UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

THAÍS BIANCA BRANDÃO

RESULTADOS DE TRATAMENTO E SOBREVIDA EM PACIENTES COM CARCINOMA ESPINOCELULAR DE BOCA SUBMETIDOS À FOTOBIOMODULAÇÃO PARA PREVENÇÃO DA MUCOSITE ORAL

TREATMENT AND SURVIVAL OUTCOMES OF ORAL SQUAMOUS CELL CARCINOMA PATIENTS SUBMITTED TO PHOTOBIOMODULATION FOR THE PREVENTION OF ORAL MUCOSITIS

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

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

Orientador: Prof. Dr. Alan Roger dos Santos Silva

ESTE EXEMPLAR CORRESPONDE À VERSÃO FINAL DA TESE DEFENDIDA PELA ALUNA THAÍS BIANCA BRANDÃO E ORIENTADA PELO PROF. DR. ALAN ROGER DOS SANTOS SILVA.

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A Comissão Julgadora dos trabalhos de Defesa de Tese de Doutorado, em sessão pública realizada em 04 de Agosto de 2017, considerou a candidata THAÍS BIANCA BRANDÃO aprovada.

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

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RESUMO

Objetivo: Descrever os padrões de resposta ao tratamento e sobrevida em pacientes com carcinoma espinocelular (CEC) de cavidade oral submetidos à fotobiomodulação (FBM) profilática para mucosite oral (MO). **Material e métodos:** Estudo clínico longitudinal retrospectivo realizado entre os anos de 2009 e 2014, baseado em pacientes diagnosticados com CEC de cavidade oral (C02; C03; C04; C05; C06) que concluíram protocolos curativos de radioterapia (RT) adjuvante à cirurgia ou quimiorradioterapia (QRT), bem como protocolos profiláticos de FBM para MO (InGaAlP; 660 nm, 40 mW, densidade de energia 10 J/cm^2; 10 s/ponto; *spot size* 4mm^2). Os prontuários digitais dos pacientes incluídos no estudo foram avaliados para coleta e análise de dados clínicos referentes ao grau de MO (*Common Terminology Criteria for Adverse Events*, *National Cancer Institute, Version* 4.0, 2010). Adicionalmente, foram coletadas informações relacionadas aos padrões clínicos de resposta tumoral ao tratamento oncológico e sobrevida. **Resultados:** Cento e cinquenta e dois pacientes com doença avançada ao diagnóstico foram incluídos no estudo, 88 (57,9%) foram submetidos à cirurgia, 152 (100%) à radioterapia e 100 (65.8%) à quimioterapia. Após um período médio de 40,84 (±11,71) meses de acompanhamento pós-tratamento, as taxas de sobrevida global e sobrevida livre de doenças foram de 46,7% e 51,8%, respectivamente. Quarenta e cinco pacientes (29.6%) desenvolveram recorrência locorregional, 10 (6,57%) pacientes desenvolveram metástase à distância e 19 (12,5%) pacientes desenvolveram segundos tumores primários. **Conclusão:** Os resultados de resposta ao tratamento multimodal e de sobrevida descritos no presente estudo foram similares aos encontrados em estudos clínicos previamente publicados na literatura pertinente a pacientes com CEC de boca em estágios avançados. Em suma, protocolos contemporâneos de FMB profiláticos para a MO não parecem gerar impacto negativo na sobrevida de pacientes com CEC de boca.

Palavras-chave: Câncer; Radioterapia; Mucosite; Fotobiomodulação; Laserterapia; Sobrevida.

ABSTRACT

Aim: To describe the patterns of treatment response and overall survival in patients with oral squamous cell carcinoma (OSCC) which were submitted to prophylactic photobiomodulation (PBM) for oral mucositis (OM). **Material and Methods:** This was a retrospective longitudinal clinical study carried out in the period between the years 2009 and 2014, based on patients diagnosed with OSCC (C02; C03; C05; C06) that have concluded curative protocols of radiotherapy (RT) adjuvant to surgery or chemoradiotherapy (CRT), as well as prophylactic protocols of PBM for OM (InGaAlP; 660nm, 40Mw, density of energy 10J/cm2; 10 s/spot; spot size 4mm2). Digital medical records of the patients included in the study were assessed for data collection and analysis of clinical data referent to the OM grade (Common Terminology Criteria for Adverse Events, National Cancer Institute, Version 4.0, 2010). Additionally, data related to clinical patterns of tumor response to oncological treatment and overall survival were collected. **Results:** One hundred and fifty-two patients with advanced disease at the diagnosis were included in the study, 88 (57.9%) were submitted to surgery, 152 (100%) to RT and 100 (65.8%) to chemotherapy (QT). After a mean time of 40.84 (±11,71) months of post-treatment follow-up the overall survival and disease-free survival rates were 46.7% and 51.8%, respectively. Forty-five patients (29.6%) developed locoregional recurrence, 10 (6.57%) patients developed distant metastasis and 19 (12.5%) patients developed second primary tumors. **Conclusion:** The results of the response to multimodality treatment and of overall survival described in the present study were similar to the results found in clinical trials previously published in the literature regarding patients with OSCC in advanced stages. In conclusion, contemporary protocols of prophylactic PBM for OM do not seem to cause a negative impact on the overall survival of patients with OSCC.

Keywords: Cancer; Radiotherapy; Mucositis; Photobiomodulation; Laser Therapy; Survival.

