submitted to PBM during RT. This is in agreement with the current literature [14, 19, 20, 40, 41, 44, 50]. Furthermore, no relevant negative effects of PBM therapy on tumor biology was demonstrated, also in agreement with other similar studies [14, 19, 40, 50, 52]. No differences in OS were seen in the current study in PBM versus placebo groups. Additional data will be available upon the final analysis of 18 months of follow-up.

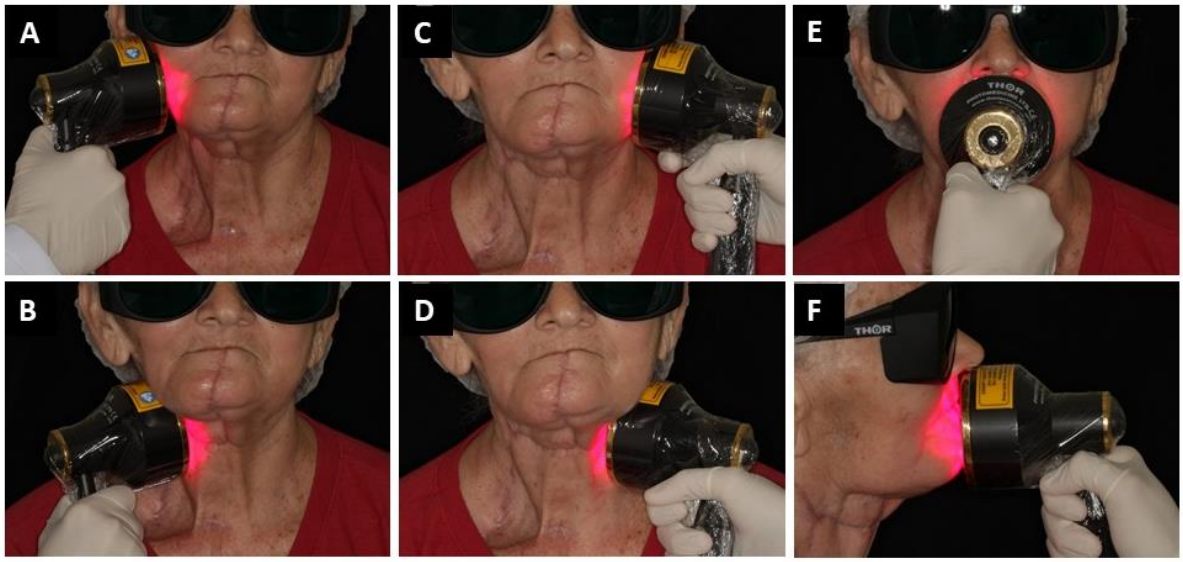
The OM outcomes observed in the present study suggest a possible indication of the extraoral application in OSCC patients submitted to RT. Adjustments in the extraoral PBM protocol need to be optimized with the goal of achieving greater efficacy in OM control, by including high risk sites in therapy with selected sites of intraoral PBM delivery. The use of extraoral application plus selected high risk oral regions per radiation treatment plan, may enhance compliance and reduce time for light application in the clinical setting. Additional studies comparing different extraoral protocols in addition to intraoral complementation therapy are warranted. Furthermore, the evaluation of site-specific patterns of OM, have been suggested with the goal of improving the development of PBM protocols [27, 53]. It is important to highlight that the extraoral PBM therapy is considered to be a simple, well-tolerated and easy application therapy. This is desired in patients with significant limitation of mouth opening and painful tissues that can be observed in HNC patients [26, 38]. As PBM mechanisms continue to be studied, the effects of different parameters on tumor heterogeneity

will add information based on solid science. This will increase safety while using this technology in cancer patients [4, 19, 49,51].

Conclusions

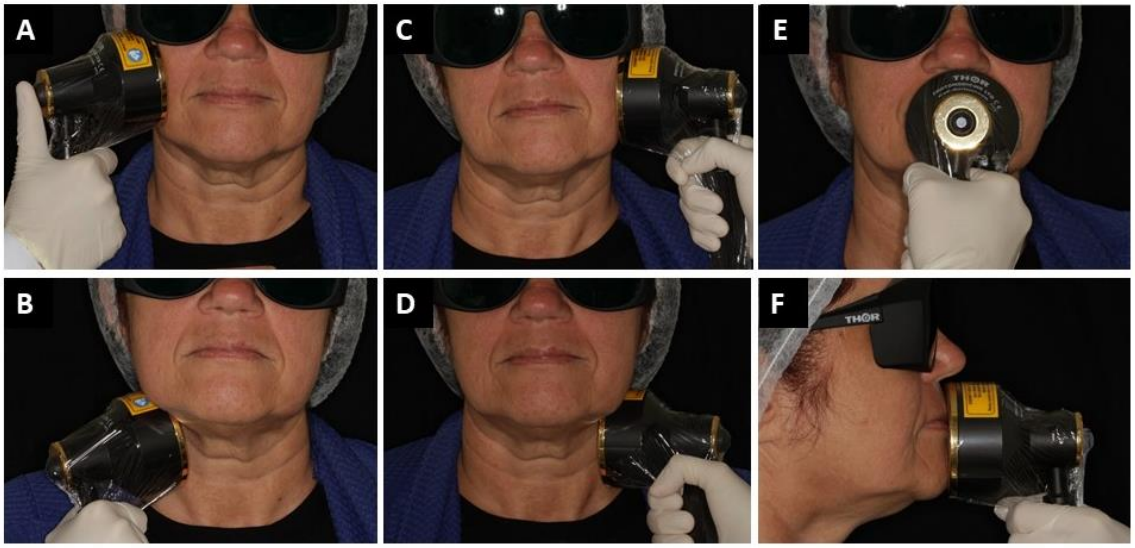
This prospective double-blind randomized clinical trial assessed clinical and oncological outcomes of prophylactic extraoral PBM in radiation-induced OM in OSCC patients. Extraoral PBM was well tolerated and did not cause any adverse effects. This preplanned interim analysis supports the indication of prophylactic PBM to prevent the early onset of OM, to reduce pain levels and reduce the need of analgesics and anti-inflammatory medications. Furthermore, extraoral PBM did not impact survival outcomes within the limits of the interim results of this clinical trial.

Fig 1: Extraoral PBM protocol - the LED probe was applied flat against the patient's face and neck for 60 seconds per point, at five treatment sites: right face side (A), right neck (B), left face side (C), left neck (D) and central face (E and F) (50 mW/cm2 x 60 s = 3.0 J/cm2 per location).



