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Photobiomodulation for restoring salivary flow after radiotherapy in head and neck cancer: a randomised placebo-controlled trial

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Abstract

Background Head and neck cancer (HNC) treatment modalities, especially radiotherapy (RT), often lead to salivary gland dysfunction, resulting in hyposalivation and xerostomia, which impair patients' quality of life. Photobiomodulation (PBM) therapy, a noninvasive approach using nonthermal red/near-infrared light, has shown promise in mitigating these side effects. This study evaluated the impact of PBM therapy on salivary flow, biochemical biomarkers, patient-reported outcome measures and mouth opening in patients with HNC suffering from chronic xerostomia after RT.

Methods In a prospective, two-arm, randomised, placebo-controlled, double-blinded trial, 31 adult patients with HNC in complete remission and chronic xerostomia (> 3 months after RT) were enrolled. Participants were randomised (1:1) to receive either active PBM therapy or a sham intervention. The PBM protocol employs an 830 nm diode device applied intra- and extraorally over 24 sessions (twice weekly for 3 months) targeting the major salivary glands. The outcome measures assessed at baseline, 3 months (postintervention), and 6 months included the unstimulated salivary flow rate (SFR) by sialometry, total protein and IgA (sialochemistry), quality of life via European Organisation for Research and Treatment of Cancer (EORTC) questionnaires, severity of xerostomia, dysphagia, and mouth opening. Data were analysed using repeated measures analysis of covariance (ANCOVA) (adjusting for relevant covariates) and nonparametric tests, as appropriate.

Results Compared with the placebo group, the PBM group presented a nearly significant increase in the SFR (0.22 ± 0.29 vs. 0.05 ± 0.15 ml/min, $p = 0.051$; effect size $d = 0.75$) after the intervention. A responder analysis revealed that five patients in the PBM group shifted from hyposalivation (SFR < 0.25 ml/min) to normal salivary flow, whereas no such change was observed in the placebo group ($p = 0.048$). Both groups reported similar levels of satisfaction and adherence, and no adverse events were recorded.

Conclusions PBM therapy demonstrated potential benefits in improving salivary flow among oncological patients with chronic RT-induced xerostomia, suggesting possible regenerative effects on the salivary glands. Despite the objective improvements in the SFR, changes in biochemical markers and the remaining outcome measures were

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less definitive in patients with HNC. Further studies with larger sample sizes are needed to confirm these preliminary findings and better delineate the clinical utility of this therapy.

Trial registration This trial was registered on ClinicalTrials.gov (NCT05614843) and First Posted date [2022-11-14].

Keywords Head and neck neoplasms, Low-level light therapy, Quality of life, Xerostomia

Background

Head and neck cancer (HNC) involves the mucosal surfaces of the upper aerodigestive tract, including the oral cavity, pharynx, larynx, paranasal sinuses, and major and minor salivary glands [1]. Most of these tumours are squamous cell carcinomas, for which radiotherapy (RT) is a key treatment modality that allows for organ preservation [2]. Advancements in RT techniques [3] not only provide clinical benefits but also cause undesirable side effects. Among these known effects, salivary gland dysfunction is among the most prevalent and can significantly impact the quality of life (QoL) of long-term survivors [4]. RT causes direct (damage to DNA) or indirect (release of free radicals) local toxicity to salivary glands and oral tissues [5]. Salivary changes are both quantitative (sialometry) and qualitative (sialochemistry) [6–8] and have implications for maintaining oral hygiene and facilitating a wide variety of oral functions (i.e., eating and swallowing). Additionally, xerostomia (dry mouth sensation) also plays an important role in patients' oral health [8]. Therefore, survivors with HNC can have complex ongoing needs related to the consequences of their oncological treatment, particularly RT.

Xerostomia is often associated with the use of certain medications, mainly anticholinergics, antiparkinsonian agents, antihistamines, and antidepressants [9]. Other contributing factors include polymedication in elderly individuals, radiation to the head and neck (as previously mentioned), and Sjögren's syndrome, conditions in which nearly all patients experience xerostomia [10]. Hyposalivation, defined as an unstimulated salivary flow rate (SFR) below 0.25 ml/min [11], frequently coexists with xerostomia when the SFR decreases to less than 50% of its baseline value [12]. Accordingly, a comprehensive assessment of these side effects is crucial for designing targeted interventions aimed at improving the QoL of patients.

