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Abstract	To assess the safety and efficacy of prophylactic extraoral photobiomodulation (PBM) for the prevention of oral and oropharyngeal mucositis (OM) on clinical outcomes and survival in patients with oral cavity and oropharyngeal squamous cell carcinoma (OOPSCC).OOPSCC patients who received radiotherapy (RT) were prospectively randomized to two groups: prophylactic extraoral PBM and placebo. OM grade (NCI), pain (VAS), analgesia, and anti-inflammatory prescriptions were assessed weekly. Quality of life questionnaires (QoL) were performed at the first and last day of RT. Following RT, participants were evaluated quarterly for oncological outcomes follow-up.Fifty-five patients met the inclusion criteria. The first occurrence of OM was observed at week 1, for the placebo group ($p = 0.014$). Later, OM onset and severity was observed for the PBM group, with first occurrence at week 2 ($p = 0.009$). No difference in severe OM incidence was observed ($p > 0.05$). Lower mean pain score was noted at week 7 for the PBM group (2.1) compared to placebo group (4.5) ($p = 0.009$). Less analgesics (week 3; $p = 0.009$/week 7; $p = 0.02$) and anti-inflammatory prescription (week 5; $p = 0.0346$) were observed for the PBM group. Better QoL scores were observed for the PBM group at last day of RT ($p = 0.0034$). No difference in overall survival among groups was observed in 1 year of follow-up ($p = 0.889$).Prophylactic extraoral PBM can delay OM onset, reduce pain, and reduce analgesic and anti-inflammatory prescription requirements. Extraoral PBM was associated with better QoL. There was no evidence of PBM impact on oncological outcomes.TRN:RBR-4w4swx (date of registration: 01/20/2020).

Keywords (separated by '-')	Photobiomodulation - Oral mucositis - Radiotherapy - Quality of life - Overall survival
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ORIGINAL ARTICLE

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

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Abstract

Purpose To assess the safety and efficacy of prophylactic extraoral photobiomodulation (PBM) for the prevention of oral and oropharyngeal mucositis (OM) on clinical outcomes and survival in patients with oral cavity and oropharyngeal squamous cell carcinoma (OOPSCC).

Methods OOPSCC patients who received radiotherapy (RT) were prospectively randomized to two groups: prophylactic extraoral PBM and placebo. OM grade (NCI), pain (VAS), analgesia, and anti-inflammatory prescriptions were assessed weekly. Quality of life questionnaires (QoL) were performed at the first and last day of RT. Following RT, participants were evaluated quarterly for oncological outcomes follow-up.

Results Fifty-five patients met the inclusion criteria. The first occurrence of OM was observed at week 1, for the placebo group ($p=0.014$). Later, OM onset and severity was observed for the PBM group, with first occurrence at week 2 ($p=0.009$). No difference in severe OM incidence was observed ($p>0.05$). Lower mean pain score was noted at week 7 for the PBM group (2.1) compared to placebo group (4.5) ($p=0.009$). Less analgesics (week 3; $p=0.009$/week 7; $p=0.02$) and anti-inflammatory prescription (week 5; $p=0.0346$) were observed for the PBM group. Better QoL scores were observed for the PBM group at last day of RT ($p=0.0034$). No difference in overall survival among groups was observed in 1 year of follow-up ($p=0.889$).

Conclusion Prophylactic extraoral PBM can delay OM onset, reduce pain, and reduce analgesic and anti-inflammatory prescription requirements. Extraoral PBM was associated with better QoL. There was no evidence of PBM impact on oncological outcomes.

Trial registration TRN:RBR-4w4swx (date of registration: 01/20/2020).

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 head and neck cancer (HNC) patients undergoing radiotherapy (RT) and chemoradiotherapy (CRT). OM often leads to debilitating and dysfunction distress due to pain with impairment in eating, swallowing, and speech functions [36, 42]. This morbidity has marked negative impact on patient's quality of life (QoL); increases treatment costs due to the need of hospitalization, nutritional support, opioids use, and antimicrobials anti-inflammatory drugs; and may lead to new or prolonged hospitalization [24]. The incidence and severity of OM depend upon several risk factors associated with the oncological treatment and patient characteristics [27].