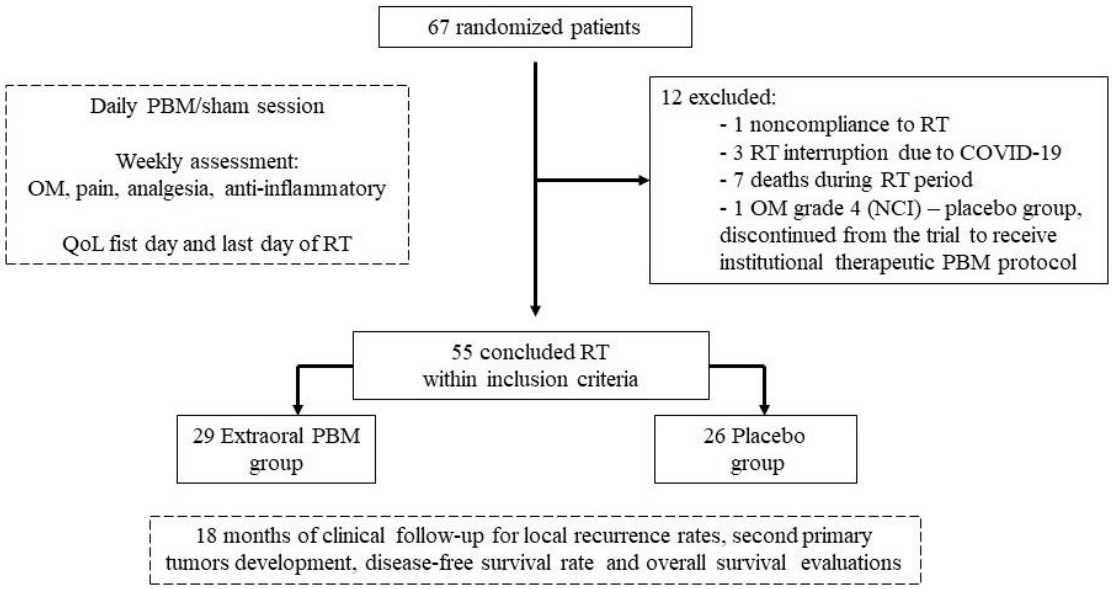
*PBM: Photobiomodulation

Fig 2: Placebo/sham extraoral PBM protocol - an inactivated probe was applied flat against the patient's face and neck for 60 seconds per point, at five treatment sites: right face side (A), right neck (B), left face side (C), left neck (D) and central face (E and F).



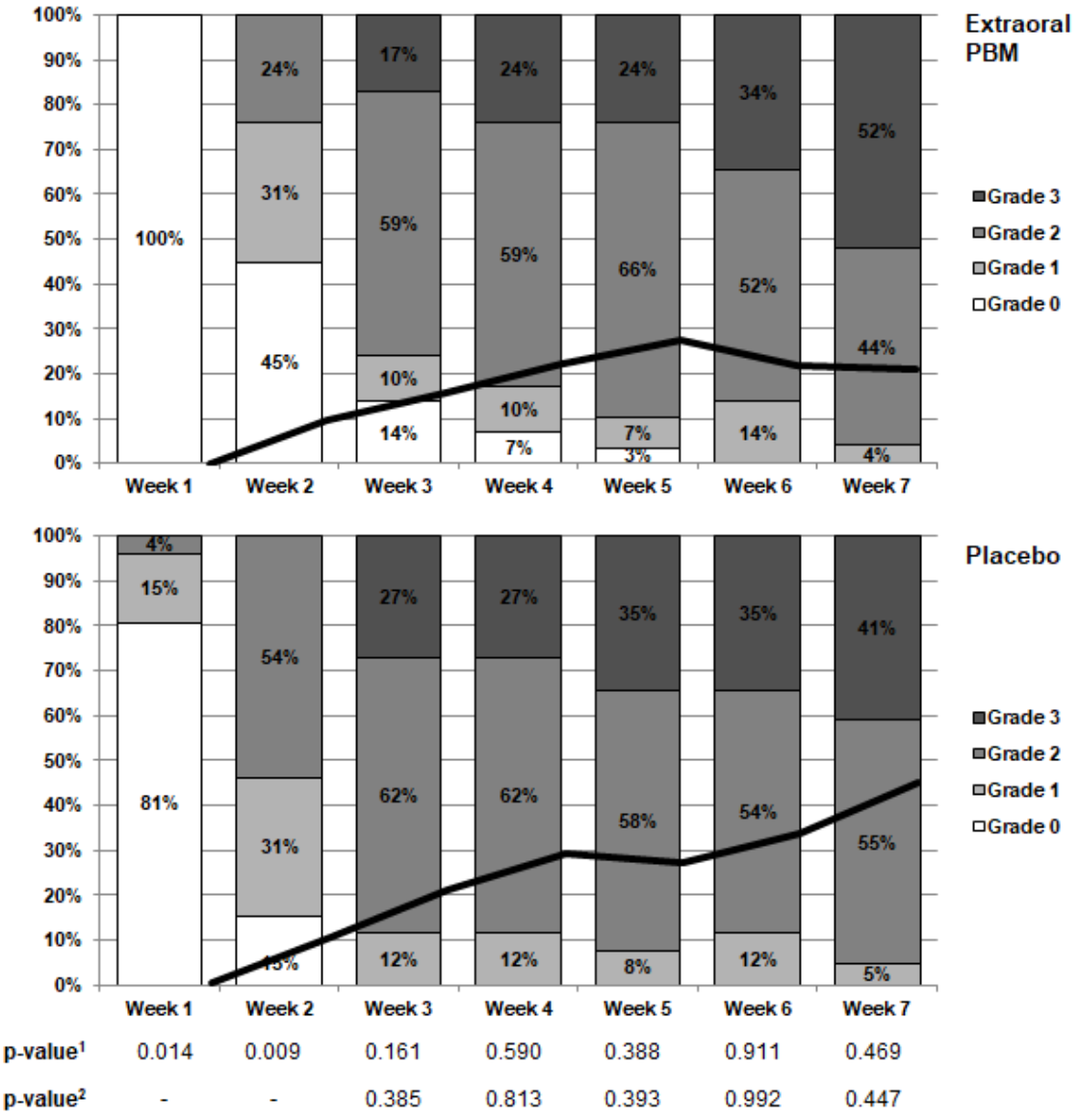
*PBM: Photobiomodulation

Fig 3: Flowchart and outcomes.



OM: oral mucositis; RT: Radiotherapy; QoL: Quality of life; PBM: Photobiomodulation; NCI: National Cancer Institute.

Fig 4: Weekly oral mucositis assessment according to the National Cancer Institute (NCI, version 4.0; 2010). Bars represents percent of cases in each oral mucositis grade and continuous lines represents mean values for each stage (score range from 0-4).