Nonpharmacologic interventions such as artificial saliva, electrical nerve stimulation, acupuncture, low-level light therapy, stem cells, chewing gum, and even probiotics have been studied as alternatives to pharmacologic saliva stimulants such as pilocarpine and cevimeline [13]. While promising, these interventions often present limitations, providing only short-term relief in most cases. In this context, low-level light therapy, renamed photobiomodulation (PBM), has emerged as a noninvasive option. PBM uses nonthermal red or near-infrared light within the 600–1100 nm wavelength range to reduce salivary gland hypofunction and enhance overall QoL in both animal and human studies [14]. However, despite growing evidence, consensus is still lacking regarding the optimal stimulation parameters for each condition [15, 16].

With respect to RT-induced salivary gland dysfunction, PBM therapy is used both as a preventive agent (before or during RT) and as a therapeutic agent (after RT). Preventive applications are more widely supported by the scientific literature, possibly because the glandular parenchyma is less structurally damaged at this stage, preserving more of its residual functional capacity [17, 18]. In contrast, managing hyposalivation/xerostomia with long-lasting effects remains a significant challenge. Development of a beneficial therapeutic strategy is a key goal; however, this requires a viable residual volume of glandular tissue after RT [19] to achieve an effective response [20]. To address these challenges, studies with larger sample sizes are crucial to substantiate the clinical potential of PBM therapy and establish standardised treatment parameters. Furthermore, including a sham control group in research designs is recommended to neutralise the recognised placebo effect [21].

Given the lack of high-quality evidence on the therapeutic application of PBM in patients with HNC suffering from chronic xerostomia, the purpose of this research was to assess the impact of PBM therapy on sialometry, sialochemistry, QoL, xerostomia, dysphagia, and mouth opening after RT.

We hypothesised that patients receiving active PBM therapy would show significantly greater improvements in objectively measurable outcomes, specifically in sialometry and sialochemistry, than those receiving placebo treatment.

Methods

Study design and ethical aspects

This study was conducted in accordance with the CONSORT guidelines for reporting randomised clinical trials. A prospective, two-arm, randomised, placebo-controlled, double-blinded trial was conducted among patients with HNC who experienced chronic xerostomia (> 3 months) [22] after RT to determine the preliminary efficacy of PBM therapy. The trial was prospectively registered at Clinicaltrials.gov (NCT05614843, First Posted date 2022-11-14). Patients were recruited through the Departments

Table 1 Eligibility of criteria

Nº	Inclusion criteria	Exclusion criteria
1	Adult patients with oncological treatment finished and in complete remission of HNC	Presence of metastases
2	Enough time since the end of RT to avoid the possible presence of oral mucositis and/or radiodermatitis, which limits adherence	Karnofsky Performance Status Scale < 60
3	Grade 3 oral dryness according to CTCAE version 5.0	Contraindications to receiving PBM therapy
4	No use of drugs/devices/products to prevent or treat xerostomia prior to study inclusion, or stability in type and dose for at least two months	Other comorbidities such as diabetes and polymedication

RT must be received in parotid, submandibular and/or sublingual salivary glands; Drugs/devices/products such as pilocarpine, cevimeline, amifostine, oral devices, humidifiers, or herbs; Contraindications to receiving PBM therapy such as cardiac arrhythmias, pacemakers, photosensitivity, drugs with photosensitizing action, or pregnancy

Abbreviations:CTCAE Common Terminology Criteria for Adverse Events version 5.0, *HNC* Head and Neck Cancer, *PBM* Photobiomodulation, *RT* Radiotherapy

of Radiation Oncology from both Virgen de las Nieves University Hospital (Granada) and Jaén University Hospital (Jaén).

