Supportive Care in Cancer (2025) 33:842
https://doi.org/10.1007/s00520-025-09877-w

RESEARCH

Intraoral vs. extraoral photobiomodulation therapy for oral mucositis in head and neck cancer patients: a multicenter, randomized, single-blind clinical trial

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Received: 11 February 2025 / Accepted: 18 August 2025 / Published online: 10 September 2025

Abstract

Purpose To compare the efficacy of intraoral (IOPBM) and extraoral photobiomodulation (EOPBM) protocols for the prevention and treatment of oral mucositis (OM) in patients with oral or oropharyngeal squamous cell carcinoma (SCC) to submitted radiotherapy (RT).

Methods This randomized, blinded, multicenter clinical trial enrolled 58 patients with oral or oropharyngeal SCC, who were allocated into two groups matched by treatment type, clinical stage, and RT modality. Group I (IOPBM) received intraoral photobiomodulation (PBM) with a continuous InGaAlP diode laser (660 nm, 100 mW, 0.03 cm^2 spot size, 3 s per point, fluence 10 J/cm^2). Group II (EOPBM) received extraoral PBM using a superpulsed diode laser with dual wavelengths (810/980 nm, 1000 mW, 4.91 cm^2 spot size, 30 s per point, fluence 6.11 J/cm^2). PBM was performed five times per week during RT or until complete resolution of oral mucositis lesions.

Results A total of 58 patients were included from February 2021 to August 2023. The mean age of patients was 59.41 years. Forty (69%) were male, and 18 (31%) were female. All patients experienced some degree of OM during RT. No significant differences were observed between the groups for all OM grades (WHO scale, $p = 0.69$; NCI scale, $p = 0.82$) or in the meantime to the development of ulcerated OM (WHO scale, $p = 0.63$; NCI scale, $p = 0.61$). On day 20 (week 4) and day 30 (week 6), patients in the EOPBM group reported significantly less difficulty swallowing compared to the IOPBM group (Mann-Whitney test, $p = 0.02$ and $p = 0.04$, respectively). On day 25 (week 5), the EOPBM group demonstrated a significantly smaller decline in taste perception compared to the IOPBM group, as determined by the Mann-Whitney test ($p = 0.01$).

Conclusion The EOPBM protocol was found to be as effective as IOPBM in managing OM, with the added benefit of providing greater patient comfort during application.

Trial registration Registered with ClinicalTrials.gov (NCT05242991).

Keywords Head and neck cancer · Photobiomodulation · Oral mucositis · Radiotherapy

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Introduction

Head and neck cancer (HNC) is the seventh most common cancer worldwide and accounts for over 800,000 new cases annually. Incidence is anticipated to continue rising with more than one million new cases each year predicted by 2030 [1]. More than 90% of all head and neck tumors are squamous cell carcinomas (HNSCC). Tobacco use and alcohol consumption are still important risk factors for HNSCC in developing countries [2]. Although most of these patients present with locally advanced disease, they are generally treated with curative intent. Treatment may involve surgery, radiotherapy (RT), chemotherapy (CT), or typically, a combination of these approaches, particularly in cases in advanced stages. Surgical resection of high-stage tumors is followed by RT that can be combined with concomitant systemic therapy, such as CT or biologicals. In patients not eligible for surgery due to an irresectable tumor, combined concomitant chemo-radiotherapy (CT-RT) is preferred [3, 4]. Despite the treatment, these tumors confer a poor prognosis, with a 5-year survival rate < 50% and nearly 432,000 annual global deaths, probably because of diagnosis at an advanced stage in 2/3 of cases [1, 5].

The most frequently used RT modern techniques for HNC include intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) with a total cumulative dose of 60–70 grays (Gy) by 2.0 Gy per day for 5–7 continuous weeks [6, 7]. Despite the IMRT or VMAT techniques reducing the radiation dose to healthy surrounding tissues, toxicities in all tissues included in the irradiated area still poses many adverse effects [8, 9]. Increasing considerably when therapies are combined, with acute and chronic toxicities. The acute oral toxicities include oral mucositis (OM), hyposalivation, dysphagia, dysgeusia, trismus, and oral infections; and the oral late comprise radiation-caries, hyposalivation, dysgeusia, osteoradionecrosis, among others [10–13].

OM represents a major debilitating toxicity in HNSCC patients undergoing RT or RT-CT, occurring in almost all patients treated for cancers of the oral cavity, oropharynx, and nasopharynx [14–16]. It represents a complex condition characterized by an inflammatory response triggered by RT or RT-CT [17]. Clinical presentation includes atrophic changes, such as erythema and soreness, that begin at the end of the first week of exposure and are followed by ulceration, which can last for up to 6 weeks after completion of RT. A 10–20 Gy dose provokes an initial clinical sign accompanied by pain and functional impairment by the 2nd week of treatment [14]. As the cumulative dose increases, ulceration occurs, which can last for up to 6 weeks after RT completion [18].

According to WHO, OM is classified in 4 stages being the grades 3 and 4 considered severe stages because ulcerative lesions interfere in the ability to eating and drinking capacity which led to weight loss and reduce patient's quality of life [8, 14]. RT and RT-CT are responsible for worse OM grades (3 and 4) in 50% of patients [19]. In addition, OM can predispose the patient to increased infection risk, opioid consumption, and increased need for parenteral nutrition which in turn can increase hospitalization/prolonged hospital stay and treatment cost [20]. Sometimes severe OM can entail the need for reducing the dose of CT and inappropriate breaks in RT, which would have a negative impact on overall treatment effectiveness and patients' prognoses [18].

The Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) developed a guideline for the management of OM. The guideline suggests that implementation of *multiagent combination* oral care protocols, *benzydamine* mouthwash, sucralfate (topic and systemic), natural and miscellaneous (oral glutamine and honey), and PBM are beneficial for the prevention of OM during RT or RT-CT for HNC [21, 22]. The impact of benefit of PBM in the management of OM is reported as reduction in the incidence and severity of OM [23–26].

PBM is a therapy that uses lasers, light-emitting diodes (LED), and broadband light. It is a non-invasive technique, corresponding to a simple and painless application on mucosa of a high-density monochromatic narrow band light source with various wavelengths. PBM stimulates and promotes wound healing, regeneration, and immune responses and mediates inflammation, pain, and aberrant immune responses [27, 28]. Most studies have used low-level laser therapy (LLLT) showing positive effects of different IOPBM laser protocols in the management of OM [7, 25, 29–33]. However, few studies have reported the benefits of high-level laser therapy (HLLT) using EOPBM appliances [34, 35]. EOPBM technique reduces patient discomfort offering a more comfortable solution for patients since it does not require opening a mouth with wounds. Moreover, EOPBM may also allow the simultaneous management of oropharyngeal mucositis, an area that cannot be reached with an IO laser [34, 36–40]. This study is aimed at comparing the effectiveness of IOPBM and EOPBM in preventing and treating OM and evaluating their impact on pain and functional outcomes in HNSCC patients undergoing RT.