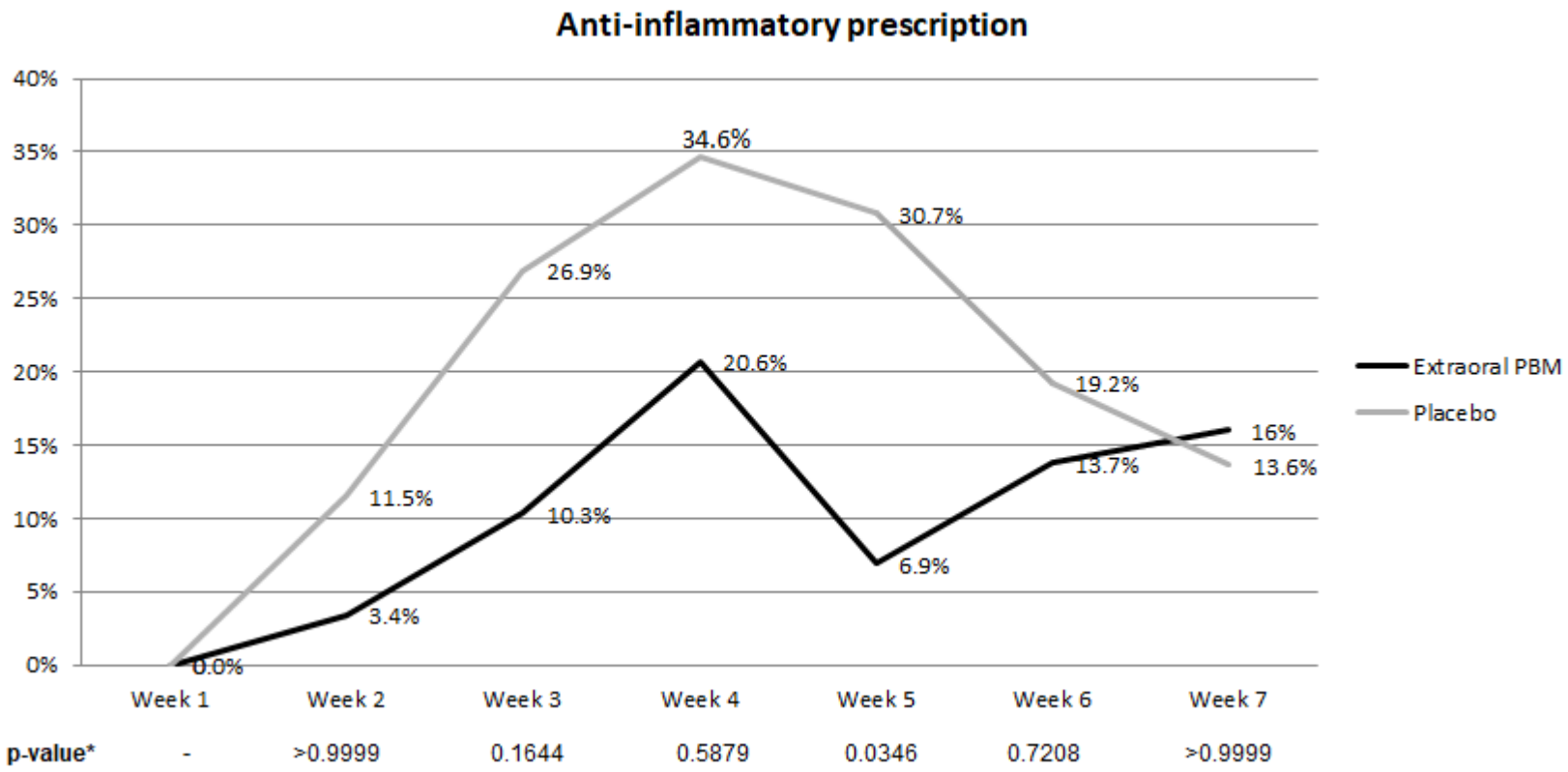
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7
p-value[1]	0.014	0.009	0.161	0.590	0.388	0.911	0.469
p-value[2]	-	-	0.385	0.813	0.393	0.992	0.447

p-value[1:] Mann-Whitney test for between-groups overall OM comparison (Extraoral PBM vs Placebo)

p-value[2]: Chi-square test for between-groups severe OM comparison (Extraoral PBM vs Placebo)

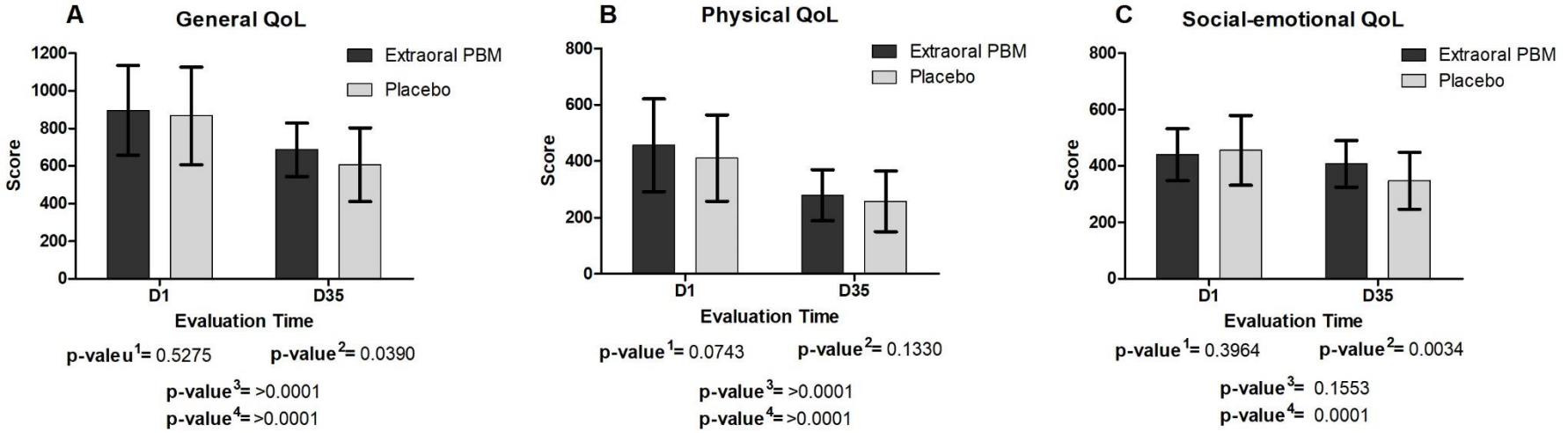
PBM: Photobiomodulation; OM: Oral mucositis; NCI: National Cancer Institute

Fig 5: Anti-inflammatory prescription patterns at different weeks of RT.