With level I scientific evidence, the Multinational Association of Supportive Care in Cancer/International Society

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of Oral Oncology (MASCC/ISOO) recommends the use of photobiomodulation (PBM) as an adjuvant intervention for prevention of OM in the HNC setting [43]. Although PBM is well established and accessible, there is great variability in PBM parameters, protocols, and equipment, which hampers consistent evaluation [7, 19]. 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 [8, 17, 21, 37]. 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 [39].

We conducted a randomized, double-blind clinical trial aimed to evaluate the effect of extraoral PBM prophylactic delivery on OM, OM-related pain, QoL, and cancer safety outcomes in oral and oropharynx squamous cell carcinoma (OOPSCC) patients during RT.

Methods

This double-blind, prospective clinical trial was conducted at Instituto do Cancer do Estado de São Paulo (ICESP), São Paulo, Brazil. Ethical approval was obtained from the National Human Research Ethics Committee (CAAE: 21,648,819.9.0000.5418). The study was conducted in accordance with the Declaration of Helsinki and reported according to the Consolidated Standards of Reporting Trials guidelines (CONSORT) [35]. The trial was registered in the International Clinical Trials Registry Platform (ICTRP-WHO) and Brazilian Registry of Clinical Trials (ReBec) (Registration Number: RBR-4w4swx) [32]. We present the results of a planned interim analysis when at least 55 participants had completed a minimum of 1 year of follow-up. All participants included in the study provided informed consent.

Patients

Patients diagnosed with OOPSCC in stage III or IV (*International Union Against Cancer, 8th edition*) [9], over the age of 18 years, treated with curative RT protocols (60–70 Gy–2.0–2.12 Gy/day, 5 sessions/week) as a single modality or in association with CT were included. 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 oral health such as complete oral prophylaxis, restorations, dental scaling/polishing, endodontic therapy, and tooth extraction if necessary [39]. Demographics and clinicopathological information were obtained from the electronic medical record system (Tasy, Java version; Koninklijke Philips N.V., 2004–2017).

Patients were excluded if they had distant metastasis, had previously received RT to the head and neck, or were scheduled to receive palliative RT.

Participants 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 chlorhexidine 0.12% for daily use, verbal and written instructions about oral hygiene, abstinence from tobacco and alcohol, and risk of oral toxicities related to head and neck RT [23].

PBM protocol

Patients in the extraoral PBM group received daily prophylactic PBM for 5 consecutive days/week (Monday to Friday), from the first to the last day of RT. Two trained dentists administered the PBM by using the THOR LX2 unit with the red and near-infrared light emitting diode (LED) probe (THOR Photomedicine Ltd, Chesham, UK). The probe contains 69 diode LED, composed of 34 × 660 nm (red; 10mW) and 35 × 850 nm (near-infrared; 30mW) with a total power output of 1390mW, an outer diameter probe of 70 mm, 63 mm of active area diameter, 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 s, at five treatment sites: right face side, central face on the lip area, left face side, cervical area on the left, and right sides (50 mW/cm^2 × 60 s = 3.0 J/cm^2 per location) [40] (Fig. 1). 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. 1). 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 all participants wore dark safety googles. For safety and infection control purposes, a systematic disinfection routine with 70% alcohol ethylic was completed before and after each session; also, a disposable plastic film was used to cover the probe.

Oral mucositis

The same calibrated dentist, blinded to the allocation group, completed the clinical outcomes assessment, prior to the PBM session. All patients were evaluated weekly for the presence, topography, and severity of OM following the *Common Terminology Criteria for Adverse Events* (NCI, *version* 4.0, 2010), graded 0–4 [31].