Materials and methods

Study design

This was a randomized, blinding, multicenter clinical trial. The study was approved by the Ethics Committee of the

Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil (no. 2020-0189); A.C.Camargo Cancer Center, São Paulo, Brazil (no. 3033/21); and the Instituto do Cancer do Estado de São Paulo, São Paulo, Brazil, in accordance with Good Clinical Practice guidelines and Brazilian law. The study was conducted in accordance with the Declaration of Helsinki and reported according to the Consolidated Standards of Reporting Trials guidelines (CONSORT) [41]. Written informed consent was obtained from all participants. Register Number of Trial (ClinicalTrials.gov ID): NCT05242991.

Patients

Patients diagnosed with HNSCC involving the oral cavity or oropharynx were recruited between February 2021 and August 2023 from three centers: Hospital de Clínicas de Porto Alegre (Rio Grande do Sul, Brazil), A.C. Camargo Cancer Center (São Paulo, Brazil), and Instituto do Câncer do Estado de São Paulo (São Paulo, Brazil). According to the WHO ICD-11 classification, the corresponding diagnostic codes are 2B6E.0 for SCC of the oral cavity and 2B6A.0 for SCC of the oropharynx, which reflect both the anatomical site and histopathological type of the tumor. All patients that met the criteria for participation in the study were evaluated by a dentist before starting the cancer treatment, and any required dental treatment or the removal of teeth with uncertain prognosis, including teeth with active periodontal disease, teeth requiring endodontic treatment, and teeth with cavities or extensive coronal destruction, was performed. Both patient groups received orientation standard oral hygiene.

Patients were randomized into the IOPBM and EOPBM groups, matched by treatment type (RT, RT + Surgery, RT + CT, RT + CT + Surgery), clinical stage (I, II, III, IV), and RT modality (IMRT or 3DRT) using an institutional App (Shinyapps.io) based on a sequential allocation process. The participant flowchart, as well as details on randomization and blinding throughout the study, are shown in Fig. 1.

Data were collected on demographic characteristics (gender and age), risk factors, tumor location, clinical stage, treatment type, RT modality, and enteral feeding status and medication use (opioid and non-opioid).

Patient's inclusion and exclusion

Patients included in this study were diagnosed with HNSCC (Oral or Oropharyngeal SCC) and receiving treatment of RT (with or without surgery and with or without concomitant CT). All included subjects were submitted to RT protocols with conventional fractionation (reaching 70 Gy in the tumor and affected lymph nodes, at 2 Gy per day excluding weekends), over the period of 5 to 7 weeks using tridimensional radiotherapy (3DRT) or intensity-modulated radiation therapy (IMRT). The CT protocol was cisplatin (100 mg/m^2) on D1, D22, and D43 or cisplatin (50 mg/m^2) per week. During RT treatment, the patients were orientated to use 0.12% chlorhexidine rinse twice a day to maintain oral health. In addition, if necessary, the patient used medication for pain (opioid and non-opioid).

The exclusion criteria were patients with a hypersensitivity or allergy to one of the components included in the study (e.g., platinum salts), patients with any medical condition affecting healing mechanisms (e.g., diabetes mellitus, HIV, autoimmune disease), any uncontrolled comorbidly (pulmonary, kidney, liver, or heart failure), and patients realized previous RT in the head and neck region.

PBM protocol

IOPBM and EOPBM preventive protocols were performed 5 days a week, starting on the first day of the RT treatment and ending on the last day of RT treatment or until OM wound healing. The PBM was applied by the single trained professional, and both the professional and the patient wore protective eyewear. All PBM parameters used in the study are presented in Table 1.

In group I (IOPBM), PBM was performed using a continuous InGaAlP diode laser (MM Optics Ltd., São Carlos, Brazil), applied in contact mode, perpendicular to the oral mucosa (Fig. 2A–D). Importantly, no laser application was performed on or near the tumor site. The tumor location was carefully reviewed for each patient, and the PBM application was planned to completely avoid the tumor area and its immediate surroundings. For example, in cases where the tumor was located on the right lateral border of the tongue, the entire right border of the tongue was excluded from PBM application. This approach ensured safety and compliance with current recommendations regarding PBM in patients with potentially malignant or malignant lesions. The irradiation protocol, based on previous studies [32, 42], included 33 points in total, distributed as follows: 6 on the mucosa of lip—3 upper and 3 lower and 2 on the labial commissure—1 right and 1 left (Fig. 2A); 8 points on the buccal mucosa—4 right and 4 left (Fig. 2B); 5 on the ventral surface of the tongue, and 4 on the floor of the mouth—2 on each side (Fig. 2C); 8 on lateral edges of the tongue—4 on each side (Fig. 2D).

Group II (EOPBM) consisted of a pulse diode laser (Gemini®, Ultradent Products, Inc.) with dual wavelengths of 810 and 980 nm. The irradiations were performed extraorally using protocol adapted from previous studies [34, 39] and consisted of 5 points on the face and 5 points on the anterior neck. The treatment sites were left face and neck, and 1 on lip (Fig. 2E); right face and neck, and 1 on lip (Fig. 2F); points on the face—2 on both right and left cheeks and 1