All patients received verbal and written information about the study and provided written informed consent before participating. Ethical approval was obtained from the Andalusian Biomedical Research Ethics Portal (1552-N-18 CEIM/CEI Provincial de Granada). The study was conducted in accordance with Law 14/2007 on Biomedical Research [23] and the current version (2024) of the guidelines of the World Medical Association Declaration of Helsinki [24].

Study setting

Eligible participants who met the inclusion criteria (Table 1) were referred to the facilities of the BIO277 (Cuidate) research group for baseline assessment.

Sample size

The sample size calculation was based on repeated measurements within factors. The parameters included a 95% confidence level, 76% statistical Power, and a two-sided alpha of 5% [25]. Using an effect size (ES) of 0.45 (Cohen's d), a minimum of 15 participants per group was needed, as reported in a previous study detecting differences in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module 35 (EORTC QLQ-H&N35) on dry mouth [26]. Considering a dropout rate of 5%, 32 patients were ultimately included (16 per group).

Intervention

PBM therapy was performed with the model IIIb BTL-458-10IC BTL-4000 Smart (approved by the Food and Drug Administration). The parameters were standardised following previously published guidelines to ensure reproducibility [27]. PBM therapy in this study involved the use of a device with the following machine and user-determined settings: a wavelength of 830 nm, a spot size of 0.021 cm^2, an application time of 3 s per point, and a Power output of 53 mW; even though the irradiation power was relatively low, the irradiance was supraoptimal [14] with a value of 2.52 W/cm^2 and achieved an energy density of 7.5 J/cm^2. All intervention parameters have been detailed elsewhere as PBM-A [28], and have previously been applied following a similar protocol in patients after RT in a study led by Palma et al. [29]. The intervention encompassed intra- and extraoral applications after RT, which were conducted twice weekly over 24 sessions within a 3-month period. Each session targeted 6 extraoral points per parotid gland, 3 extraoral points per submandibular gland, and 2 intraoral points per sublingual gland, resulting in 22 points per session. Figure 1 shows the number of irradiated points (extraoral and intraoral) per gland. Any adverse event (AE) with a direct relationship to study participation constituted a reason to discontinue the allocated intervention.

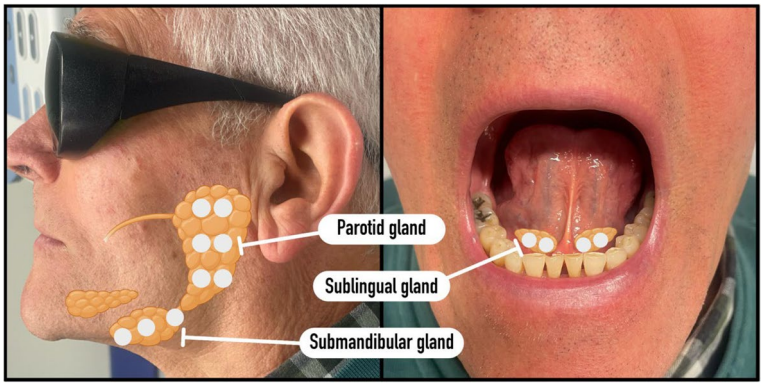

Fig. 1 Number of irradiated points (extraoral and intraoral per gland)

During the sessions, the physiotherapist and patients wore safety goggles with special lenses, and the hand device was covered with disposable transparent plastic wrap in intraoral applications. The device was disinfected with a 70% alcohol solution. The same procedure was used for the sham PBM therapy; however, the device was turned off, and a recording with emission sounds was used.

Randomisation and blinding

After baseline assessments, the participants were randomised into two groups using a computer-based random number generator (www.randomizer.org) with a 1:1 allocation ratio. Blinding was implemented to minimise bias: the assessor who conducted evaluations of saliva and its biochemical biomarkers as well as all patients were blinded to which intervention they received; however, the research staff responsible for delivering the intervention and assigning patients to groups were not blinded. For ethical reasons, patients in the placebo group were offered the option to receive active PBM therapy after completing the study.

Outcome measures

Assessments were conducted at the beginning of the study before randomisation (T0), 3 months postintervention (T1) and 6 months postintervention (T2).