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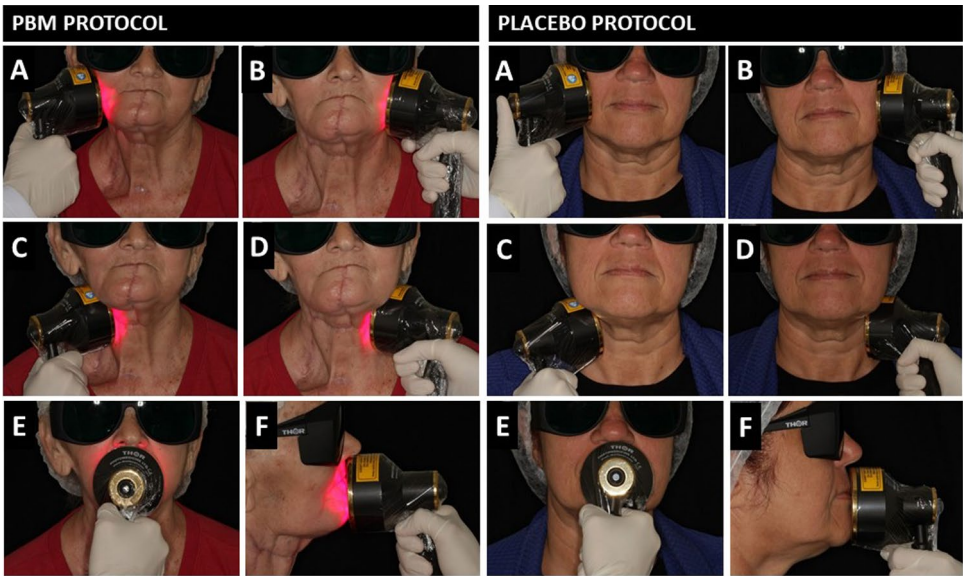

*PBM: photobiomodulation

AQ3 **Fig. 1** Extraoral PBM—the LED probe is applied flat against the patient's face and neck for 60 s, at five treatment sites (50 mW/cm^2 × 60 s = 3.0 J/cm^2 per location). Placebo/sham extraoral PBM protocol—an inactivated probe is applied flat against the patient's face and neck for 60 s, at five same treatment sites as PBM protocol. Treatment sites: right face side (**A**), right neck (**B**), left face side (**C**), left neck (**D**), and center face (**E** and **F**). *PBM photobiomodulation

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 and non-opioid analgesics (VAS 1–3; paracetamol or dipyrone and/or ketoprofen or celecoxib); level 2, moderate pain and weak opioid (VAS 4–6; codeine or tramadol or dipyrone and/or ketoprofen); and level 3, severe pain and strong opioid (VAS 7–10; morphine or oxycodone + paracetamol or dipyrone and/or ketoprofen) [12, 14] and with or without adjuvants at each level.

Anti-inflammatory prescriptions

The prescription of anti-inflammatory agents for OM was also recorded weekly. All prescriptions were made by the medical team who were providing routine care and who were blinded to the study group allocation.

Quality of life

The University of Washington Quality of Life Questionnaire *(UW-QOL v4)* validated for the Portuguese version [41] was completed before the first day of RT (D-1) and at the last day of RT (D35). The UW-QoL is composed of 12 objective questions of specific variables, ranging 0 to 100, where 100 represent the best possible condition. The analysis was divided into physical and social-emotional function domains.

Oncological 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 to assess oncological outcomes. 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 the primary outcome measures [8].

Statistical analysis

Effectiveness was defined as the proportion of 30% less severe OM in the PBM group compared to placebo, as proposed by the hypothesis of Legouté et al. [25]. Results of this interim analysis were expressed as mean values and percentages. Statistical significance rate of 5% ($p \leq 0.05$) was considered. Per protocol analysis of the data obtained from the present study, including Kaplan–Meier curve for 12-month 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.

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Results

A total of 67 patients were randomized from June 2019 to 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 ($n=7$), and OM grade 4 with medical request to discontinue the trial to receive therapeutic PBM ($n=1$/placebo group). Fifty-five participants who met inclusion criteria and completed the planned RT treatment were included in the clinical follow-up. The flow-chart and exclusion reasons are presented in Fig. 2.