SUMÁRIO

1 INTRODUÇÃO

As estimativas anuais globais para novos casos de câncer de cavidade oral são de aproximadamente 270 mil casos, ocasionando, no mesmo período, cerca de 130 mil mortes (Marta et al., 2015). No cenário nacional, o Instituto Nacional de Câncer (INCA) estima cerca de 15 mil novos casos de câncer de cavidade oral para o ano 2017 (INCA, 2016). O consequente desafio epidemiológico é agravado por evidências sugerindo que mais de 70% dos pacientes com carcinomas espinocelulares de boca (CEC), subtipo clinicopatológico mais prevalente do câncer em boca, são diagnosticados em estádios clínicos avançados da doença (Baujat et al., 2014). Este fato, por sua vez, gera baixas taxas médias de sobrevida global para esse grupo de pacientes – menos de 50% deles terão sobrevida de cinco anos após a conclusão do tratamento oncológico (Napier et al., 2008; Scully, Bagan, 2009).

Protocolos contemporâneos de tratamento do CEC de boca incluem idealmente a ressecção cirúrgica do tumor primário e o esvaziamento cervical em associação à radioterapia (RT) e à quimioterapia, que podem ser combinadas à cirurgia por meio de adjuvância ou neoadjuvância. A RT adjuvante à cirurgia é administrada à maioria absoluta dos pacientes com CEC de boca, bem como em concomitância à quimioterapia (quimiorradioterapia; QRT) em pacientes com CEC de orofaringe (Amit et al., 2013; Denaro et al., 2014; Marta et al., 2014). A despeito do notório benefício da RT no controle local e regional dos CECs de cavidade oral e orofaringe, essa modalidade de tratamento está associada a uma taxa elevada de toxicidades agudas e crônicas que afetam os tecidos não-alvos presentes no campo de radiação (Zecha et al., 2016).

Nesse contexto, a mucosite oral (MO) induzida pela RT é uma toxicidade aguda altamente prevalente, de patofisiologia complexa, que se caracteriza por úlceras persistentes em mucosa oral associadas a dor intensa; diminuição das funções orais, como deglutição, fala e mastigação, e consequente morbidade que, por sua vez, pode gerar a interrupção do

tratamento oncológico. A MO implica aumento de custos hospitalares devido à necessidade da administração de medicamentos de alto custo, como opioides; uso de sondas para alimentação nasogástrica e, finalmente, um impacto negativo no prognóstico dos pacientes (Elting et al., 2003; Trotti et al., 2003; Gautam et al., 2013; Antunes et al., 2016). Entende-se, ainda, que protocolos de QRT concomitantes potencializam a frequência e a expressividade clínica da MO em paciente com CEC de boca e orofaringe (Sonis et al., 2000; Vera-Lhonch et al., 2006; Vera-Lhonch et al., 2007; Sonis et al., 2016).

A laserterapia de baixa intensidade, também conhecida como fotobiomodulação (FBM), foi originalmente introduzida na prática clínica oncológica por Mester, na década de 1960 (Sonis et al., 2016), e a evolução desta técnica aplicada à prevenção e ao tratamento da MO sugere potencial para diminuição da prevalência da gravidade das lesões que se desenvolvem por toxicidade da RT e da quimioterapia, sendo eficiente, inclusive, na redução da frequência de interrupção da RT por casos graves de MO (Bensadoun et al., 1999; Schubert et al., 2007; Kunh et al., 2009; Carvalho et al., 2011; Gautan et al., 2012; Gouvêa de Lima et al., 2012; Antunes et al., 2013; Fekrazad, Chiniforush, 2014). Um dos maiores desafios para a aceitação universal da FBM profilática à MO em pacientes oncológicos é a dificuldade de sua reprodutibilidade metodológica, que decorre principalmente da grande variabilidade nos protocolos de uso dos equipamentos de laser (Migliorati et al., 2006; Zecha et al., 2016).

Do ponto de vista técnico, a FBM consiste na utilização de equipamentos de laser (sigla em inglês para *light amplification by stimulated emission of radiation*) que possuem baixa energia, sem potencial fototérmico. Os equipamentos mais usados no campo da saúde estão na faixa do vermelho (632 a 780 nm), com fótons de energia inferior a 2,0 elétron-volt (eV), portanto, inferiores à energia da ligação das moléculas biológicas e do DNA, e por isso não podem quebrar ligações químicas e não são capazes de induzir mutação e carcinogênese

(Bensadoun et al., 2006). Entretanto, a FBM é capaz de estimular a atividade celular por meio da liberação de fatores de crescimento, gerando proliferação de queratinócitos, recrutamento e degranulação de mastócitos e angiogênese. Estes efeitos biológicos podem promover a otimização de processos de cicatrização, sobretudo por amenizar processos inflamatórios agudos (Sandoval et al., 2003).

Outro desafio que parece limitar a disseminação da prática da FBM profilática para a MO, em centros oncológicos e odontológicos, é a crescente preocupação com o potencial dessa técnica em estimular o crescimento de células malignas residuais que evadiram o tratamento oncológico, gerando, assim, risco aumentado para recidivas tumorais e segundos tumores primários (Sonis et al., 2016).