Sociodemographic and clinical characteristics

Sociodemographic characteristics included age, height, race, sex, educational level, and tobacco and alcohol consumption, whereas clinical characteristics included cancer stage, type of RT received and dose, among others. In addition, body weight, lean mass and fat content were also assessed via an InBody720 bioelectrical impedance device (Biospace, Seoul, Korea) following the instructions of the user's manual [30]. The intraclass correlation coefficient (ICC) for this technique was 0.95 for muscle mass and 0.93 for body fat [31].

Salivary flow rate and volume (sialometry)

The unstimulated SFR was calculated in millilitres per minute (ml/min). Saliva was obtained with the patient seated and the head slightly inclined forwards. Patients expelled the saliva into sterile and graduated tubes for 3 min [32]. All salivary samples were collected in the early morning between 10:00 and 11:30 AM; this timing was consistently maintained for initial and subsequent assessment samplings to ensure comparability.

To ensure the purity and reliability of the saliva samples, patients were asked to refrain from the following before the assessment: a) drinking alcohol, coffee or stimulant substances within the previous 8 h; b) performing intense physical exercise within the previous 24 h; c) brushing their teeth (due to possible gum bleeding) within the previous 2 h; d) eating within the previous 2 h; e) chewing gum within the previous 2 h; f) smoking within the previous 2 days; g) applying lipstick; and h) taking any nonroutine medication on the day of the assessment (e.g., painkillers, anti-inflammatories, antibiotics).

The volume of each sample was calculated in microlitres (µl), and the sputum was manually pipetted to measure the volume. From this measurement, the SFR was calculated (volume/time in minutes). The mixture was subsequently centrifuged at 3,500 rpm for 15 min at 4 °C to remove possible debris, such as insoluble material, cells and food debris. The supernatant of each sample was fractionated in Eppendorf tubes of at least 100 µl and frozen at −80 °C until analysis.

Salivary biochemical biomarkers (sialochemistry)

Total protein and immunoglobulin A (IgA) concentrations were determined in saliva samples. For total protein, a Coomassie (Bradford) protein assay kit (Thermo Scientific, MA, USA) was used. The assay was performed according to the manufacturer's standard microplate protocol. Briefly, 10 µl of bovine serum albumin (BSA) standard or saliva sample and 300 µl of Pierce™ Bradford protein assay reagent were added to each well. The absorbance at 595 nm was determined after shaking (30 s) and incubation at room temperature for 10 min. Finally, the subtracted absorbances for the blank replicates were plotted for each BSA standard, and the total protein amount in the saliva was calculated. The results are expressed as micrograms per millilitre (µg/ml). The concentration of IgA in the saliva samples was determined via the Human IgA ELISA kit (ab137980; Abcam, Cambridge, UK) according to the supplier manual. Briefly, 50 µl of each saliva sample (diluted 1:1000) was added to each well and incubated at room temperature for 2 h. After washing, the wells were incubated with biotinylated IgA antibody at room temperature for 1 h. After washing again, the wells were incubated with the conjugate at room temperature for 30 min and with the chromogen substrate in ambient light for 12 min. Finally, the stop solution was added, and the absorbances at 450 nm and 570 nm were read. Subtracted absorbances (450–570 nm readings) were plotted for each IgA standard, and the saliva IgA concentration was calculated after multiplication by the dilution factor. The results are expressed as µg/ml.

Patient-reported outcome measures

QoL was evaluated using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 version 3.0 (EORTC QLQ-C30) [33]. All the single items and scales range in score from 0 to

100, with higher scores for functional and global health status indicating better functioning or global QoL. In our study, we only used the global health and physical function scales [34, 35]. This is a Spanish validated and reliable questionnaire in HNC, with good reliability levels for both scales (Cronbach's alpha > 0.70) [36]. Additionally, the head and neck module (EORTC QLQ-H&N35) [37] was assessed. Higher scores indicate greater symptom severity. This module has also been shown to be reliable (Cronbach's coefficient > 0.70) [38]. Only single items and a multi-item scale directly related to oral health, i.e., dry mouth, sticky saliva, mouth opening and swallowing, were considered [35, 39].