Clinicopathological characteristics of the analyzed 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 groups.

A total of 918 PBM sessions were performed for the PBM group and 832 sham sessions for the placebo group. There was no difference in the mean number of sessions

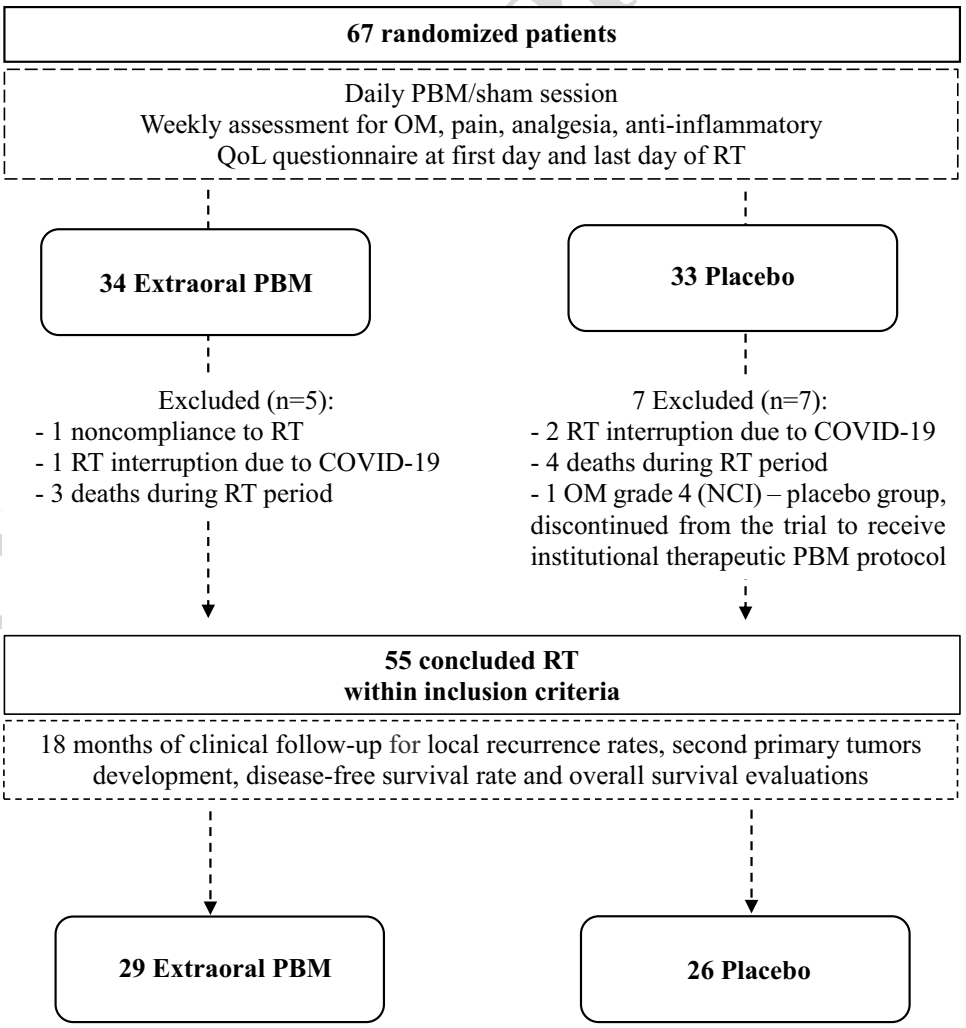

Fig. 2 Flowchart and outcomes. OM oral mucositis; RT radiotherapy; QoL quality of life; PBM photobiomodulation; NCI National Cancer Institute

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

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%)	
p16 status**					
Positive	**3**	(23.1%)	**3**	(25.0%)	
Negative	**7**	(53.8%)	**5**	(41.7%)	
Not available	**3**	(23.1%)	**4**	(33.3%)	
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
60 Gy	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)	