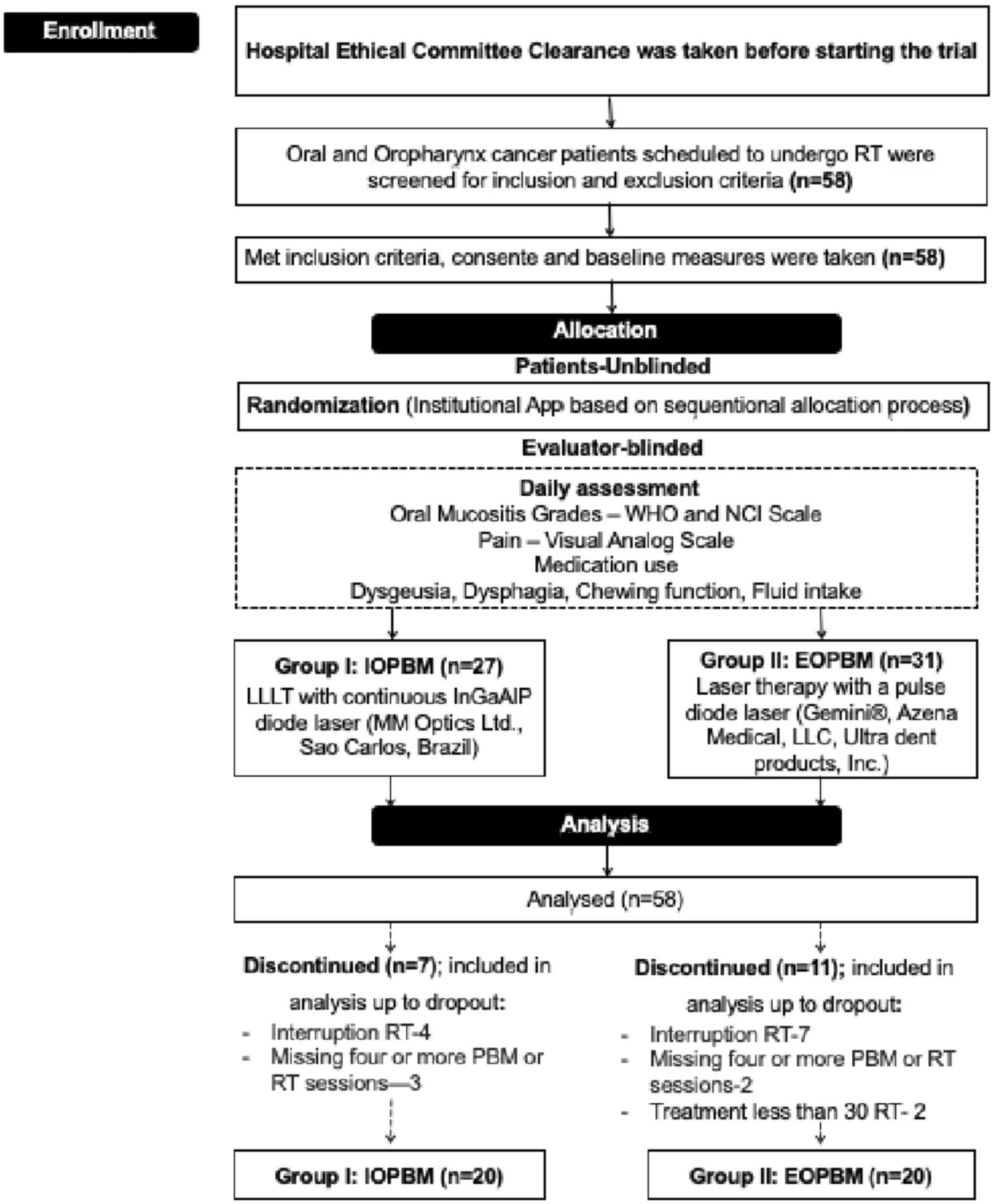

Fig. 1 Flowchart of participants through the trial (CONSORT chart)

Table 1 PBM parameters of IOPBM and EOPBM groups

	Group I	Group II
Parameters	IOPBM	EOPBM
Center wavelengths (nm)	660 ± 10 nm	810 nm + 980 nm (50%/50%)
Operating mode	Continuous	Pulsed
Frequency (Hz)	~50/60	50
Pulse duration (ms)	Contínuous	1
Peak power (W)	0.01	10
Average power (mW)	100	1000
Spot size (cm^2)	0.03	4.91
Beam shape	Round	Round
Beam profile	Gaussian	Gaussian
Irradiance at target (mW/cm^2)	3.333	407
Fluence (J/cm^2)	10	6.11
Exposure duration (s)	3	30
Total radiante energy (J)	0,3	30
Photon fluence ($p.J/cm^2$)	19	8.5
Photon fluence (Einstein)	4.2	1.9
Number of points irradiated	33	10
Application technique	Contact	Contact
Frequency of sessions	5 days a week	5 days a week

on each lip; and points on the anterior neck—right and left submandibular spaces, submental space and right and left neck region (Fig. 2G). Additionally, patients were instructed to position their tongue against the buccal mucosa during irradiation to ensure that the lateral borders of the tongue were exposed to the laser. Special precautions were taken to minimize any unintended irradiation of the tumor area. For instance, in cases where the tumor was located on the tongue, irradiation of the skin adjacent to the tumor area was avoided.

Patients who missed consultation (≥ 4 of applications) for the application of either group were noncompliant and were discontinued from the trial. OM was not evaluated after it.

Clinical evaluation

The primary endpoint of this study was presence and severity of OM. Secondary endpoints were oral pain, functional scores (chewing, swallowing, fluid intake, and taste perception), and use of medication (opioid and non-opioid).

Evaluations included recording the presence of OM, oral pain, functional scores, and use of medication 5 days a week, starting from the first day of RT, and continuing until the final day of RT. All assessments were conducted by a blinded observer who was unaware of the intervention group. All patients were assessed daily

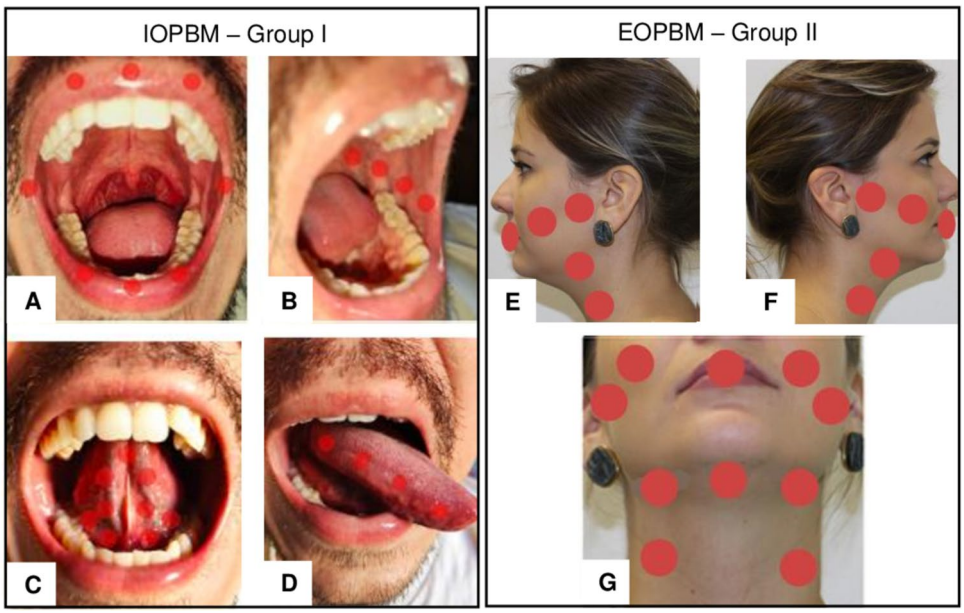

Fig. 2 IOPBM (group I): the irradiations were applied intraorally at a total of 33 points ($3.33\ mW/cm^2 \times 3\ s = 19\ J/cm^2$). Treatment sites: 6 on the mucosa of lip—3 upper and 3 lower and 2 on the labial commissure—1 right and 1 left (**A**); 8 points on the buccal mucosa—4 right and 4 left (**B**); 5 on the ventral surface of the tongue, and 4 on the floor of the mouth—2 on each side (**C**); 8 on lateral edges of the tongue—4 on each side (**D**). EOPBM (group II): the irradiations were performed extraorally at a total of 5 points on the face and 5 points on the anterior neck ($407\ mW/cm^2 \times 30\ s = 8.5\ J/cm^2$). Treatment sites: left face and neck, and 1 on lip (**E**); right face and neck, and 1 on lip (**F**); points on the face—2 on both right and left cheeks, and 1 on each lip; and points on the anterior neck—right and left submandibular spaces, submental space, and right and left neck region (**G**)

for the presence, location, and severity of OM according to the WHO (World Health Organization) [43] and NCI (National Cancer Institute) [44], with severity graded on a scale of 0 to 4. Oral pain was subjectively evaluated using a visual analog scale (VAS), where zero represents no pain and ten indicates the worst possible pain. Patients were instructed to rate their pain level 5 times per week [39]. Additionally, opioid use was monitored according to WHO guidelines for managing oral or oropharyngeal pain, with dosage expressed in morphine equivalents. Functional scores evaluated patients' abilities in chewing, swallowing (dysphagia), fluid intake, and taste perception (dysgeusia). These were rated as no difficulty (zero points), mild difficulty (1 point), moderate difficulty (2 points), severe difficulty (3 points), and impossible (4 points) [45].