*chi-square test; RT: Radiotherapy; PBM: Photobiomodulation

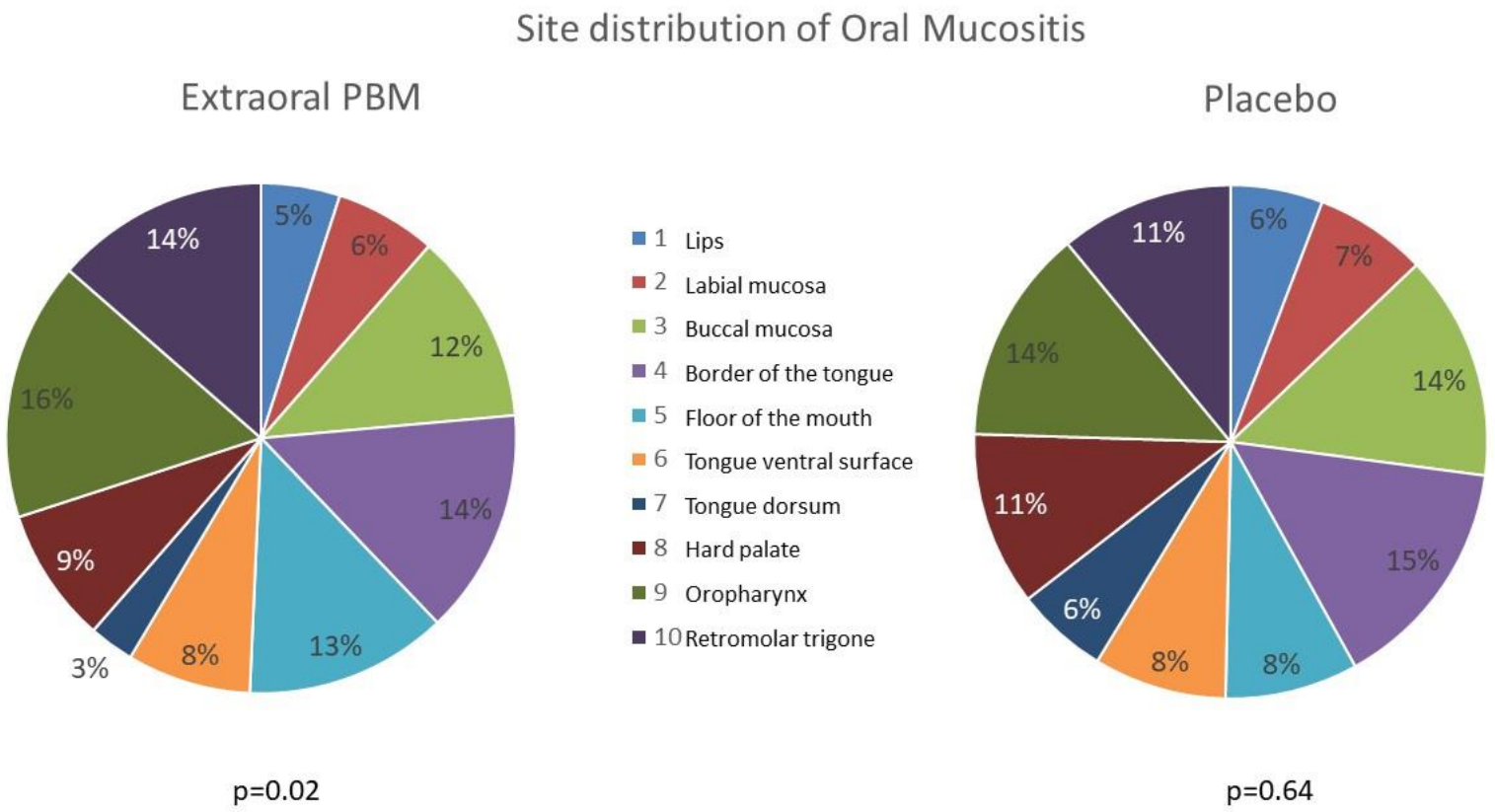
Fig 6: Graphs comparing mean (± SD) University of Washington Quality of Life Questionnaire (UW-QoL v4) score at baseline (D1) and final session of radiotherapy (D35). Graph A: General QoL; Graph B: Physical QoL; Graph C: Social-emotional QoL.



[1]: Mann-Whitney test for betw een-groups comparison in D1 evaluation time (Extraoral PBM vs. Placebo)
[2]: Mann-Whitney test for betw een-groups comparison in D35 evaluation time (Extraoral PBM vs. Placebo)
[3]: Wilcoxon paired signed rank for betw een evaluation time comparison (Extraoral PBM group - D1 vs. D35)
[4]: Wilcoxon paired signed rank for betw een evaluation time comparison (Placebo group - D1 vs. D35)

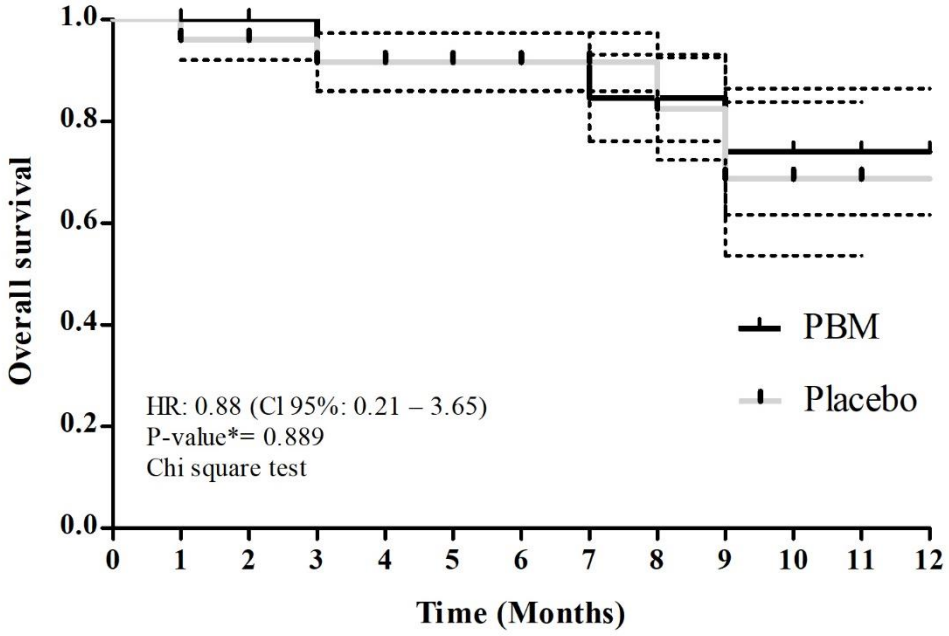
SD: Standard deviation; QoL: Quality of life; PBM: Photobiomodulation

Fig. 7: Oral mucositis distribution per oral site (grade ≥2 – NCI version 4.0)



*Chi-square test for adherence; NCI-National Cancer Institute; PBM: Photobiomodulation

Fig. 8: Interim analysis of the overall survival with the follow-up period of 12 months.



PBM: Photobiomodulation

Table 1. Clinicopathological characteristics of included patients.

	PBM		Placebo		p-value*
Patients (*n*)	**29**		**26**		
Gender					0.73
Male	23	(79.3%)	22	(84.6%)	
Female	6	(20.7%)	4	(15.4%)	
Age (years)					0.31
Mean ± SD	59.5	(±8.1)	62.1	(±8.7)	
Smoking status					0.42
Never-smokers	5	(17.3%)	2	(7.7%)	
Smokers	3	(10.3%)	6	(23.1%)	
Smoking cessation	21	(72.4%)	18	(69.2%)	
Smoking load (pack/years)					0.32
Mean ± SD	46	(±33.9)	50,8	(±30.8)	
Alcohol consumption					0.12
No	9	(31.0%)	5	(19.2%)	
Yes - active use	0	(0.0%)	3	(11.5%)	
Yes - Alcohol withdrawal	20	(68.1%)	18	(69.3%)	
Primary tumor site					
Base of tongue	5	(17.2%)	4	(15.4%)	
Tongue	2	(6.9%)	6	(23.1%)	
Gingiva	2	(6.9%)	2	(7.7%)	
Floor of mouth	3	(10.4%)	2	(7.7%)	
Hard palate	1	(3.4%)	0	(0.0%)	
Buccal mucosa	3	(10.4%)	0	(0.0%)	
Palatine tonsil	2	(6.9%)	4	(15.4%)	
Oropharynx with oral extension	11	(37.9%)	8	(30.7%)	
Tumor stage					0.23
III	11	(37.9%)	6	(23.1%)	
IV	18	(62.1%)	20	(76.9%)	
Histopathological differentiation					0.92
Well-differentiated	3	(10.3%)	2	(7.7%)	
Moderately differentiated	15	(51.7%)	12	(46.2%)	
Poorly differentiated	5	(17.3%)	5	(19.2%)	
Unknown	6	(20.7%)	7	(26.9%)	
Cancer treatment					0.31
RT	2	(6.9%)	3	(11.5%)	
RT + surgery	6	(20.7%)	8	(30.8%)	
CRT+ surgery	6	(20.7%)	5	(19.2%)	
CRT	15	(51.7%)	10	(38.5%)	
RT dose					0.20
60Gy	4	(13.8%)	4	(15.4%)	
66 Gy	10	(34.5%)	14	(53.8%)	
70 Gy	15	(51.7%)	8	(30.8%)	
PBM (sessions)					0.38
Mean ± SD	32	(±2.0)	32	(±1.7)	

*Mann-Whitney test for between-groups comparison (Extraoral PBM vs placebo)
RT: Radiotherapy; CRT: Chemoradiotherapy

Table 2: Oral mucositis associated pain score (visual analogue scale – VAS) and oral mucositis-related analgesia protocol throughout radiotherapy course.