Uma série de estudos experimentais *in vitro* e *in vivo* baseada em modelos de cultura celular de queratinócitos, linhagens celulares de CECs orais e modelos experimentais animais já foi realizada com foco na mencionada problemática e apontou resultados francamente controversos. Parte desses trabalhos de pesquisa sugere que a FBM – otimizada de modo a simular protocolos profiláticos para MO – é capaz de influenciar os processos metabólicos celulares a ponto de estimular a proliferação de células malignas e de modular o microambiente tumoral de modo a aumentar o volume tumoral (Hawkins et al., 2005; Frigo et al., 2009; de Monteiro et al., 2011). Trabalhos de outro grupo de autores sugerem que a FBM induz apoptose e morte celular em células neoplásicas malignas de maneira dose-dependente, não possuindo potencial para ativar células malignas residuais (Schartinger et al., 2012; Barasch et al., 2015; Tsai et al., 2015; Sonis et al., 2016; Zecha et al., 2016).

Apesar das evidências experimentais do efeito bioestimulatório da FBM sobre células tumorais, até o presente momento não existem evidências clínicas sobre um efeito carcinogênico genuíno (Kreisler et al., 2003). Contudo, ainda existem muitas questões a serem esclarecidas acerca do efeito da FBM nas células malignas, principalmente quando essa

técnica é aplicada – com princípio profilático para a MO – nas adjacências de topografias bucais já afetadas por CECs ou ainda em áreas próximas a tumores ativos (Hawkins et al., 2005; de Monteiro et al., 2011; Myakishev et al., 2012).

Tendo em vista o conteúdo exposto na revisão de literatura apresentada, é imperioso compreender se existe potencial biológico para que a FBM direcionada para a prevenção da MO aumente o risco de recidiva ou progressão tumoral em pacientes com CEC de cavidade oral. Recentemente, consórcios de pesquisadores internacionais considerados referências no tema em questão formalizaram, por meio de publicações, a premente necessidade de estudos observacionais clínicos que demonstrem que os benefícios anti-MO da FBM são independentes do risco de um impacto negativo no comportamento biológico dos tumores (Sonis et al., 2016; Zecha et al., 2016). Nesse sentido, esta tese de doutoramento se propôs a desenvolver um estudo clínico longitudinal retrospectivo com a finalidade de descrever os padrões de resposta ao tratamento e de progressão tumoral em pacientes com CEC de cavidade oral submetidos à FBM profilática para MO.

2 ARTIGO

Este trabalho foi realizado no formato alternativo, conforme a Informação CCPG/001/2015, da Comissão Central de Pós-Graduação (CCPG) da Universidade Estadual de Campinas.

Locally-Advanced Oral Squamous Cell Carcinoma Patients Treated With Photobiomodulation Therapy for Prevention of Oral Mucositis: Retrospective Outcomes and Safety Analyses.

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Locally-Advanced Oral Squamous Cell Carcinoma Patients Treated With Photobiomodulation Therapy for Prevention of Oral Mucositis: Retrospective Outcomes and Safety Analyses.

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Abstract

Purpose: The well-established clinical efficacy of Photobiomodulation (PBM) therapy in management of Oral Mucositis (OM) is leading to increasing use in oncology care. This protection and enhanced repair of damage to mucosal tissue has led to the question of the potential effects of PBM therapy on pre-malignant and malignant cells. The purpose of this study was to examine the outcome of cancer therapy and incidence of tumor recurrence in locally advanced oral squamous cell carcinoma (OSCC) patients treated with PBM therapy for OM.

Methods: A retrospective clinical analyses of 152 advanced OSCC patients treated with prophylactic PBM therapy for radiotherapy-induced OM from January 2009 to December 2014 was conducted.

Results: Of the 152 OSCC patients treated with PBM therapy in this study, 19 (12.5%) had stage III and 133 (87.5%) had stage IV tumors. Of these, 52 (34.2%) received initial treatment with surgery followed by adjuvant radiotherapy, 94 (61.8%) with exclusive chemoradiation and 6 (4%) with induction chemotherapy followed by surgery and radiotherapy. After a mean follow-up of 40.84 (±11.71) months, the overall survival and disease-free survival rates were 46.7% and 51.8%, respectively. Forty-five (29.6%) patients developed local-regional recurrence, 10 (6.57%) patients developed distant relapse, and 19 (12.5%) developed new (second) primary tumors.

Conclusions: Clinicopathological features and survival outcomes in the PBM treated patients were similar to previously published data for conventional treatments in patients with advanced OSCC. The prophylactic use of PBM therapy does not appear to negatively impact treatment outcomes of the primary cancer, recurrence or new primary tumors, or survival in advanced OSCC patients.

Keywords: Cancer; Radiotherapy; Mucositis; Photobiomodulation; Laser Therapy.

Introduction

Photobiomodulation (PBM), previously known as low-level light/laser therapy (LLLT), has been used for many years to treat patients with a variety of diseases and conditions. Due to its stimulatory biological effects, the potential of PBM to promote malignant transformation or tumor cell proliferation has been questioned. With the growing popularity of this therapy, this appears to be a key unresolved question [1]. The wavelengths used in PBM therapy (visible and near-infrared) have non-ionizing characteristics and their low dose has been shown to be incapable of inducing mutagenesis or genotoxicity *in vitro* [2]. However, concern regarding the potential for PBM therapy to stimulate malignant cell proliferation *in vivo* remains to be investigated in the clinical context.