Statistical analysis

The sample size was determined based on the results of a preliminary pilot study conducted at our center. The pilot study was used to estimate a proportion of mucositis in the groups. A power analysis was performed using a two-sided test with a significance level (α) of 0.05 and a statistical power (1–β) of 80%. The calculation aimed to detect a difference in the incidence of grades III–IV oral mucositis (OM), with an expected average proportion of 20%, based on WHO criteria. Using these parameters, the estimated minimum sample size required was 21 patients per group. Data were analyzed descriptively by calculating median, mean, standard deviation, absolute value, and percentage of the mean considering day 0 (1st session RT) as the beginning of analysis. The Chi-square and Fisher's exact tests were applied to verify associations between covariables (demographic and clinical features) and the outcomes of OM, to verify the distribution of oral mucosal sites affected by ulcerated mucositis (grade 2 to grade 4), and to verify the mean intensity of oral and throat pain. The Mann-Whitney correlation test was used to evaluate the mean time to OM development and the mean functional scores in both groups. The data were analyzed using IBM SPSS Statistics software version 25.0, and the significance level of 5% ($p < 0.05$) was used.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used ChatGPT in order to review English and reduce the content of the manuscript. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Results

A total of 58 patients were randomized. During the study, 18 patients were discontinued: 11 due to interruption of radiotherapy (RT), 5 due to missing four or more PBM or RT sessions, and 2 because their planned treatment involved fewer than 30 RT sessions. These patients were analyzed based on available data up to discontinuation, and the timing of discontinuation varied among them. The reasons for discontinuation were not related to the intervention. Ultimately, 40 patients completed the full treatment protocol and were included in the per-protocol final analysis.

The demographic and clinical characteristics of the analyzed patients are summarized in Table 2. Among the 58 patients included in the study, 23 were from Hospital de Clínicas de Porto Alegre, 20 from Instituto do Câncer do Estado de São Paulo, and 15 from A.C. Camargo Cancer Center. The mean age of patients was 63.2 years (range 45–80) for the IOPBM group and 56.0 years (range 27–95) for the EOPBM group. Patients in both the IOPBM and EOPBM groups had similar clinical characteristics; the majority were male (69% vs. 31%) and had a history of tobacco and alcohol use. The most common cancer treatment was surgery combined with RT. Most patients (91.4%) received IMRT. There were no statistically significant differences in the demographic and clinical characteristics between groups. Excellent tolerance, with no pain or adverse events, was reported in association with the PBM protocols.

All patients developed some degree of OM during RT. No significant differences were observed between the IOPBM and EOPBM groups across all OM grades (Table 3 and Fig. 3). Additionally, the mean time to the development of ulcerative OM was similar in both groups. Results graded using the NCI and WHO scales were comparable in terms of severity and mean duration of OM.

The distribution of affected mucosal sites in both groups is illustrated in Fig. 4, with the buccal mucosa being the most frequently affected area in both groups. No statistically significant differences were found in the prevalence of ulcerative OM (grades 2, 3, and 4) between the IOPBM and EOPBM groups or in the distribution of affected sites.

Pain was measured daily, but the results were reported in weeks of RT (1 to 6). In general, both groups were similar exhibiting lower mean pain score (maximum of 4.68 and minimum of 1.12). The pain score was similar in the IOPBM when compared in the EOPBM (Table 3 and Fig. 5). Pain analysis separating patients according to whether they had undergone surgery to remove the cancer was performed. Patients who underwent surgery, the mean of VAS was 5.16 (IOPBM group) and 5.88 (EOPBM group), and there was no statistically

Table 2 Demographic and clinical characteristics of participants

Characteristics	IOPBM	EOPBM	Total	*p*-value
Patients (*n*)	27	31	58	-
Age—yr mean (SD)	63.22 (9.92)	56.09 (14.38)	59.41 (12.90)	0.01
Gender, n (%)				
Male	21 (77.80)	19 (61.30)	40 (69.00)	0.28
Female	6 (22.20)	12 (38.70)	18 (31.00)	
Risk factors, *n* (%)				
Tobacco	25 (92.20)	23 (74.20)	48 (82.75)	0.17
Alcohol	22 (81.50)	21 (67.80)	43 (74.10)	0.19
Tumor topography, *n* (%)				
Tongue	13 (48.10)	14 (45.20)	27 (46.60)	1.00
Floor of mouth	1 (3.70)	2 (6.50)	3 (5.20)	1.00
Retromolar área	4 (14.80)	3 (9.70)	7 (12.10)	0.69
Hard palate	0 (0.00)	1 (3.20)	1 (1.70)	1.00
Alveolar	1 (3.70)	0 (0.00)	1 (1.70)	0.46
Gingiva	1 (3.70)	1 (3.20)	2 (3.40)	1.00
Buccal mucosa	1 (3.70)	4 (12.90)	5 (8.60)	0.35
Oropharynx	10 (37.00)	10 (32.30)	20 (34.50)	1.00
Clinical stage, *n* (%)				
Oral, 38 (65.50)				
Stage II	1 (5.30)	0 (0.00)	1 (2.50)	
Stage II	7 (36.80)	5 (23.80)	12 (30.00)	0.52
Stage III	3 (15.80)	6 (28.60)	9 (22.50)	
Stage IV	8 (42.10)	10 (47.60)	18 (45.00)	
Oropharynx, 20 (34.50)				
Stage I	0 (0.00)	1 (10.00)	1 (5.00)	0.43
Stage II	3 (30.00)	3 (30.00)	6 (30.00)	
Stage III	4 (40.00)	1 (10.00)	5 (25.00)	
Stage IV	3 (30.00)	5 (50.00)	8 (40.00)	
Treatment, *n* (%)				
RT	0 (0.0)	1 (3.2)	1 (1.7)	1.00
RT+Surgery	9 (33.3)	11 (35.5)	20 (34.5)	
RT+CT	9 (33.3)	10 (32.3)	19 (32.8)	
RT++Surgery+ CT	9 (33.3)	9 (29.0)	18 (31.0)	
RT protocol, *n* (%)				
IMRT	23 (85.2)	30 (96.8)	53 (91.4)	0.17
3DRT	4 (14.8)	1 (3.2)	5 (8.6)	

significant difference between groups (Mann-Whitney test, $p = 0.52$). Patients who had not undergone surgery had a mean pain score of 7.44 in the IOPBM group and 8.09 in the EOPBM, and there was no statistically significant difference (Mann-Whitney test, $p = 0.94$). The oral analgesic medications used to OM pain control were similar in both groups. Table 3 shows that the mean duration of opioid analgesic use was lower in the IOPBM group (9.91) when compared with EOPBM group (12.47), but there were no significant intergroup differences (Mann-Whitney test, $p = 0.22$).