	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7	
Pain Score (VAS)	**PBM**	**Placebo**	**PBM**	**Placebo**	**PBM**	**Placebo**	**PBM**	**Placebo**	**PBM**	**Placebo**	**PBM**	**Placebo**	**PBM**	**Placebo**
Mean (±SD)	0.0 (±0.00)	0.03 (±0.19)	1.0 (±2.42)	1.0 (±2.06)	1.6 (±2.34)	2.1 (±2.61)	2.2 (±2.66)	2.9 (±2.33)	2.8 (±2.52)	2.7 (±2.56)	2.2 (±2.85)	3.3 (±2.82)	2.1 (±2.94)	4.5 (±3.42)
p-value*	0.291		0.643		0.310		0.165		0.918		0.064		0.009	
Analgesic scale														
No analgesic	29 (100%)	25 (96.2%)	23 (79.3%)	15 (57.8%)	15 (51.8%)	6 (23.1%)	14 (48.3%)	6 (23.1%)	8 (27.6%)	6 (23.1%)	12 (41.4%)	5 (19.2%)	13 (52.0%)	3 (13.6%)
Level 1	0 (0.0%)	1 (3.8%)	4 (13.8%)	7 (26.9%)	11 (37.9%)	11 (42.3%)	8 (27.6%)	9 (34.6%)	7 (24.1%)	9 (34.6%)	10 (34.5%)	10 (38.5%)	5 (20.0%)	5 (22.7%)
Level 2	0 (0.0%)	0 (0.0%)	1 (3.4%)	3 (11.5%)	3 (10.3%)	7 (26.9%)	6 (20.7%)	9 (34.6%)	12 (41.4%)	9 (34.6%)	5 (17.2%)	6 (23.1%)	6 (24.0%)	8 (36.4%)
Level 3	0 (0.0%)	0 (0.0%)	1 (3.4%)	1 (3.8%)	0 (0.0%)	2 (7.7%)	1 (3.4%)	2 (7.7%)	2 (6.9%)	2 (7.7%)	2 (6.9%)	5 (19.2%)	1 (4.0%)	6 (27.3%)
p-value*	0.291		0.091		0.009		0.053		0.936		0.052		0.002	

* Mann-Whitney test for between-groups comparison (Extraoral PBM vs. placebo); PBM: Photobiomodulation; SD: standard deviation.

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3 DISCUSSÃO

No cenário médico atual, o sucesso do tratamento do paciente com câncer depende de estratégias multidisciplinares para potencializar o controle da doença e minimizar os impactos negativos da terapia oncológica na forma e na função de estruturas não-alvo adjacentes à área tumoral (Montero e Patel., 2015). Neste contexto, a FBM é atualmente reconhecida como uma importante ferramenta para a prevenção e o gerenciamento de diversas toxicidades bucais do tratamento oncológico. A MO é considerada como a toxicidade bucal mais prevalente e uma das mais mórbidas, principalmente, em pacientes submetidos à RT de cabeça e pescoço (Sonis et al., 2016; González-Arriagada et al., 2018; Paglioni et al., 2019b). Sabe-se que a prevenção e o gerenciamento das toxicidades do tratamento oncológico podem otimizar a QoL dos pacientes e minimizar desfechos clínicos de morbi-morbidade, além de potencialmente reduzir custos associados ao tratamento oncológico (Benzinelli et al., 2014).

Muitos estudos discutem os possíveis benefícios econômicos da FBM associada ao suporte oncológico, no entanto, os estudos que consolidam avaliação de custo-efetividade são escassos (Piller and Thelander, 1995; Nooze et al., 2008; Bezinelli et al., 2014; Antunes et al., 2016, Martins et al., 2020). A revisão sistemática que abre esta dissertação incluiu apenas 4 estudos que realizaram abrangente avaliação de custos associados ao uso da FBM para suporte de toxicidades relacionadas ao tratamento oncológico (Kauark-Fontes et al., 2021). Neste contexto, foi possível observar o potencial da FBM para reduzir custos incrementais através da otimização de resultados clínicos como gravidade de MO, redução de uso de medicamentos e internações hospitalares. Estudos adicionais baseados em protocolos de análise econômica já estabelecidos e com protocolos de FBM recomendados são necessários para possibilitar maiores conclusões acerca do real benefício econômico da FBM, tendo em vista que seus resultados podem ter sido subnotificados e subvalorizados (Calhoun and Bennet, 2003).

No início do ano de 2020, o cenário internacional desafiador da pandemia COVID-19 trouxe novos desafios a todos os profissionais de saúde sobre a necessidade de minimizar riscos de transmissão, inclusive durante assistência a paciente oncológicos, considerados do grupo de risco para os desfechos mais graves da COVID-19 (Thorp 2020; Galloway et al., 2020; Kowalski et al., 2020). Neste complexo cenário sanitário, a FBM extraoral surgiu como nova perspectiva de manutenção de assistência oncológica no contexto da prevenção da MO por apresentar boa aceitação por parte dos pacientes e da comunidade clínica multiprofissional envolvida no tratamento do câncer e, sobretudo, pelo potencial em minimizar riscos de transmissão Sars-Cov-2 por não demandar manipulação intraoral e salivar como acontece na

técnica de FBM intraoral. Em suma, os desafios impostos pela pandemia impulsionaram a necessidade da otimização dos protocolos de FBM mais dinâmicos como aqueles baseados no uso de sondas extraorais (Hodgson et al., 2012; Treister et al., 2016).

O perfil clínico e demográfico dos pacientes com CEC de cavidade oral e orofaringe incluídos no estudo clínico realizado por meio desta dissertação foi semelhante a uma série de outros estudos presentes na literatura, composto principalmente de pacientes do sexo masculino, com histórico de tabagismo e etilismo e diagnóstico oncológico tardio com predomínio de pacientes em estadiamento clínico avançado (III/IV) (Genot-Klastersky et al., 2008; Antunes et al., 2017; Legouté et al., 2019). As modalidades de tratamento oncológico aqui descritas para os pacientes incluídos no ensaio clínico foram similares ao proposto em centros internacionais de referência em oncologia e baseadas em abordagem multimodal (Elting et al., 2008; Antunes et al., 2017).