Most of the PBM studies on tumor cells have been performed in laboratory settings and their results remain equivocal [4-10]. In addition, *in vitro* cell culture based studies do not account for effects of the tumor microenvironment and immune system that play critical roles *in vivo*, making it very difficult to extrapolate laboratory experimental results to human outcomes. Interestingly, a few animal studies have noted tumor-suppressing effects of PBM therapy suggesting there maybe indirect, synergistic effects on tumor cells or the host immunosurveillance system [4-10].

Oral mucositis (OM) is a severe complication of high-dose radiation therapy and chemotherapy for head and neck tumors that generates intense pain, interferes with nutrition (need for parenteral nutritional support), increases risk for local and systemic infections, result in increased utilization of analgesics including opioids, may lead to hospital admission and affects overall prognosis of cancer therapy [11]. The Multinational Association of Supportive Care in Cancer (MASCC) and International Society of Supportive Care in Cancer (ISOO) have developed comprehensive evidence-based mucositis management guidelines. In its most

recent update, PBM therapy is recommended as an effective adjunctive treatment in managing OM. This group recommended that PBM be used to prevent OM in patients receiving hematopoietic stem cell transplant conditioned with high-dose chemotherapy, with or without total body irradiation. The guidelines also suggest the use of PBM to prevent OM in patients undergoing head and neck radiotherapy [12]. Because of these recommendations and the potential for broader use of PBM treatment, it is imperative clinical safety of PBM therapy be documented.

Although PBM therapy has been used for many years to prevent and treat OM in head and neck cancer populations, there has been no attempt, to our knowledge, examining its effects on clinical incidences of tumor recurrences or new primary tumors. The present study examined a single-center database retrospectively to examine clinicopathological features, treatment and survival outcomes in locally advanced oral squamous cell carcinoma (OSCC) patients treated with radiotherapy, with or without chemotherapy, that used PBM therapy to prevent OM.

Methods

Study protocol

This study was approved by the Ethics Committee of the School of Medicine of the University of Sao Paulo, Sao Paulo, Brazil (Protocol# 1.897.352) and was conducted in accordance with the Declaration of Helsinki. This retrospective, observational clinical study examined clinicopathological features, treatments and survival outcomes of locally advanced (stage III and IV, M0) OSCC patients. The data collection followed the guideline for reporting observational studies as per Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [13]. The study included data from a single institution (Sao Paulo State Cancer Institute, ICESP, Brazil), from January 2009 to December 2014. A

total of 152 cases of histologically-confirmed OSCC patients who had received PBM therapy for OM prevention were investigated. All enrolled patients were subjected to post-surgical or cisplatin chemotherapy with concomitant radiotherapy using a 6MV linear accelerator (Synergy Platform, Elekta AB, Stockholm, Sweden).

Clinical parameters and follow-up

The institutional electronic medical record system was reviewed and the following data were abstracted: age, gender, tumor topography, alcohol consumption and smoking habit, clinical cancer stage classification (American Joint Committee on Cancer Staging System, 7th edition), and treatment modalities used in cancer treatment, including total radiation dose prescribed to the primary tumor volume (Gy). Patients were evaluated clinically every three months and with imaging using computed tomography and ultrasonography 12 months after completing therapy. The outcomes of therapy were recorded, as well as any clinical evidence of new potentially malignant or malignant lesions in the oral cavity or regional sites. The time that patients were followed post-radiation therapy was recorded. Overall survival (OS) rate, disease-free survival (DFS) rate, the incidence of recurrences (local-regional and distant relapse rates) or new (second) primary tumors were used as primary outcome measures.

Photobiomodulation protocol

All patients underwent full oral examination and comprehensive dental treatment before beginning radiotherapy. Trained dentists administered PBM therapy on an outpatient basis and treatment consisted of daily applications for 5 consecutive days (Monday to Friday) throughout radiation therapy, immediately before each radiotherapy session. All patients were treated by a Twin Flex (MMOptics, São Carlos, Brazil) PBM device. Details of PBM parameters used are described in **Table 1**. During each intraoral PBM session, the treatment

probe was turned on when positioned perpendicular to several points of 7 different oral mucosa sites, 10 s per point (**Figure 1**). These sites included the oral commissures (1 point for each commissure), lips mucosae (3 points for each lip), buccal mucosae (3 points for each side), lateral borders of the tongue (3 points for each side), ventral tongue (2 points), anterior floor of the mouth (2 points) and soft palate (2 points)**.** PBM therapy was never delivered over an active tumor site. When tumors were surgically removed prior to radiation, the laser probe was activated over the entire surgical site.

Oral Mucositis assessments

Participants were assessed for OM at baseline (first day of radiotherapy), then daily (excluding weekends) until the last day of therapy. OM was graded using the Common Terminology Criteria for Adverse Events, National Cancer Institute (CTAE, Version 4.0, 2010). PBM sessions were documented daily in electronic medical records by dentists who performed full oral examinations and OM assessments. Patients who missed a PBM session (incomplete treatment) were excluded from the study.

Statistical analysis

Data obtained in the study were analyzed statistically with SAS software version 9.3 (SAS Institute Inc., Cary, N.C., USA) by using descriptive statistics. Results were expressed as mean values, standard deviation, and percentages. Clinicopathologic results, treatment outcomes, and survival data were compared with previously published randomized controlled trials including survival rates of advanced OSCC patients treated with multimodal therapy.