Both groups showed significant changes in the four functions evaluated throughout the treatment (Friedman test, $p < 0.01$). At two evaluation points—day 20 (week 4) and day 30 (week 6)—patients in the EOPBM group reported significantly better swallowing capacity (dysphagia) compared to the IOPBM group (Mann-Whitney test, $p = 0.02$ and $p = 0.04$, respectively; Fig. 6B). This trend was also observed in patients who had undergone surgery, with those in the EOPBM group showing less difficulty in swallowing (mean score of 0.46) compared to the IOPBM group (mean score of 1.50) on day 20 (week 4) (Mann-Whitney test, $p = 0.02$).

Table 3 Clinical characteristics of participants

Characteristics	IOPBM	EOPBM	Total	*p*-value
Oral candidiasis nº (%)	17 (58.6)	13 (47.6)	30 (50.0)	0.30
Oral mucositis—WHO, nº (%)				
Grade 0	2 (7.4)	3 (9.6)	5 (8.6)	0.69
Grade 1	0 (0.0)	2 (6.4)	2 (3.4)	
Grade 2	10 (37.0)	9 (29.0)	19 (32.7)	
Grade 3	11 (40.7)	15 (48.3)	26 (44.8)	
Grade 4	4 (14.8)	2 (9.6)	6 (10.3)	
Oral mucositis—NCI, nº (%)				
Grade 0	2 (7.4)	3 (9.6)	5 (8.6)	0.82
Grade 1	0 (0.0)	2 (6.4)	2 (3.4)	
Grade 2	14 (51.9)	12 (38.7)	26 (44.8)	
Grade 3	11 (40.7)	13 (41.9)	24 (41.3)	
Grade 4	0 (0.0)	1 (3.2)	1 (1.7)	
Days of grade 3 of oral mucositis—WHO, mean (SD)	6.86 (6.01)	8.93 (6.84)	7.93 (6.43)	0.44
Days of grade 4 of oral mucositis—WHO, mean (SD)	3.50 (2.38)	1.50 (0.70)	2.83 (2.13)	0.53
Days of grade 3 of oral mucositis—NCI, mean (SD)	8.54 (6.26)	8.64 (5.65)	8.60 (5.80)	1.00
Days of grade 4 of oral mucositis—NCI, mean (SD)	0.0 (0.0)	6.0 (0.0)	6.0 (0.0)	-
VAS, mean (SD)				
Week 1	1.12 (2.22)	1.81 (3.17)	1.48 (2.75)	0.79
Week 2	1.45 (1.99)	3.08 (3.20)	2.32 (2.79)	0.08
Week 3	4.04 (3.44)	4.68 (3.10)	4.37 (3.25)	0.57
Week 4	2.48 (2.79)	2.78 (2.84)	2.63 (2.79)	0.68
Week 5	3.75 (3.94)	4.55 (2.43)	4.15 (3.26)	0.46
Week 6	4.50 (4.16)	3.15 (3.37)	3.83 (3.80)	0.49
Days of opioid analgesic use, mean (SD)	9.91 (12.48)	12.47 (10.86)	11.41 (11.41)	0.22
Use of medication, nº (%)				
Opioid use	11 (55.00)	17 (70.80)	6 (10.34)	0.44
Non-opioid use	9 (45.00)	7 (29.20)	28 (63.60)	

On day 25 (week 5), the EOPBM group demonstrated significant improvement in the sense of taste (dysgeusia) compared to the IOPBM group (Fig. 6D), with statistically significant differences (Mann-Whitney test, $p = 0.01$).

At Table 3, the results of IOPBM and EOPBM groups regarding mean of days and the use of medications are detailed. The findings indicate that both groups had comparable patterns of opioid and non-opioid use during the treatment, without significant differences with the overall mean days of opioid analgesic use of 11.41 days.

Discussion

HNC is a highly prevalent malignancy worldwide, and RT—an essential component of its standard treatment—has been strongly associated with the development of OM, a debilitating condition that significantly impacts nutritional intake, quality of life, and treatment adherence [14, 46, 47]. PBM has been established as an effective, non-invasive intervention for the prevention and management of OM, particularly through IOPBM, which is already supported by robust clinical evidence. However, the clinical utility of EOPBM remains less explored [34, 35, 39, 48]. In this context, our study was the first multicenter, randomized, single-blind, controlled clinical trial to directly compare the effects of IOPBM and EOPBM in patients undergoing RT for HNC. Our results demonstrated that both protocols proved to be safe, well tolerated, and similarly effective in reducing OM severity, onset, duration, and pain intensity, with no significant differences in analgesic use. Additionally, EOPBM showed superior outcomes in swallowing function and taste perception at specific time points, suggesting that this approach may offer additional functional benefits and greater comfort in clinical practice.

Since the 1990 s, numerous studies have demonstrated the efficacy of PBM with varied protocols in both the prevention and reduction of the severity of OM, with consistent evidence from clinical trials and systematic reviews confirming its ability to reduce the incidence, duration, and