The severity of xerostomia was assessed using the Xerostomia Inventory (XI), which consists of 11 items (scores ranging from 1–5), with a total score ranging from 11–55 points, where a higher score indicates more severe xerostomia. The Spanish version of the XI has Cronbach's alpha values of 0.89 and 0.87 in the first and second applications, respectively [40]. The scores are expressed as the means and medians.

Dysphagia was measured using the Eating Assessment Tool (EAT-10). This questionnaire has 10 items related to swallowing difficulties (score range 0–4, 0 = no problems, 4 = severe problems), with a Cronbach's alpha value of 0.96 [41].

Range of motion

Mouth opening was determined by the range of motion (ROM) using a sliding calliper, which measures the maximal interincisal distance in centimetres (cm).

Other outcome measures

Safety, satisfaction, and adherence rates

The occurrence of any AEs was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [42], whereas satisfaction was registered by a questionnaire (yes/no) previously used in other clinical settings at the end of the intervention [43] in addition to the mean level of satisfaction (0–10). Adherence was calculated as the number of sessions that the patient received in total.

Data analysis

Descriptive statistics were used to summarise the sociodemographic and clinical characteristics of the sample. The normal distribution of numerical variables was assessed using the Shapiro–Wilk normality test. Baseline comparisons between groups were performed using the independent t test for continuous variables (or their nonparametric equivalents) and the chi-square test (or Fisher's exact test) for categorical variables.

To evaluate the effect of the intervention over time, repeated measures analysis of covariance (ANCOVA) with Bonferroni adjustment for multiple comparisons was applied to normally distributed variables. Analyses were adjusted for the following covariates: age, cancer stage, time since the end of RT, type of RT, RT dose, glandular dissection and xerostomia drug/product intake. ESs were calculated using Cohen's d with 95% confidence intervals (CIs). For variables not meeting parametric assumptions, square root transformation was applied. If normality could not be achieved, between-group effects were evaluated using the Mann–Whitney U test, whereas within-group effects were assessed using the Friedman test, with Wilcoxon signed–rank tests conducted post hoc if significant differences were identified.

A responder analysis was also performed to identify patients who achieved an SFR > 0.25 ml/min postintervention [11], followed by a chi-square test to identify significant differences between groups.

The intention-to-treat principle was adopted, and multiple imputations were conducted (20 imputations) for patients with missing data on outcomes (see Fig. 2).

All analyses were performed using IBM SPSS Statistics version 26 (Armonk, NY), with the significance level set at $p < 0.05$. Higher p values ($p < 0.10$–0.15) are considered exploratory in smaller sample sizes owing to potential clinical relevance [44]. Analytical decisions were guided by recommendations against sole reliance on p values [45].

Results

Among the 56 patients eligible for inclusion in the study, 32 agreed to participate (Fig. 2). After applying the inclusion and exclusion criteria, 31 patients completed the baseline assessment and were subsequently randomised to start the assigned intervention. After allocation, one patient declined to participate, leaving 16 patients in the PBM group and 15 patients in the placebo group.

The sociodemographic and clinical characteristics were comparable between the groups (Table 2). The cohort study included different primary tumour locations following the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) [46] and National Comprehensive Cancer Network (NCCN) [47] guidelines for HNC, with the most common location being the nasopharynx (37.5%) in the PBM group and the oropharynx/larynx (26.7% each) in the placebo group.

Baseline analysis did not reveal significant differences between the groups for any study outcome measure, indicating their balance at the commencement of the study.

No significant group × time interaction effect was observed for the SFR ($F = 3.24$, $p = 0.154$). The influence of covariates had no effect on the interaction. Bonferroni post hoc ANCOVA revealed a nearly significant improvement in the SFR in the PBM group compared with that in the placebo group (0.22 ± 0.29 vs. 0.05 ± 0.15 ml/