Results

Clinicopathologic patient characteristics, treatment modalities, and survival outcomes are summarized in **Table 2**. The mean age was 59.2 years and there were more men (74.3%) than women (25.7%). Most patients were diagnosed with primary lateral border of the tongue (46%) squamous cell carcinomas, followed by the floor of the mouth (17.1%), and retromolar area (9.9%). All patients presented with local-regionally advanced disease, of which 19 (12.5%) were classified as stage III and 133 (87.5%) as stage IV. Of these patients, 52 (34.2%) received initial treatment with surgery followed by adjuvant radiotherapy, 94 (61.8%) were treated with chemoradiation and 6 (4%) with induction chemotherapy followed by surgery and radiotherapy.

All patients were subjected to clinical postoperative or cisplatin-associated radiation protocols. Radiation volumes encompassed the primary site and areas of lymph nodes at risk, and received cumulative doses that ranged from 60 to 70 Gy (2 Gy/day; 5 days/week from Monday to Friday). Six patients (4%) received induction chemotherapy with paclitaxel 175 mg/m^2 combined with cisplatin 75 mg/m^2 intravenously repeating every 21 days (TP regimen); 94 (61.8 %) patients received concomitant chemotherapy based on cisplatin 100 mg/m^2 on days 1, 22, and 43 of radiotherapy (CDDP regimen) and 52 (34. 2%) patients received post- radiotherapy.

Systematic examination of the oral mucosa was performed daily before each intraoral PBM session and failed to detect any evidence of new potentially malignant or malignant lesions in the oral cavity or regional sites during the PBM protocol (**Figure 2**). After a mean follow-up of 40.8 (± 11.7) months, the OS and DFS rates were 46.7% and 51.8%, respectively. Forty-five (29. 6%) patients developed local-regional recurrence, 10 (6.6%) patients developed distant relapse, and 19 (12. 5%) patients developed new (second) primary tumors (**Table 2**). All patients experienced some grade of OM during the treatment period.

The appearance of severe mucositis (grades 3/4) was delayed to the last two weeks of treatment. The incidence of grade 3 and grade 4 mucositis in the last week of radiotherapy were 23% and 1%, respectively**.**

Discussion

This was a retrospective, single-center study examining 152 patients with locally advanced OSCC patients treated PBM therapy to prevent OM. Despite aggressive cancer treatment protocols, after a mean follow-up time of 40.8 (± 11.7) months, OS and DFS rates in the current series were only 46.7% and 51.8%, respectively. The survival outcomes of the present study compare favorably with those reported in the literature where OS rates ranged from 42% to 73% and DFS rates ranged from 45% to 85% (**Table 3**) [14-17]. Similarly, recent reports described local-regional recurrence rates that ranged from 10% to 34% [18] as reported in this study as well (29.6%) and represented the most frequent cause of treatment failure. Distant failures rates (6.6%) were in accordance with previous randomized clinical trials in which the incidence of distant metastasis has ranged from 5% to 12.9% [17]. The incidence of new (second) primary tumors observed in the current series (12.5%) was also comparable with that of previous clinical studies, which found an approximate incidence of 15% in all stages of OSCC [14].

The demographic characteristics of the patients included in this study were also similar to those of other OSCC series and mainly composed of elderly male patients with a history of tobacco and alcohol consumption [14-16]. The treatment approaches used in this study were similar to those used at most major oncology centers that includes surgery followed by radiotherapy and chemotherapy in case of high-risk pathological features or primary chemotherapy and radiation for patients whose tumors are technically or functionally

unresectable [17]. All patients included in the present study were managed with postoperative radiotherapy or cisplatin-associated chemo-radiation protocols.

Multiple primary tumors can arise by ‘field cancerization’ in which the oral and oropharyngeal mucosa has been preconditioned by long-term exposure to tobacco and alcohol-related carcinogens. As a consequence, multiple carcinomas may develop as a result of independent or additional mutations. Results of the present study suggest that PBM therapy is not capable of promoting mutagenesis in clonally-related dormant tumor cells. Thus, PBM therapy does not appear to increase risk of recurrent or new primary tumors within the treatment field [1]. Despite the aggressive multi-modality therapy noted in this study, disease outcomes have remained poor as noted with high incidences (87.5%) of stage IV tumors. Long-term overall survival and tumor control rates still remain unsatisfactory in advanced OSCC and remains a challenging disease to treat effectively [19,20]. A summary of results reported in the literature from randomized controlled trials on treatments and survival outcomes in patients with OSCC is presented in **Table 3**. These analyses showed treatment with multimodal therapy and disease outcomes do not demonstrate a significant difference compared to results from the current series that had additional PBM therapy.

Our study failed to identify discrete relationship between the PBM protocol used for preventing OM and increased rates of local-regional recurrences, distant failures, new (second) primary tumors and, finally reduced OS or DFS. Similarly, no evidence of malignant transformation of potentially malignant lesions, such as oral leukoplakia or erythroplakia, was identified in the oral cavity or regional sites during the PBM sessions. It should be noted that the current PBM protocol followed previous suggestions for higher dose administration for increased efficacy in reducing incidence of grade 3 (23%) and grade 4 (1%) mucositis compared to prior clinical studies [21]. A review of the current literature noted one prior controlled, human study with long-term follow-up of 94 patients with nasopharynx,

oropharynx and hypopharynx tumors [22]. The authors noted PBM therapy appeared to improve survival outcomes in head and neck cancer patients treated with chemoradiation. The authors attribute these to the improved quality of life enabling compliance with cancer treatment regimens as well as better overall general health likely leading to improved response to therapy.