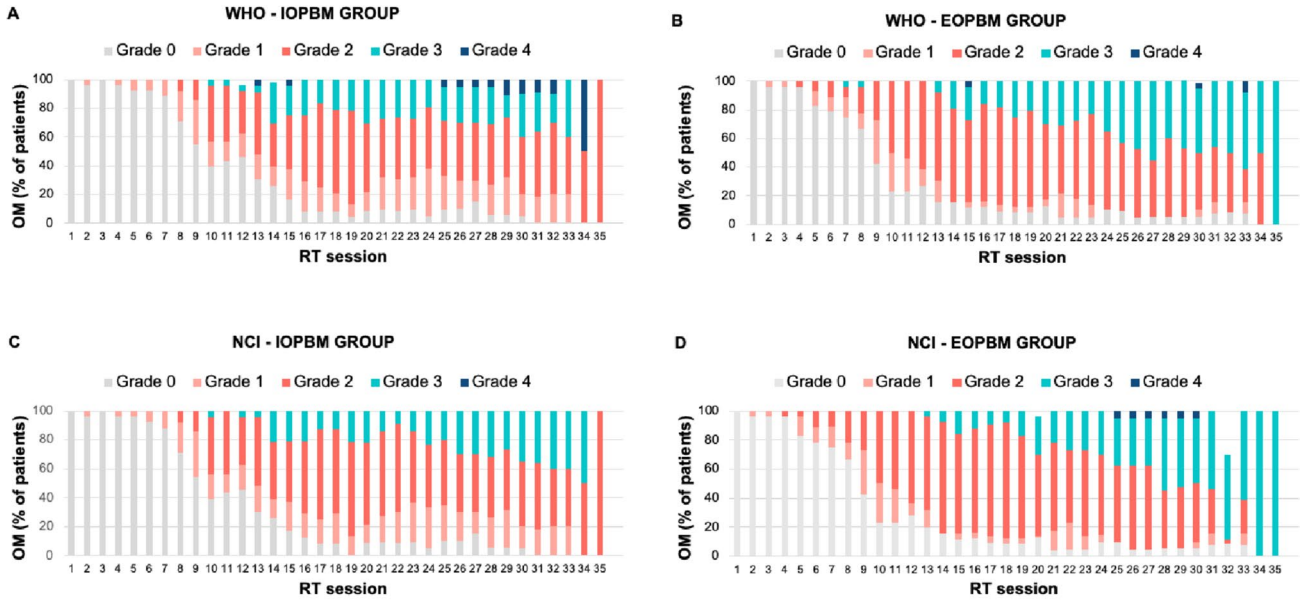

Fig. 3 Comparison of OM incidence between IOPBM and EOPBM groups. **A, B** WHO scale. **C, D** NCI scale

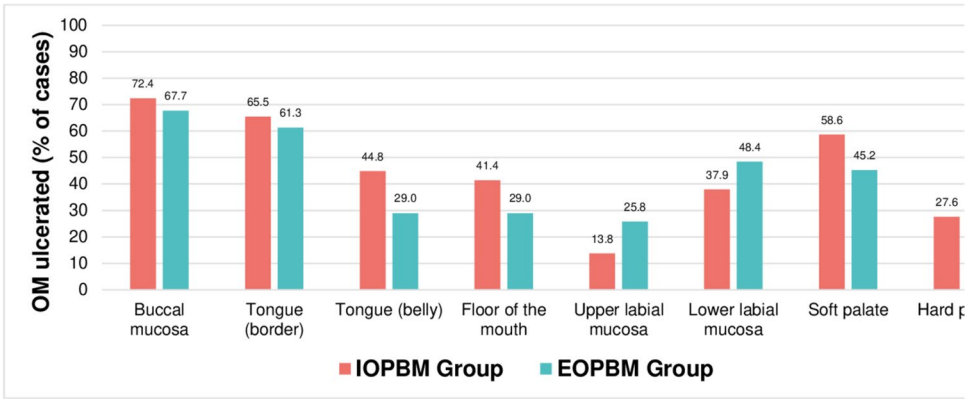

Fig. 4 Comparison of anatomic sites of ulcerated OM (grades 2, 3, and 4) according to IOPBM and EOPBM group

intensity of OM in patients undergoing CT and/or RT [6, 24, 25, 30, 42, 49, 50]. As a result, IOPBM has become well established and is now incorporated into clinical guidelines from the WALT [51] and the MASCC [31]. Patients who do not receive PBM during RT often present with more severe OM [30], while several studies have demonstrated the clinical benefit of various IOPBM protocols [7, 24, 25, 29, 30, 32, 33]. However, the intraoral technique may be uncomfortable or unfeasible in patients with severe oral ulcerations, nausea, trismus, or those undergoing enteral feeding. In this context, EOPBM has emerged as a promising, less invasive alternative, though it remains less explored. In the present study, randomized clinical trials that compared IOPBM and EOPBM demonstrated that both protocols were equally effective in reducing OM severity. IOPBM resulted in grade 3 OM in 40.7% of patients and grade 4 OM in 14.8%. EOPBM showed grade 3 OM in 48.3% and grade 4 OM in only 9.6% of patients. No significant differences were found in the timing or distribution of severe lesions between groups, indicating that light energy applied extraorally was adequately absorbed and bioactive at target tissues. These findings align with those of Thieme et al. who demonstrated that superpulsed EOPBM was more effective than other modalities in reducing mucosal injury and oxidative stress in a hamster model of OM [35]. Similarly, da Cruz Santos et al. and Ramos-Pinto et al. showed that EOPBM was similarly effective to IOPBM in the management of OM in HSCT patients [34, 38]. Notably, Ramos-Pinto et al. reported fewer lesions in the buccal mucosa among patients treated with the extraoral protocol, suggesting a potential advantage in anatomical coverage and clinical comfort [34]. In addition, Yaroslavsky et al. have provided strong support for the anatomical and physiological rationale behind EOPBM, demonstrating through imaging, computational modeling,

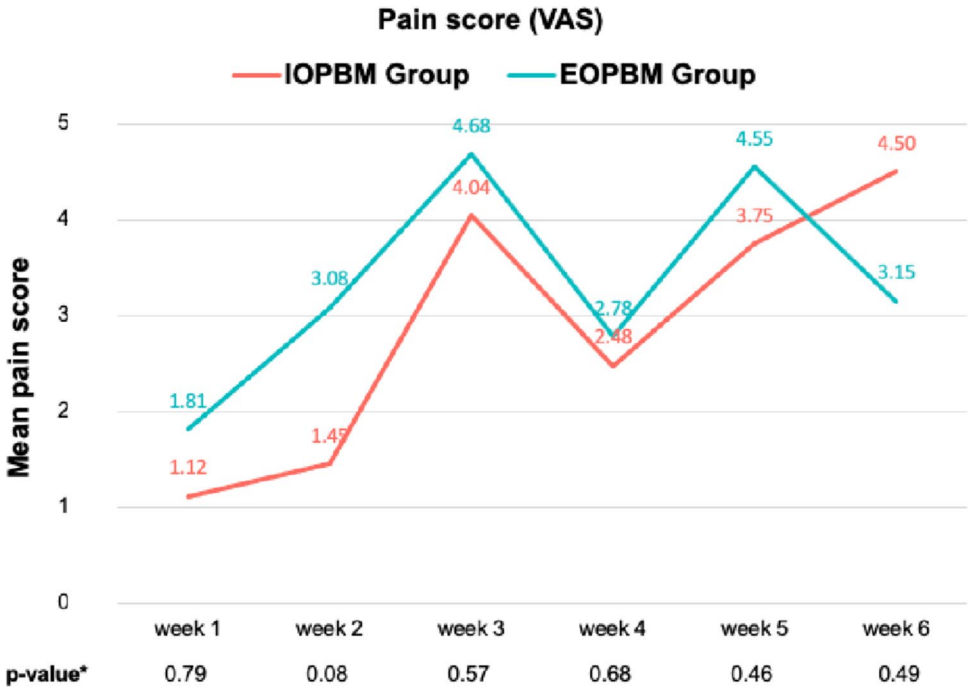

Fig. 5 Comparison of mean pain score according to IOPBM and EOPBM groups. There were no statistician differences between the groups (Mann-Whitney test)