RT radiotherapy; *CRT* chemoradiotherapy; *PBM* photobiomodulation

*Mann–Whitney test for between-groups comparison (extraoral PBM vs. placebo)

**p16 status was assessed for palatine tonsil and oropharynx tumors

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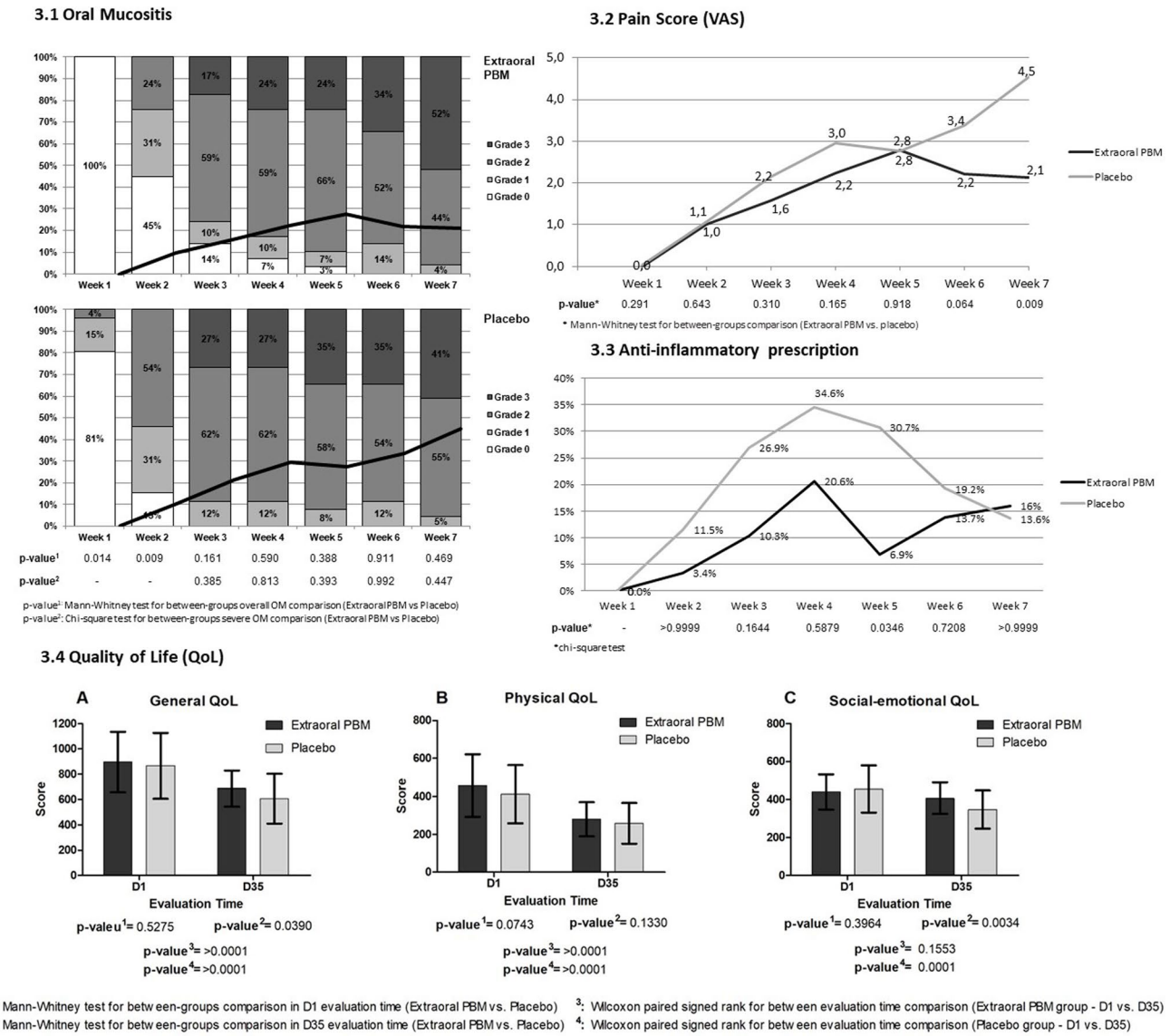
for both groups (32 sessions/patient; $p = 0.38$). Excellent tolerance to PBM was reported by 54 (98.1%) patients, while 1 (1.9%) patient reported moderate tolerance associated with discomfort and nausea due to the smell of the disposable plastic film that covered the probe. No pain or adverse events were reported.