The lack of deleterious effects of PBM therapy upon tumor recurrence rates or patient survival should be interpreted with caution given the small number of patients as well as the retrospective nature of this study. In addition, the current study did not include a concurrent control group as all OSCC patients are treated at our institution with PBM for prevention of OM as routine standard of care. We attempted to address this issue by comparing the results of this study with previously published, randomized controlled trials that included treatment and survival outcomes of patients with OSCC treated with multimodal therapy [2, 17, 23]. Therefore, the present findings should be considered hypothesis-generating rather than concrete proof of PBM safety and can be used to design of future definitive clinical studies.

In summary, this retrospective analyses attempted to objectively assess treatment outcomes in advanced OSCC patients that were treated with PBM therapy for prevention of OM. The results of this study noted PBM did not impact incidence of local-regional or distant control and survival outcomes in OSCC patients compared to conventional interventions alone. This suggests PBM therapy is a safe and effective clinical modality for prevention of OM in OSCC patients. Future prospective, randomized controlled trial would be ideal to further validate these results.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Table 1. Parameters for Photobiomodulation therapy used in this study.

Wavelength	**660 nm**
Average power	40 mW
Beam area	0.04 cm^2
Irradiance	1 W/cm^2
Time per point	10 s
Energy	0.4 J
Fluence	10 J/cm^2

Table 2. Clinicopathological features and survival outcomes of 152 patients with advanced oral squamous cell carcinoma patients treated with Photobiomodulation therapy to prevent oral mucositis.

Age (mean)	**59.2 years**
Gender	
Male	114 (74.3%)
Female	38 (25.7%)
Tumor topography	
Tongue (lateral border)	70 (46%)
Floor of mouth	26 (17.1%)
Retromolar area	15 (9.9%)
Lower lip	4 (2.7%)
Soft palate	24 (15.8%)
Gingiva	5 (3.3%)
Buccal mucosa	4 (2.6%)
Oropharynx with oral extension	4 (2.6%)
Risk factors	
Tobacco	131 (86.2%)
Alcohol	126 (82.9%)
Clinical Stage	
Stage III	19 (12.5%)
Stage IV	133 (87.5%)
Treatment	
Surgery + Radiotherapy	52 (34.2%)
Chemoradiation	94 (61.8%)
Induction chemotherapy + Surgery/Radiotherapy	6 (4%)
Survival	
Follow-up (mean, months)	40.8 (±11.7)
Overall survival rate	46.7%
Disease-free survival rate	51.8%
Local-regional recurrence	45 (29.6%)
Distant relapse	10 (6.6%)
Second primary tumors	19 (12.5%)

Table 3. Summary of results reported in the literature from randomized controlled trials including treatment outcomes and survival rates of patients with oral squamous cell carcinoma treated with multimodal therapy. *Abbreviations used*: OS - overall survival; DFS - disease-free survival; CT - chemotherapy; y - year.

Author	*Year*	*No. patients*	*Stage*	*OS%*	*DFS%*	*Local-regional relapse*	*Distant relapse*	*Second Primaries*
Licitra et al., 2003	1989 – 1999	195	II – IV	57% (5 y)	-	31%	6.1%	8.2%
Including CT								
Excluding CT				68.2% (2 y)	63.6% (2-y)	30.5%	8.7%	-
Zhong et al., 2013	2008 – 2010	256	III or IVA					
Including CT				68.8% (2 y)	62.2% (2 y)	31.3%	5.5%	-
Excluding CT				68.2% (2 y)	63.6% (2 y)	30.5%	8.7%	-
Bossi et al., 2014	-	198	II – IV					
Including CT				46.5% (10 y)	48.5% (10 y)	29.6% (10 y)	4.1% (10 y)	10.6%
Excluding CT				37.7% (10 y)	36% (10 y)	32% (10 y)	9.3% (10 y)	22.1%
Zhong et al., 2015	2008 – 2015	256	III or IVA					
Including CT				61.1% (5 y)	52.7% (5 y)	31.3%	7%	3.1%
Excluding CT				61.1% (5 y)	52.7% (5 y)	39.1%	10.9%	7%
Current series	2009 – 2014	152	III – IV	46.7% (3.4 y)	51.8% (3.4 y)	29.6%	6.57%	12.5%