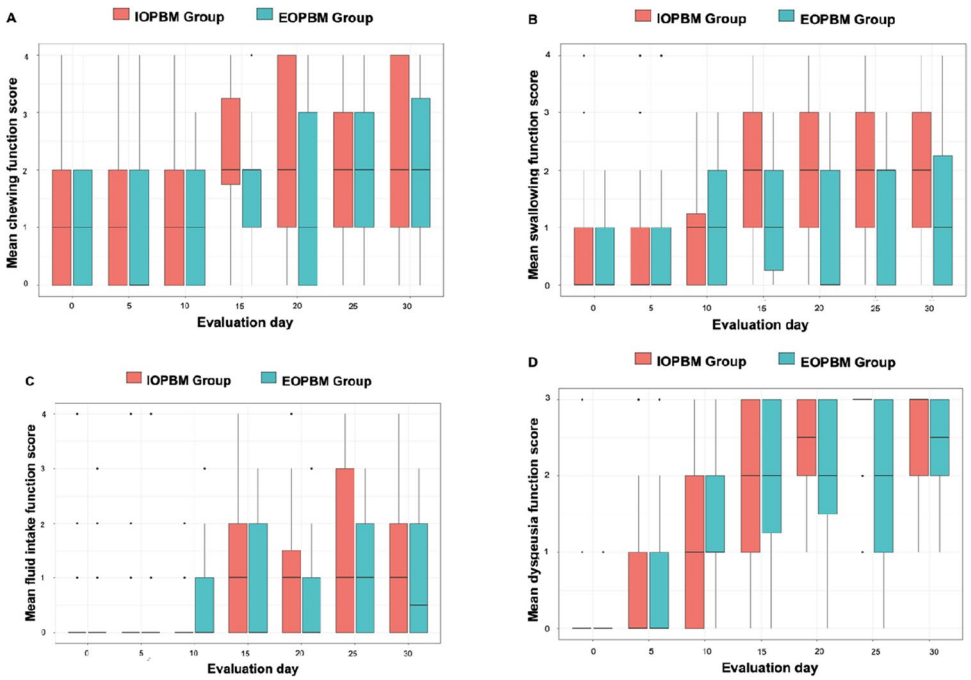

Fig. 6 Mean functional scores (standard error of mean) in IOPBM and EOPBM groups during experimental period. Both groups demonstrated worsening in chewing (**A**), swallowing (**B**), fluid intake (**C**), and dysgeusia (**D**) throughout treatment. Statistically significant differences between the groups were found at day 20 (week 4) and 30 (week 6) of RT in swallowing functional scores (Mann-Whitney test, significant at $p = 0.02$ and $p = 0.04$) and at day 25 (week 6) in dysgeusia functional score (Mann-Whitney test, significant at $p = 0.01$)

and feasibility studies that infrared light (810–980 nm) effectively penetrates orofacial tissues, allowing therapeutic coverage of oral and oropharyngeal regions [52]. Their clinical investigations in both pediatric and adult oncology populations further confirmed the safety, tolerability, and practicality of EOPBM in real-world settings. Froehlich et al. contributed by validating, through Monte Carlo simulations, that therapeutic fluence levels are achievable with optimized dual-wavelength protocols, independent of variations in tissue thickness or skin pigmentation [53]. Although MASCC has not yet endorsed specific EOPBM protocols due to limited high-level evidence, the growing body of data—including our own findings—indicates that EOPBM is not only a viable substitute for IOPBM but may offer logistical and comfort-related advantages in selected clinical scenarios. The WALT guidelines already incorporate

dosing suggestions for both IOPBM and EOPBM, providing a practical framework for clinical application. Thus, the integration of EOPBM into supportive care for cancer therapy-induced OM is justified, evidence-based, and aligned with current trends.

The effect of PBM is attributed to enhanced respiratory metabolism and increased ATP production, which result in elevated cell proliferation and protein synthesis, thereby supporting tissue repair and modulating pain and inflammation [54]. While IOPBM has proven effective, EOPBM, particularly when delivered using high-power defocused superpulsed diode lasers like Gemini®, may offer additional therapeutic benefits. This is largely due to the enhanced tissue penetration afforded by devices that combine dual longer wavelengths (810–980 nm) with a superpulsed emission mode capable of delivering peak powers of up to 100 W. Experimental data have shown that superpulsed lasers (e.g., 904 nm) achieve significantly greater tissue penetration than continuous wave lasers (e.g., 810 nm), with penetration increasing linearly over time and reaching up to 58% of output power after 150 s of exposure [55, 56]. These characteristics allow efficient photonic transmission through biological structures with minimal thermal damage, optimizing photobiological effects in deeper regions such as the oropharynx and upper esophagus. This may help explain the broader therapeutic impact of EOPBM and the improved functional outcomes observed in swallowing (dysphagia) and taste perception (dysgeusia) [57]. Additionally, animal studies have shown that superpulsed 904 nm lasers reduce inflammation, enhance cellular proliferation, promote collagen deposition, and accelerate wound contraction in burn models [58]. Reviews also indicate that pulsed modes (10–100 Hz), including superpulsed emission, may promote superior tissue repair and analgesia when compared to continuous modes, potentially through resonance effects with mitochondrial ion channels [59]. Notably, the World Association for Laser Therapy (WALT) has issued differentiated dosage guidelines based on these differences, recommending lower doses for superpulsed lasers due to their superior penetration and therapeutic efficiency [60, 61].

Although some in vitro, animal, and clinical studies have reported that PBM, when applied using parameters recommended for the management of oral mucositis, does not appear to alter the biological behavior of oral SCC cells, the potential risks remain a matter of debate. Given the current lack of consensus in the literature and in alignment with the precautionary principle, our protocol intentionally excluded the tumor site from PBM application. We understand that PBM is not necessary in the tumor area for effective mucositis management, and its omission does not compromise the therapeutic benefits. Therefore, in all cases, irradiation was carefully planned to avoid the tumor and its immediate surroundings, prioritizing patient safety while adhering to the best available evidence [62–68].

PBM promotes tissue healing and analgesia primarily through the absorption of light by intracellular chromophores, such as cytochrome c oxidase, leading to enhanced mitochondrial respiratory metabolism and increased ATP production. This bioenergetic stimulus results in elevated cell proliferation, protein synthesis, and modulation of oxidative stress and inflammation, thereby supporting tissue repair and reducing pain [54]. While IOPBM has demonstrated clinical effectiveness, EOPBM represents a compelling alternative—especially when delivered using high-power defocused superpulsed diode lasers, such as Gemini®. This approach combines dual longer wavelengths (typically 810–980 nm) with superpulsed emission capable of delivering peak powers up to 100 W, allowing deeper and more effective light penetration through biological tissues with minimal thermal impact. Experimental evidence shows that superpulsed lasers, particularly at 904 nm, outperform continuous wave lasers (e.g., 810 nm) in terms of tissue penetration, reaching up to 58% of output power after 150 s of exposure, with increasing efficacy over time [55, 56]. These optical properties make EOPBM especially suitable for targeting deeper anatomical sites, such as the oropharynx and upper esophagus, and may contribute to improved outcomes in swallowing (dysphagia) and taste perception (dysgeusia) reported in clinical studies [57]. Moreover, animal models have demonstrated that superpulsed 904 nm lasers reduce inflammation, stimulate cell proliferation, enhance collagen deposition, and accelerate wound contraction, reinforcing their biological effectiveness [58]. In addition, pulsed and superpulsed modes (10–100 Hz) appear to offer superior therapeutic effects compared to continuous wave emission, potentially through resonance interactions with mitochondrial ion channels [59]. Given these mechanistic and dosimetric differences, the World Association for Laser Therapy (WALT) has issued specific guidelines recommending lower doses for superpulsed lasers, acknowledging their greater penetration capacity and enhanced therapeutic efficiency [60, 61].