Diferentes resultados de efetividade da FBM para MO são atribuídos a variedade de protocolos e fatores específicos relacionados ao tratamento oncológico, à experiência da equipe médica e se suporte, de infraestrutura e também do paciente (Bensadoun 2018; Guedes et al., 2018). Por se tratar de uma proposta original no campo do uso profilático da FBM extraoral na mitigação da MO com câncer em boca e orofaringe, os resultados do presente estudo clínico alcançaram desfechos favoráveis quanto à incidência e ao momento do início da MO, apesar da ausência de benefícios relacionados à gravidade da MO quando registrada no final da RT. Interessantemente, a intervenção extraoral também se mostrou eficiente no controle da dor associada à MO e na redução do uso de analgésicos e anti-inflamatórios quando comparados aos pacientes do braço placebo, o que corrobora com outros estudo já publicados por meio da intervenção intraoral em populações oncológicas semelhantes à alvo deste ensaio clínico (Lima et al., 2010; Bjordal et al., 2011; Antunes et al., 2013). Estes resultados, embora de natureza interina, geram novas perspectivas para o uso da FBM extraoral como uma tecnologia na prevenção e na atenuação de toxicidades oncológicas e dos sintomas associados em pacientes com câncer em boca e orofaringe.

O curso do tratamento multimodal do CEC de boca e orofaringe está relacionado a complicações não apenas de ordem físicas, mas, também, de natureza psicológica e funcional com impacto significativo na QoL dos pacientes (Franco et al., 2017). Neste sentido, os resultados interinos deste estudo clínico sugerem que a FBM extraoral tem potencial para preservar desfechos mais favoráveis de QoL entre pacientes com câncer de boca e orofaringe

avançados e submetidos à RT como modalidade de tratamento oncológico (Elting et al., 2008; Bjordal et al., 2011; Hodgson et al., 2012; Antunes et al., 2017; Legouté et al., 2019).

A despeito da crescente aceitação internacional dos protocolos de FBM na prevenção e no gerenciamento das toxicidades relacionadas ao tratamento do câncer, sobretudo no campo da MO, a questão da segurança oncológica destes protocolos continua sendo amplamente discutida na literatura científica internacional (Sonis et al., 2016; Antunes et al., 2017; Bensadoun 2018; Legouté et al., 2019; Paglioni et al., 2019), até o momento, sem evidências clínicas de efeitos adversos relevantes ou prejuízos em termos prognósticos oncológicos para pacientes com câncer em cabeça e pescoço. Estas evidências favoráveis à ampliação do uso da FBM como parte dos protocolos de suporte a pacientes oncológicos foram renovadas com os resultados do estudo clínico cujos resultados estão apresentados no capítulo 3 desta dissertação. No sentido de que apesar da natureza interina dos achados deste ensaio clínico controlado, a FBM extraoral se mostrou bem tolerada pelos pacientes e segura do ponto de vista oncológico.

4 CONCLUSÃO

- Existe evidência científica para sugerir que FBM pode ser capaz de reduzir o impacto clínico de toxicidades da RT e consequentemente reduzir custos incrementais do gerenciamento da MO e do linfedema;
- A pandemia COVID-19 despertou atenção para a demanda de desenvolvimento e validação dos protocolos de FBM extraoral que gerou novas perspectivas para a prevenção da MO com baixo risco de transmissão do SARS-CoV-2;
- A FBM extraoral tem potencial profilático para MO em pacientes com CEC de cavidade bucal e orofaringe tratados por RT;
- A FBM extraoral tem potencial para controlar a dor associada à MO em pacientes com CEC de cavidade bucal e orofaringe tratados por RT, reduzindo o uso de analgésicos, de anti-inflamatórios e preservando desfechos mais favoráveis de QoL;
- A FBM extraoral foi bem tolerada por pacientes com CEC de cavidade bucal e orofaringe tratados por RT e se mostrou, interinamente, como uma estratégia segura - em termos oncológicos- na prevenção da MO.

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*De acordo com as normas da UNICAMP/FOP, baseadas na padronização do Internacional Commitee of Medical Journal Editors – Vancouver Group. Abreviaturas dos periódicos em conformidade com o PubMed.

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ANEXOS

Anexo 1 - Comprovante de publicação artigo 2.1 **DOI:** 10.1007/s00520-020-05949-1

Supportive Care in Cancer
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REVIEW ARTICLE

Cost-effectiveness of photobiomodulation therapy for the prevention and management of cancer treatment toxicities: a systematic review

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Abstract

Purpose To identify and summarize the evidence on the cost-effectiveness of photobiomodulation (PBM) therapy for the prevention and treatment of cancer treatment-related toxicities.

Methods This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE). Scopus, MEDLINE/PubMed, and Embase were searched electronically.

Results A total of 1490 studies were identified, and after a two-step review, 4 articles met the inclusion criteria. The included studies analyzed the cost-effectiveness of PBM therapy used in the context of lymphedema for breast cancer and oral mucositis (OM) induced by chemotherapy and radiotherapy. Better outcomes were associated with PBM therapy. The incremental cost-effectiveness ratio ranged from 3050.75 USD to 5592.10 USD per grade 3–4 OM case prevented. PBM therapy cost 21.47 USD per percentage point reduction in lymphedema in comparison with 80.51 USD for manual lymph drainage and physical therapy.

Conclusion There is limited evidence that PBM therapy is cost-effective in the prevention and treatment of specific cancer treatment-related toxicities, namely, OM and breast cancer-related lymphedema. Studies may have underreported the benefits due to a lack of a comprehensive cost evaluation. This suggests a wider acceptance of PBM therapy at cancer treatment centers, which has thus far been limited by the number of robust clinical studies that demonstrate cost-effectiveness for the prevention and treatment of toxicities.

Keywords Photobiomodulation · Cancer toxicities · Cost · Systematic review

Introduction

Economic evaluation of the management of health conditions is essential in supporting decision-making by clinicians, policymakers, and planners to shape healthcare policy and health services delivery [1–4]. Cancer treatment toxicities consist of several adverse consequences that often affect quality of life and may result in increased medical consultations,

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COMMENTARY

Impact of pandemic COVID-19 outbreak on oral mucositis preventive and treatment protocols: new perspectives for extraoral photobiomodulation therapy

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Abstract
This communication discusses the current challenges of oral mucositis (OM) management during the pandemic COVID-19 outbreak and reflects about an extraoral photobiomodulation protocol as an optimal alternative for preventing and treating OM in advanced cancer patients while minimizing the risk of infection by avoiding intraoral manipulation.

Keywords COVID-19 · Oral mucositis · Cancer · Photobiomodulation therapy · Laser therapy

Introduction

The recent 2019 novel coronavirus disease (COVID-19) pandemic has dramatically changed several aspects of worldwide communities, evoking many changes in the routine activities of populations as well as impacting economic burden and functioning capacity of the healthcare system [1]. Since December 2019, when the first cases emerged in Wuhan (Hubei Province of China) [2, 3], an exponential number of infected patients with the SARS coronavirus 2 (SARS-CoV-2), the known etiologic agent of the COVID-19, has spread across multiple countries with rapid community dissipation of the virus [4, 5]. Acute inflammatory distress syndrome is one of the most life-threatening complications of COVID-19 and usually requires intensive care and mechanical ventilation [1], most frequently in more vulnerable patients, which include patients undergoing anticancer treatment or diagnosed with malignancies associated with an immunosuppressive state. Cumulative evidence suggests that cancer patients are at increased risk of COVID-19 infection [6], and early published reports estimated a significant higher risk of mortality over 3.5 times on cancer patients [7].