Oral mucositis

All patients experienced some grade of OM during RT (Fig. 3). The first occurrence was observed earlier in the placebo group (week 1) than the PBM group (week 2). Differences in the overall OM comparison were noted during week 1, in which no case of OM was observed in the PBM



PBM: photobiomodulation therapy group; OM: oral mucositis; NCI: National Cancer Institute; VAS: Visual Analogue Scale; QoL: Quality of Life

Fig. 3 Clinical assessments. 3.1: Oral Mucositis—Weekly oral mucositis assessment according to the National Cancer Institute (NCI, version 4.0; 2010). Bars represent percent of cases in each oral mucositis grade and continuous lines represent mean values for each stage (score range from 0 to 4); 3.2 Pain Score—Oral mucositis associated pain score (visual analogue scale – VAS); 3.3: Anti-inflammatory prescription at the different weeks of RT treatment; 3.4 Quality of life—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. PBM photobiomodulation therapy group; OM oral mucositis; NCI National Cancer Institute; VAS visual analogue scale; QoL quality of life AQ4

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compared to the OM incidence of 19% in the placebo group ($p = 0.014$) and during week 2, where OM incidence was 55% for the PBM group in comparison with 85% for the placebo ($p = 0.009$). Comparison over the time of RT showed a later OM onset for 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.

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 vs. 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 ($p = 0.447$).

For the PBM group, the OM incidence was associated with oral mucosal sites distant from the direct contact with the extraoral probe. At the last week of treatment, oropharynx (16%), border of the tongue (14%), and retromolar trigone (14%) were the most affected sites for the PBM group. The results for the placebo group were border of the tongue (15%), oropharynx (14%), and buccal mucosa (14%), an area with direct contact with the extraoral probe (Supplementary Fig. 1).

Pain and analgesia

Pain evaluations are shown in Fig. 3. During most of the periods of assessment, lower mean pain score was observed for the PBM group; the highest mean score was 2.8 during week 5 of RT. Moderate pain score (VAS, 3–7) was observed in the placebo group during week 6 (3.3) and week 7 (4.5), representing the highest mean level of pain in the placebo group during the observation period. Significant statistical difference was observed at week 7 with mean pain score of 2.1 for the PBM group vs. 4.5 for the placebo group ($p = 0.009$), the highest mean pain score observed in the study.

During all periods of evaluation, the PBM group had a lower percentage of patients that required analgesics (Table 2). During week 3, 48.2% of PBM vs. 76.9% of placebo required analgesics for pain relief, and while no patient in the PBM group used opioids, 2 (7.7%) ($p = 0.009$). Similar results were observed during week 7 where 48% of PBM patients vs. 86.4% of placebo were using any analgesic for OM-related pain relief, and a higher prevalence of opioids analgesic use was observed 4.0% of PBM vs. 27.3% of placebo patients ($p = 0.02$).

Anti-inflammatory prescription

The numbers of anti-inflammatory prescriptions were higher in the placebo group (Fig. 3). At week 4 of RT, the maximum

Table 2 Oral mucositis-related analgesia protocol throughout radiotherapy course

Analgesic scale	Week 1				Week 2				Week 3				Week 4				Week 5				Week 6				Week 7			
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

PBM photobiomodulation therapy group

*Mann–Whitney test for between-groups comparison (extraoral PBM vs. placebo)

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number of prescriptions 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, a difference of anti-inflammatory prescription between groups was seen, with 30.8% for the placebo and 6.9% for the PBM group ($p=0.0346$).