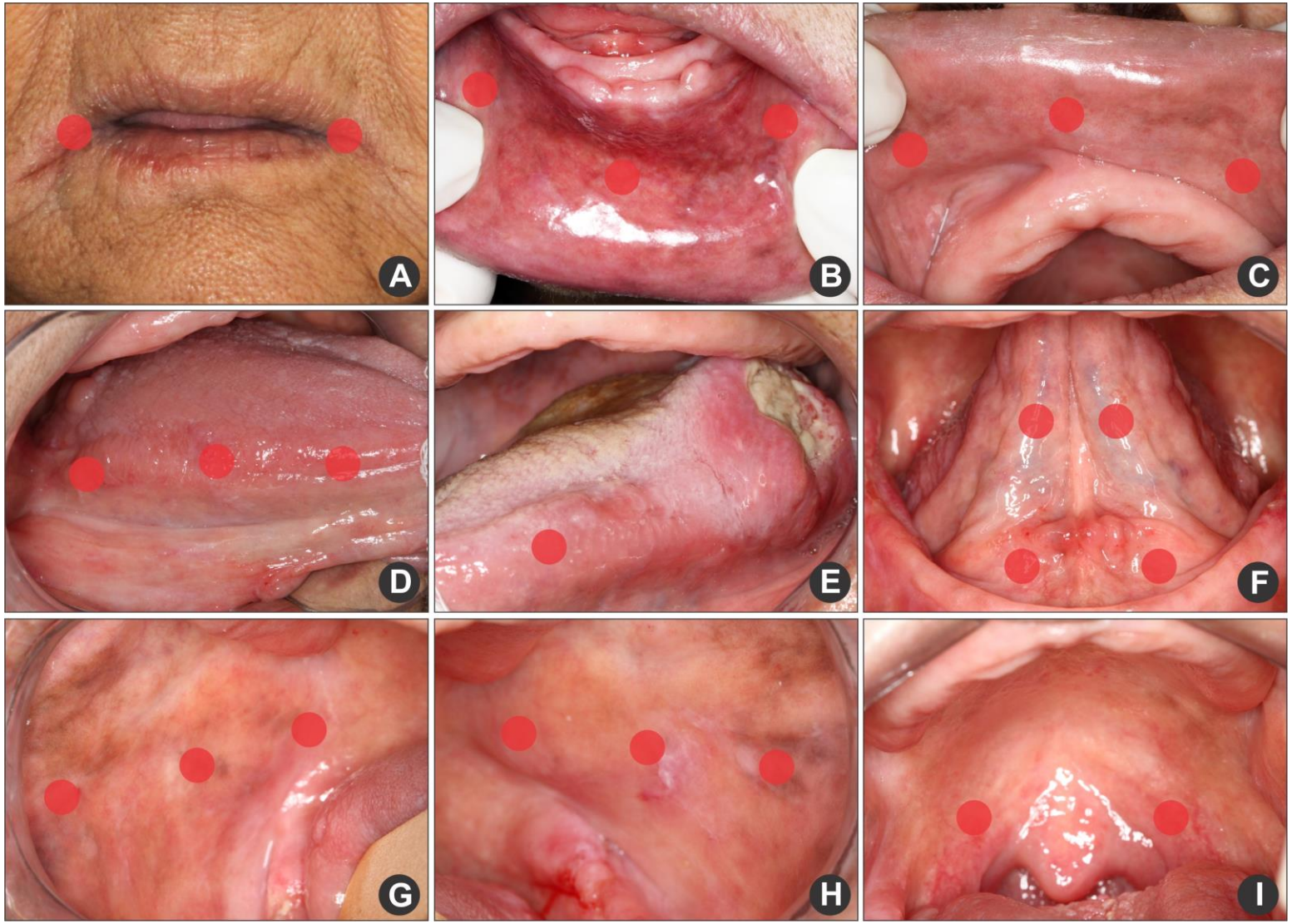

Figure 1. Clinical images simulating the study's intraoral photobiomodulation protocol. The laser probe is represented by the red circles on the surface of 7 different oral mucosa topographies, including oral commissures **(A)**, labial mucosae **(B, C)**, lateral borders of the tongue **(D, E)**, ventral tongue **(F)**, anterior floor of the mouth **(F)**, buccal mucosae **(G, H)**, and soft palate **(I)**. PBM therapy was not delivered over the active tumor area **(E)**.