The person-to-person spread of COVID-19 disease seems to be rapid and may quickly overwhelm the care settings from primary to tertiary levels. In this scenario, oncologic care facilities have faced the dilemma of how to maintain cancer

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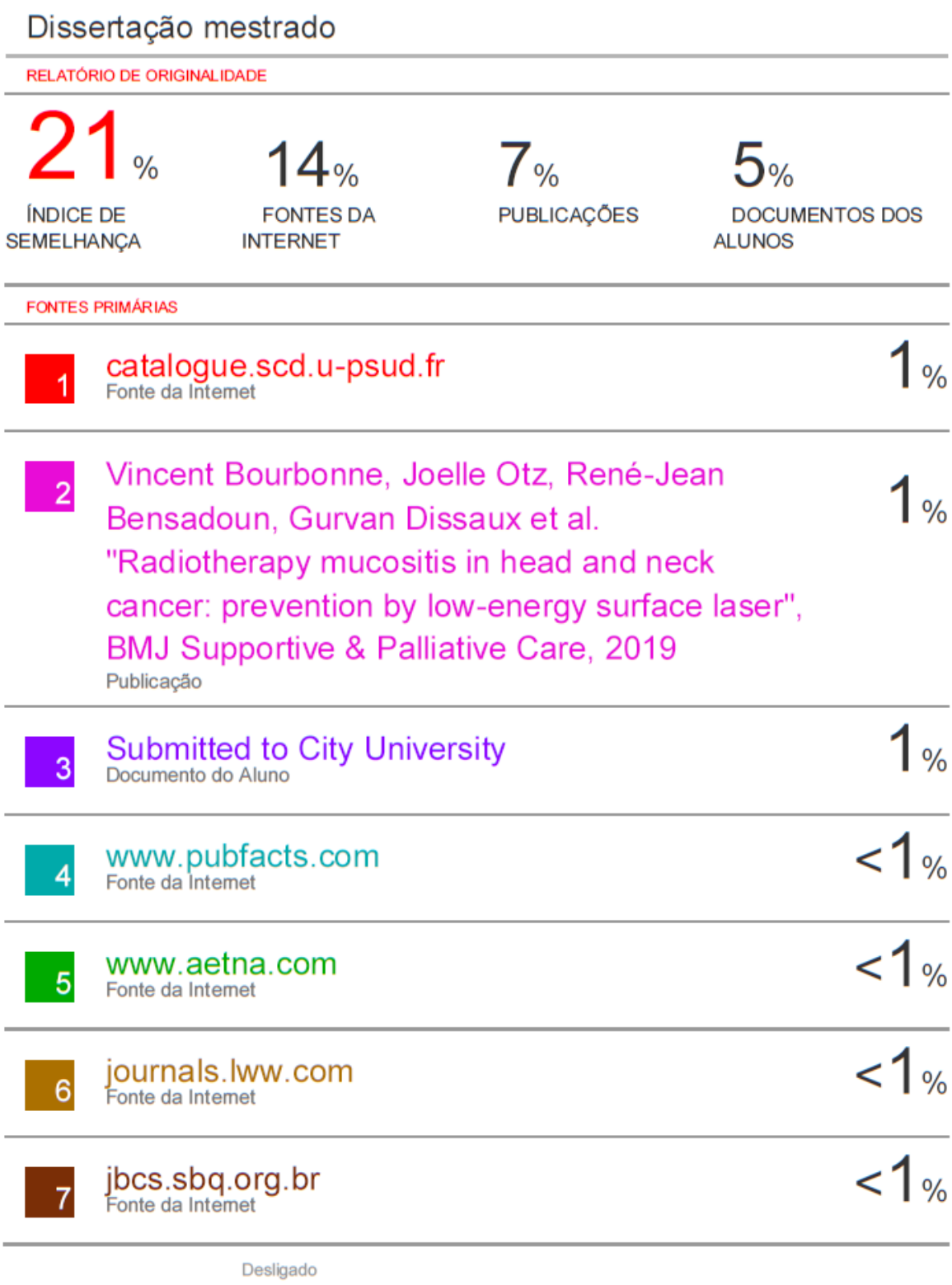
Published online: 21 July 2020

Anexo 3: Verificação de originalidade e prevenção de plágio



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PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Segurança oncológica no uso da fotobiomodulação intraoral e extraoral em pacientes com carcinoma espinocelular de cavidade oral e orofaringe.

Pesquisador: ELISA KAUARK FONTES

Área Temática:

Versão: 2

CAAE: 21648819.9.0000.5418

Instituição Proponente: Faculdade de Odontologia de Piracicaba - Unicamp

Patrocinador Principal: FUNDACAO DE AMPARO A PESQUISA DO ESTADO DE SAO PAULO

DADOS DO PARECER

Número do Parecer: 3.692.842

Apresentação do Projeto:

Transcrição editada do conteúdo do registro do protocolo e dos arquivos anexados à Plataforma Brasil

Delineamento da pesquisa: Trata-se de estudo clínico prospectivo, duplo cego, com 120 pacientes diagnosticados com cancer espinocelular de cavidade oral e orofaringe que iniciarão protocolos curativos de radioterapia (RT) adjuvante ou quimiorradioterapia (QRT) nos Serviços de Odontologia Oncológica e Oncologia Clínica do ICESP. Os pacientes serão alocados randomicamente em 4 grupos; fotobiomodulação profilática intraoral (n=30); fotobiomodulação profilática extraoral (n=30); fotobiomodulação placebo sham laser intraoral (n=30) e placebo sham laser extraoral (n=30).

Haverão dois grupos placebos que não receberão a intervenção (fotobiomodulação intraoral e extraoral - descritos no desenho do estudo). Segundo os pesquisadores, "a existência de grupo placebo se faz necessária para análise comparativa da sobrevida dos pacientes com câncer de cabeça e pescoço que realizam fotobiomodulação profilática para controle de mucosite oral induzida por radioterapia, visto que a terapia é aplicada em regiões adjacentes a área tumoral. Assim avaliando se a fotobiomodulação apresenta algum efeito a longo prazo nesses pacientes. Apesar de estudos in vitro e in vivo já terem sido realizados, essa comparação em pesquisa clinica

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Bairro: Areião **CEP:** 13.414-903
UF: SP **Município:** PIRACICABA
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UNICAMP - FACULDADE DE ODONTOLOGIA DE PIRACICABA DA UNIVERSIDADE DE CAMPINAS - FOP/UNICAMP

Continuação do Parecer: 3.692.842

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PIRACICABA, 08 de Novembro de 2019

Assinado por:
jacks jorge junior
(Coordenador(a))

Endereço: Av.Limeira 901 Caixa Postal 52
Bairro: Areião **CEP:** 13.414-903
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Anexo 5: Certificado de Aprovação do Comitê de Ética (Faculdade de Medicina da Universidade de São Paulo)

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

PARECER CONSUBSTANCIADO DO CEP

Elaborado pela Instituição Coparticipante

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Segurança oncológica no uso da fotobiomodulação intraoral e extraoral em pacientes com carcinoma espinocelular de cavidade oral e orofaringe.

Pesquisador: ELISA KAUARK FONTES

Área Temática:

Versão: 1

CAAE: 21648819.9.3001.0065

Instituição Proponente: FUNDACAO FACULDADE DE MEDICINA

Patrocinador Principal: FUNDACAO DE AMPARO A PESQUISA DO ESTADO DE SAO PAULO

DADOS DO PARECER

Número do Parecer: 3.730.041

Apresentação do Projeto:

Trata-se projeto em co-participação que tem como centro coordenador a FOP-UNICAMP.