Quality of life

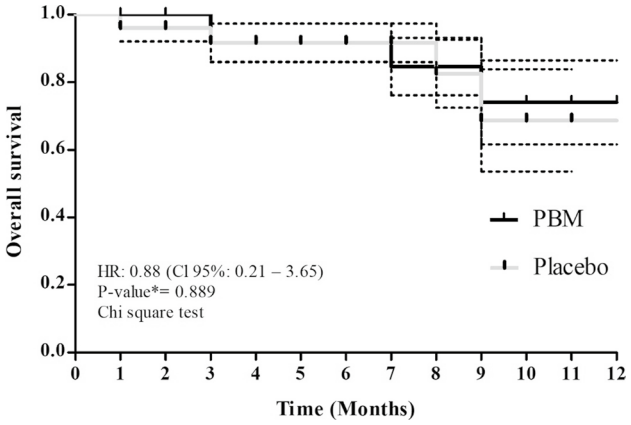
The QoL assessments are presented in Fig. 3. The general UW-QoL score at D1 and D35 for the PBM group was 910 and 687, respectively, while for the placebo group were 868 and 607, respectively. Statistically significant results were found at D35 for general QoL for between groups comparison ($p=0.0390$).

At D35, the physical QoL mean score was lower for the placebo group (258 vs. 279 for the PBM group ($p=0.1330$)), similar to the social-emotional QoL with scores of 348 for the placebo group vs. 408 for the PBM group ($p=0.0034$).

In terms of treatment period comparison (D1 vs. D35), a negative impact of RT on patients QoL was observed at D35 for both groups and in all QoL outcomes. A statistically significant difference in general and physical outcomes for both placebo and PBM groups were observed ($p>0.0001$) and social-emotional outcome for placebo group. The social-emotional QoL outcome for PBM group was an exception ($p=0.1553$).

Oncological outcomes

In 1 year of follow-up, no local or systemic adverse events due to the PBM were observed. One local recurrence was recorded 6 months follow-up in the placebo group. No second primary tumors were observed. An interim analysis of the OS with the mean follow-up period of 12 months was possible, and a slight tendency for better overall survival was observed in the PBM group (74.0 vs. 68.7%; $p=0.889$; HR 0.88; CI 95% 0.21–3.65) (Fig. 4). These data will be updated after a total follow-up period of 18 months after the last patient enrollment.



PBM : photobiomodulation

Fig. 4 Interim analysis of the overall survival with the follow-up period of 12 months. PBM photobiomodulation

Discussion

We evaluated the effects of a prophylactic extraoral PBM in the outcomes of RT-induced OM and oncological outcomes. The demographic characteristics of the included patients in this interim analysis were similar to those presented in the literature, patients with advanced OOPSCC, mostly males, with history of tobacco and alcohol use [2, 17, 20, 25]. Additionally, the oncological treatment reflected the standard of care from international cancer centers, based on a multimodal approach, associated with a better prognosis, but also with an increase of acute side effects, particularly OM [2].

In our study, a delay in the development of OM for the PBM group, along with a difference on severity duration due to later OM onset, 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. While there is robust evidence of the effectiveness of PBM in OM [43], different PBM effectiveness results can be attributed to many factors including PBM parameters, oncological treatment regimen, and patient's characteristics [10, 11, 19, 25]. One of the challenges when comparing PBM results between studies is the heterogeneity of PBM protocols and parameters used [5, 8, 10, 17, 44]. Few studies have evaluated the effectiveness of extraoral PBM for OM [16, 18, 41], due to the lack of evidence and the lack of validated protocols for extraoral PBM for OM [21].

During the last week of RT, we observed severe OM primarily in the oropharynx, and posterolateral border of the tongue. The oropharynx was the most frequent primary tumor site for both groups, with the primary radiation dose the area and greater difficulty in OM management. Also, these areas with greater OM grade 3 were distant from the extraoral light surface, and the literature shows that light delivery to target tissue is affected by its distance from the light source [5, 10, 22, 44, 45]. For extraoral PBM, tissues with greater energy delivered include the buccal mucosa, the vestibule, and the oral surfaces of the lips [5, 10, 44, 45].