OM-related pain is reported by many patients during RT exacerbating morbidity related to the treatment and worsening quality of life, nutrition, communication, and sleep disturbance [14, 46, 47]. In general, the mean pain score throughout the present study was lower in both groups since VAS > 7 is considered severe pain [69]. EOPBM group presented the peak of mean pain (4.68) at 3 weeks, whereas in IOPBM, the highest mean of pain (4.50) was in week 6 (day 30). In general, both groups were very similar, and clinically, the patients do not present different pattern of oral lesions. Also, during all periods of evaluation, the mean duration of opioid analgesic use was 9.91 days in the IOPBM group and 12.47 days in the EOPBM group being similar statistically

among groups. PBM has been considered as an alternative to opioid analgesia for the management of OM-related pain [65]. Some studies reported significantly less severe oral pain scores and reduced opioid use for PBM-treated patients compared to placebo during RT [7, 24, 48].

The functional score analysis revealed very interesting results. The swallowing function (dysphagia) was improved in the end (week 4 and 6) of the treatment in the EOPBM compared to IOPBM. Usually, patients undergoing RT or CRT for HNC are at an increased risk of developing dysphagia, which is characterized by pain and difficulty swallowing. In general, patients in oncologic treatment have a prevalence of 15.4%. There is a relationship between OM, xerostomia, and dysphagia [70, 71]. Until now, few studies have evaluated the impact of PBM on dysphagia. Three of these studies showed a significant reduction of dysphagia [72–74]. De Pauli Paglioni et al. suggest that the PBM may offer the potential to reduce pain and reduce the use of enteral feeding. The authors of this study report that it is institutional protocol for placement of enteral feeding is according to the patients' needs regarding poor nutritional intake due to dysphagia [74]. Dysphagia has been reported as an endpoint in a few PBM studies; as such, it is difficult to provide protocols of PBM for the management of dysphagia. IOPBM also limits treatment to the distal oral mucosa and oropharynx, areas that are often impacted by OM. EOPBM requires longer wavelengths compared to IOPBM (i.e., 800–900 nm) to increase penetration depth in the tissues. EOPBM would offer a broader treatment area, allowing for the inclusion of the oral cavity, the oropharynx, and the upper esophagus [53]. However, in the present study, it was a positive aspect of EOPBM therapy that could be explained by the fact that the extraoral application of high-power defocused infrared wavelengths (810 + 980 nm) with a super-pulsed laser probably permits the laser light to penetrate more and target deeper tissues improving the PBM efficacy [34, 35, 38, 75]. Another oral function that improved with EOPBM towards the end (week 5) of the RT or RT-CT protocol was dysgeusia. Dysgeusia is a taste disorder characterized by a persistent gustatory sensation in the absence of taste stimuli or a distorted taste perception. This complication is common, affecting approximately 66.5% of patients after RT alone and 76% following CRT [76]. So far, there are no adequate management options to decrease the prevalence of taste problems [76, 77]. While a few studies have reported positive outcomes [72, 78], only one clinical trial has investigated the use of PBM for managing dysgeusia [79]. As a result, the potential utility of PBM in addressing dysgeusia in cancer patients remains limited. Although existing data are insufficient to establish clinical treatment guidelines, WALT recommends both IOPBM and EOPBM applications, emphasizing the need for better-designed clinical studies. The lower dysgeusia in the EOPBM group compared to the IOPBM group can also be explained by the greater depth of light penetration in the extraoral technique.

The main limitation of this study is the absence of a concurrent control group. However, this is justified by the fact that PBM is already incorporated into international guidelines and has been part of the standard of care for the prevention of OM in our institution for over two decades. Given its well-established efficacy and the ethical considerations involved in withholding a beneficial intervention, implementing a control group without PBM would not be feasible or appropriate in our clinical setting. As such, all patients routinely receive PBM as part of supportive care during oncologic treatment, which reflects real-world practice and reinforces the translational relevance of our findings.

Additionally, in line with current safety recommendations and the precautionary principle, the tumor area and its immediate surroundings were deliberately excluded from PBM application. Although evidence from in vitro, animal, and clinical studies suggests that PBM delivered within therapeutic parameters does not promote tumor growth or alter the biological behavior of oral SCC, a definitive consensus is still lacking. As a safety measure, irradiation was carefully planned to avoid direct exposure to the tumor, without compromising mucositis prevention or treatment outcomes. This approach reflects a clinically responsible strategy that balances efficacy with patient safety, adhering to the best available evidence.

In conclusion, both the IOPBM and the EOPBM protocols produced comparable results in preventing OM in HNC patients. However, EOPBM showed promising results in terms of dysphagia and dysgeusia. Other studies are encouraged to define optimal EOPBM laser parameters and further develop this modality as a potential standard of care for the prevention and treatment of OM.

Acknowledgements This study was supported by Postgraduate Research Group of Porto Alegre Clinics Hospital (GPPG/FIPE: 2020-0189), Brazilian National Council for Scientific and Technological Development (CNPq student scholarship), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior-Brasil (CAPES). We also acknowledge the Brazilian National Council for Scientific and Technological Development (CNPq). A.R.S.S., F.A.A, and M.D.M. are research fellows of CNPq.

Author contribution Study design: Manoela Domingues Martins, Fabio Abreu Alves, Ana Carolina Prado Ribeiro e Silva, Thaís Bianca Brandão, Alan Roger Santos-Silva e Marco Antonio Trevizani Martins; Data collection: Isadora Peres Klein, Mariana Bitu Ramos Pinto, Bruna Barcelos Só, Amanda de Farias Gabriel, Nathália Felix Mendonça, Letícia Beatriz da Cruz Santos, Karina Morais Farias, Ana Leticia Mores; Data analysis: Isadora Peres Klein, Mariana Bitu Ramos Pinto, Manoela Domingues Martins; Manuscript preparation: Isadora Peres Klein, Manoela Domingues Martins, Fabio Abreu Alves, Ana Carolina Prado Ribeiro e Silva; Manuscript review: all authors.

Data availability We declare that all data used in the study are available if necessary.

Declarations

Ethics approval and consent to participate The study was approved by the Ethics Committee of the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil (no. 2020-0189); A.C.Camargo Cancer Center, São Paulo, Brazil (no. 3033/21); and the Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil, in accordance with Good Clinical Practice guidelines and Brazilian law. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Competing interests Manoela D. Martins would like to disclose that she serves on Azena Medical as a consultant.

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