Objetivo da Pesquisa:

Avaliar a segurança da utilização de fotobiomodulação intraoral e extraoral em pacientes com CEC oral e de orofaringe.

Avaliação dos Riscos e Benefícios:

Benefícios são informativos, inicialmente e os riscos são inerentes a metodologia utilizada. Nessa população especificamente,acredito que os riscos não são mínimos.

Comentários e Considerações sobre a Pesquisa:

Projeto de pesquisa que avaliará a segurança da utilização de metodologia de modulação a base de luz em pacientes com CEC oral e de orofaringe. Várias correções foram realizadas já em resposta ao CEP do centro coordenador.

Considerações sobre os Termos de apresentação obrigatória:

São apresentadas várias respostas a pendências apontadas pelo CEP do centro coordenador, inclusive com textos marcados em amarelo. A carta de anuência da Comissão de pesquisa do ICESP está incluida como Anexo.

Recomendações:

Sem recomendações.

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

Conclusões ou Pendências e Lista de Inadequações:

Sem pendências

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

SAO PAULO, 27 de Novembro de 2019

Assinado por:
Maria Aparecida Azevedo Koike Folgueira
(Coordenador(a))

Anexo 6: Aprovação Núcleo de Pesquisa do Instituto do Câncer do Estado de São Paulo

INSTITUTO DO CÂNCER DO ESTADO DE SÃO PAULO

FUNDAÇÃO FACULDADE DE MEDICINA

PARECER DE AVALIAÇÃO

Referente à solicitação de execução de estudo **"Segurança oncológica no uso da fotobiomodulação intraoral e extraoral em pacientes com carcinoma espinocelular de cavidade oral e orofaringe"**, sob registro NP 1509/19.

Pesquisador Responsável: ***Dra. Karina Morais Faria***
Pesquisador Executante: ***Dra. Elisa Kauark Fontes***

APRESENTAÇÃO DO PROJETO

Estudo clínico que visa avaliar, a nível clínico e molecular, o impacto da fotobiomodulação profilática para mucosite oral e orofaríngea (MO) na sobrevida de pacientes com carcinoma espinocelular (CEC) de cavidade oral e orofaringe. Serão avaliados prospectivamente 120 pacientes diagnosticados com CEC de cavidade oral e orofaringe que iniciarão protocolos curativos de radioterapia (RT) adjuvante ou quimiorradioterapia (QRT). Os pacientes serão alocados randomicamente em 4 grupos: fotobiomodulação profilática intraoral (n=30) (InGaAlP; 660 nm, 75 mW, densidade de energia 2J/cm2, 0.6 J de energia por ponto; 8s/ponto; *spot size* 0.26 cm2); fotobiomodulação profilática extraoral (n=30) (LED 69 diodos, 34x660 nm (10 mW) e 35x850 nm (30 mW), 1390 mW, densidade de energia 50 mW /cm2, 3.0 J de energia por cm2, 60s/ponto, *spot size área* (6 cm2); fotobiomodulação placebo *sham* laser intraoral (n=30) e placebo *sham* laser extraoral (n=30). As intensidades de MO e da dor associada serão avaliadas diariamente durante a RT (NCI, *Version* 4.0, 2010; OMS, 1975 e EVA). Serão aplicados questionário de qualidade de vida da Universidade de Washington para pacientes com câncer de cabeça e pescoço e questionário de sintomas em Câncer de Cabeça e Pescoço de Vanderbilt (Versão 2.0) em quatro etapas do estudo (D-1; D30; D+90 e D+1ano). O impacto da fotobiomodulação será avaliado trimestralmente durante os 36 meses posteriores à conclusão da RT por meio dos seguintes desfechos oncológicos: recidiva local, desenvolvimento de segundos tumores primários, tempo médio de sobrevida livre de doença e sobrevida global. Para análise do impacto da fotobiomodulação em marcadores moleculares de carcinogênese, será coletada saliva total dos pacientes em três etapas do estudo (D-1; D30 e D+30RT) seguido de análise proteômica baseada em espectrometria de massas (MS/MS).

CONSIDERAÇÕES SOBRE A AVALIAÇÃO

Equipamento concedido pelo outorgado FAPESP - Prof. Dr. Alan Roger Santos Silva da Faculdade de Odontologia de Piracicaba (UNICAMP). Segunda a pesquisadora, os equipamentos já estão em posse dos pesquisadores: Aparelho de Laser Thor LX2.3 e Container de Nitrogênio.

RECOMENDAÇÕES

1. Avaliar a exclusão de pacientes que participem de outros estudos de intervenção durante o tratamento com quimiorradioterapia.
2. Oportunamente seria interessante providenciar racional para o *n* selecionado.

EXECUÇÃO DO PROJETO CONDICIONADA À:

1. Apresentação de documentação que comprove a origem dos equipamentos.
2. Necessidade de emplacamento e cadastramento dos equipamentos na modalidade CBT - Controle de Bens de Terceiro. Para tanto, solicitamos que procure o Setor da Patrimônio ICESP para realização deste evento.

Versão 3.0 03 de Abril de 2019

HC FUNDAÇÃO FACULDADE DE MEDICINA MEDICINA USP GOVERNO DO ESTADO SÃO PAULO Secretaria de Saúde

INSTITUTO DO CÂNCER DO ESTADO DE SÃO PAULO
OCTAVIO FRIAS DE OLIVEIRA

FUNDAÇÃO FACULDADE DE MEDICINA

Informamos que sua solicitação foi DEFERIDA e condicionada ao cumprimento dos itens acima.

RESPONSABILIDADES DO PESQUISADOR

Conforme a *Resolução nº 466/12 do Conselho Nacional de Saúde, Ministério da Saúde e as diretrizes de Boas Práticas Clínicas:*

- Antes do início das atividades do projeto, submeter para apreciação do Comitê de Ética em Pesquisa (CEP) da FMUSP; Compartilhar o parecer do CEP – FMUSP com o Núcleo de Pesquisa – ICESP;
- Comunicar o Núcleo de Pesquisa – ICESP e CEP – FMUSP diante de quaisquer alterações no projeto;
- Semestralmente, submeter para apreciação do CEP – FMUSP um relatório de acompanhamento do estudo; Compartilhar o relatório e o parecer do CEP – FMUSP com o Núcleo de Pesquisa – ICESP;
- Ao final do estudo, enviar o relatório final, assim como resultados que se tornaram públicos (artigos, defesa de tese, apresentação em congressos, entre outros) para o CEP – FMUSP; Compartilhar o relatório final, os resultados e o parecer do CEP – FMUSP com o Núcleo de Pesquisa – ICESP;

Atenciosamente,

Comissão Científica de Ensino e Pesquisa - CCEP

São Paulo, 22 de set de 2019.

HC FMUSP
FUNDAÇÃO FACULDADE DE MEDICINA
MEDICINA USP
GOVERNO DO ESTADO SÃO PAULO Secretaria de Saúde

Av. Dr. Arnaldo, 251 Cerqueira César São Paulo - SP 01246-000 Tel. 11 3893 2000 www.icesp.org.br