PBM effectiveness on severe OM control may also be due to insufficient PBM parameters, and adjustments in the extraoral PBM protocol need to be optimized with the goal of achieving greater efficacy. The use of extraoral application plus intraoral delivery on selected high-risk oral

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regions per radiation treatment plan may enhance compliance and reduce time for light application in the clinical setting. Additional studies are warranted. Furthermore, the evaluation of site-specific patterns of OM may improve the development of PBM protocols [4, 12]. It is important to highlight that extraoral PBM is considered to be a simple, well tolerated, and easily applied intervention.

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. PBM is known to be associated with pain reduction and thus may lead to reduced use of opioid analgesics [22, 26, 33, 38, 45]. Similar studies, Antunes et al. [26] and Gautam et al. [1] reported significantly less severe oral pain scores for PBM-treated patients compared to placebo, in addition to reduced opioid use during RT.

Higher prescriptions of anti-inflammatory agents were observed in the placebo group, which may also have influenced the OM severity incidence. 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 [16, 18].

Oral and oropharyngeal cancer is associated with reduced QoL due to the effects of primary tumor and treatment side effects impairing patient's daily functional and self-image [3, 17]. Worsening levels of general QoL were observed at the end of the treatment, as reported in previously published studies [3, 15, 26, 33]. The variability of QoL is directly associated with cancer treatment toxicities' alterations in swallowing, chewing, saliva changes, taste, and especially OM-related pain [3]. Our study shows better social-emotional QoL in those treated with PBM, which could be explained by the positive impact in OM symptom attenuation specifically decreased pain levels [15, 26].

It is imperative that an intervention used to support cancer patients during therapy does not adversely affect tumor behavior, or tumor response to treatment [5, 25, 28, 37, 39]. 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 [13, 21, 39]. 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 oropharynx tumors [6, 8]. Our evaluation of tumor outcomes was not adversely affected by PBM.

No significant adverse side effects were noted in the present study in the setting of oral and oropharynx cancer patients submitted to PBM during RT. This is in agreement with the current literature [1, 8, 10, 13, 17, 25, 26, 30]. Furthermore, no relevant negative effect of PBM on tumor biology was demonstrated, also in agreement with other similar studies [8, 13, 25, 26, 34]. No differences in OS were seen in the current study in PBM vs. placebo groups. Additional data will be available upon the final analysis of 18 months of follow-up. As PBM mechanisms continue to be studied, the effects of different parameters on tumor heterogeneity will add information based on solid science [6, 8].

Limitations of the study

The present study is a planned interim analysis of an ongoing clinical trial and results could change at completion of the trial and enlargement of the study sample.

Conclusions

This prospective double-blind randomized clinical trial assessed clinical and oncological outcomes of prophylactic extraoral PBM in radiation-induced OM in OOPSCC patients. Extraoral PBM was well tolerated and did not cause any significant adverse effects. This planned interim analysis suggests 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 in OOPSCC patients submitted to RT. Furthermore, no impact on tumor behavior or control and survival outcomes were seen, within the limits of the interim results of this clinical trial.

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Author contribution Elisa Kauark-Fontes: study design, data acquisition, data analysis and interpretation, manuscript preparation, and editing.

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Joel B Epstein: data analysis and interpretation, manuscript preparation, and review.

Nathaniel Simon Treister: study design, quality control of data, manuscript review.

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Data availability The authors confirm that the data supporting the findings of the study are available within the article and supplementary materials.

Code availability N/A.

Declarations

Ethics approval Brazil National Human Research Ethics Committee (CAAE: 21648819.9.0000.5418).

Consent to participate All participants included in the study provided informed consent.

Consent for publication All participants included in the study provided informed consent.

Conflict of interest The authors declare no competing interests.

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