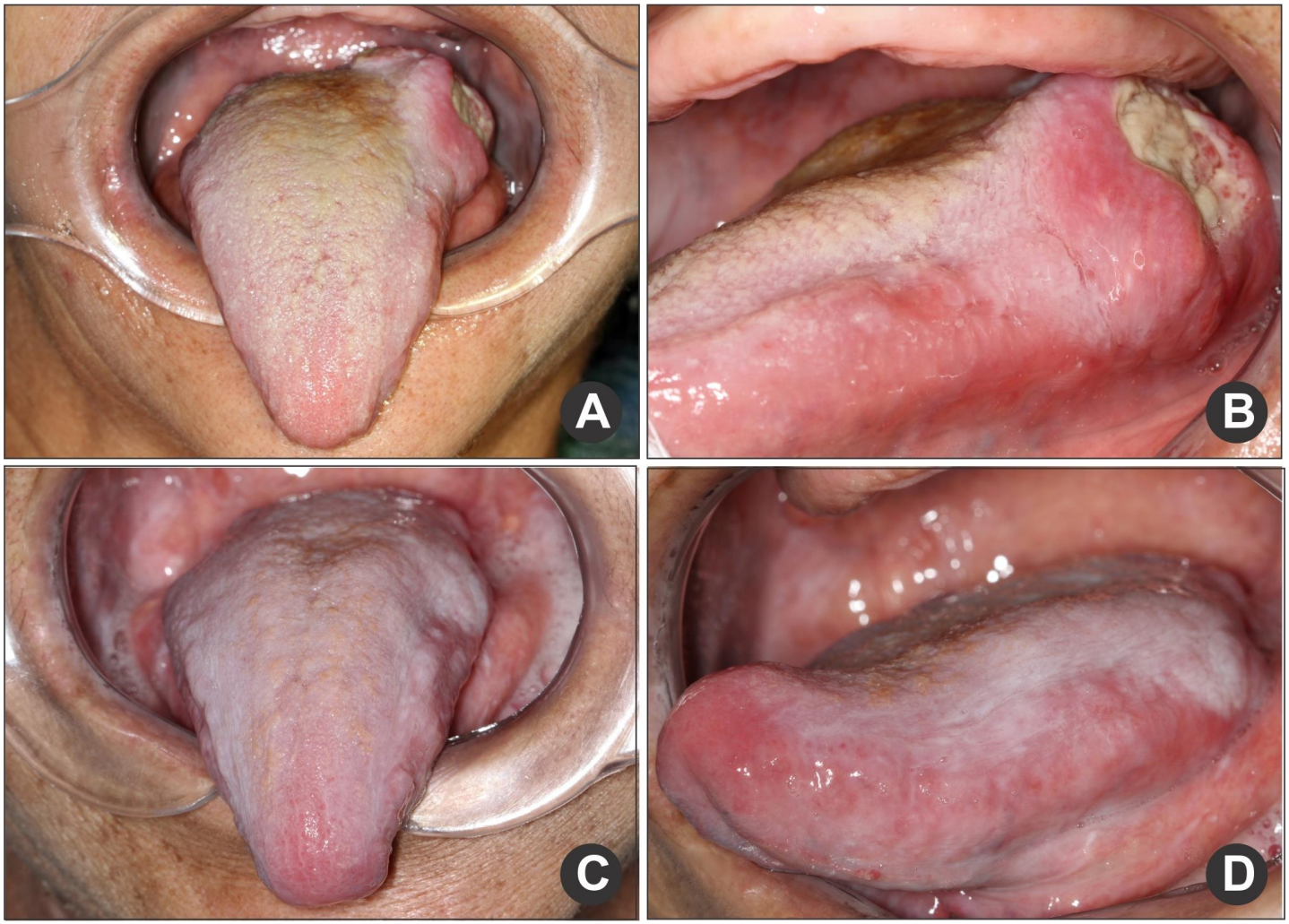

Figure 2. Intraoral aspects of a patient included in the study and submitted to photobiomodulation for the prevention of oral mucositis. Images **A** and **B** show frontal and lateral views of a locally advanced tongue squamous cell carcinoma **(A, B)** prior to the beginning of chemoradiation. Images **C** and **D** show complete clinical resolution of the primary tumor after the conclusion of the last session of radiotherapy.

3. CONCLUSÃO

1. Os resultados de resposta ao tratamento e de sobrevida encontrados no presente estudo são similares aos de estudos clínicos previamente publicados na literatura para pacientes com CEC de boca em estágio avançado, tratados por meio de protocolos oncológicos multimodais.
2. Para a mucosite oral induzida pela radioterapia, o protocolo de fotobiomodulação profilático utilizado neste estudo não gerou impacto negativo nos padrões de resposta ao tratamento ou nos resultados de sobrevida de pacientes com CEC de boca.
3. Para a mucosite oral induzida pela radioterapia, o protocolo de fotobiomodulação profilático utilizado neste estudo pode ser considerado seguro do ponto de vista oncológico.

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ANEXOS

ANEXO 1. Parecer circunstanciado do Comitê de Ética em Pesquisa

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

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Padrões de progressão tumoral em pacientes com carcinoma espinocelular de cavidade oral submetidos à fotobiomodulação.

Pesquisador: Thaís Bianca Brandão

Área Temática:

Versão: 1

CAAE: 63500217.0.0000.0065

Instituição Proponente: FUNDACAO FACULDADE DE MEDICINA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.897.352

Apresentação do Projeto:

Trata-se de projeto de Doutorado em estudo retrospectivo longitudinal.

Objetivo da Pesquisa:

Descrever os padrões de resposta ao tratamento e de progressão tumoral em pacientes com carcinoma espinocelular (CEC) de cavidade oral submetidos à fotobiomodulação (FBM) profilática para mucosite oral (MO

Avaliação dos Riscos e Benefícios:

Não existem riscos previstos.

Comentários e Considerações sobre a Pesquisa:

A laserterapia de baixa intensidade, também conhecida como fotobiomodulação (FBM), foi originalmente introduzida na prática clínica oncológica por Mester, na década de 1960 (Sonis et al., 2016) e a evolução desta técnica aplicada à prevenção e ao tratamento da MO sugere potencial para diminuição da prevalência da gravidade das lesões que se desenvolvem por toxicidade da RT e da quimioterapia, sendo eficiente, inclusive, na redução da frequência de interrupção da RT por casos graves de MO. Um dos maiores desafios para a aceitação universal da FBM profilática à MO em pacientes oncológicos é a sua dificuldade de reprodutibilidade metodológica que decorre

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ANEXO 2. Certificado de Submissão do Artigo

From: em.jscc.0.5624db.82e198ff@editorialmanager.com <em.jscc.0.5624db.82e198ff@editorialmanager.com> on behalf of Editorial Office <em@editorialmanager.com>
Sent: Tuesday, September 26, 2017 1:41 AM
To: Alan Roger Santos-Silva
Subject: JSCC: Submission Confirmation for JSCC-D-17-00812R1

Ref.: Ms. No. JSCC-D-17-00812R1
Locally-Advanced Oral Squamous Cell Carcinoma Patients Treated With Photobiomodulation Therapy for Prevention of Oral Mucositis: Retrospective Outcomes and Safety Analyses

Dear Professor Santos-Silva,

Supportive Care in Cancer has received your revised submission.

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Kind regards,

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