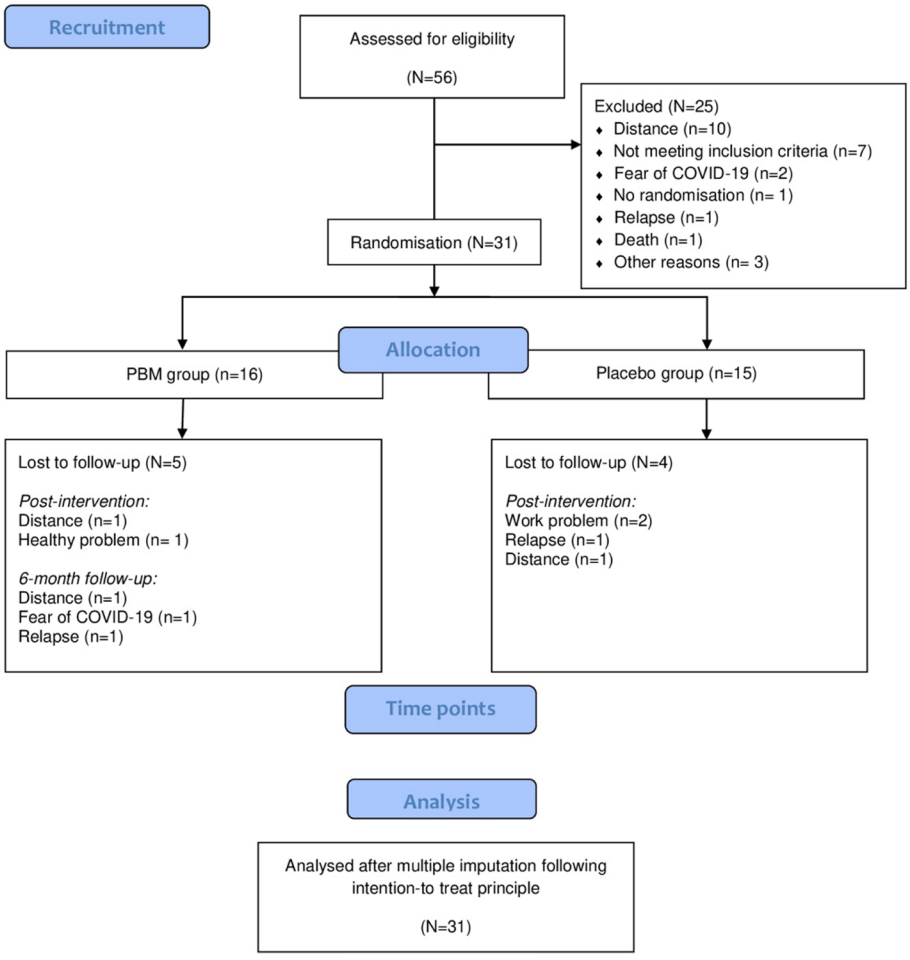

Fig. 2 Flowchart

min, $p = 0.051$) after the intervention (Table 3). The ES for between-group differences after intervention was moderate (d = 0.75 95% CI 0.67, 0.83). Nonetheless, no between-group effects were observed at the 6-month follow-up (Table 3). Within-group analysis also revealed an increase in the SFR in the PBM group (0.22 ± 0.29 ml/min, $p = 0.009$) after the intervention (Table 3 and Fig. 3a). However, the placebo group did not show significant within-group change either after the intervention (Fig. 3b) or after follow-up (Table 3).

A responder analysis was performed with the SFR using the cut-off point of > 0.25 ml/min for a normal SFR. At the baseline assessment, both groups had similar SFRs, and more than half of the patients in both groups experienced hyposalivation (low SFR < 0.25 ml/min). However, after PBM therapy, the SFR of 5 patients in the PBM group changed from low to normal (Table 4), whereas the SFR of none of the patients in the placebo group changed. There was a statistically significant difference in the postintervention SFR distribution between the groups ($p = 0.048$).

Consistent with previous results, no significant group × time interaction effect (F = 2.00, $p = 0.407$) was observed for salivary volume. The influence of covariates had no effect on the interaction. Within-group analysis revealed a significant increase in the PBM group (387.30 ± 351.54 µg/ml, $p = 0.001$) after the intervention; this increase was maintained during the follow-up period in the PBM group (465.74 ± 460.69 µg/ml, $p = 0.022$). The placebo group did not show significant within-group differences at any time point ($p > 0.05$) (Table 3).

With respect to sialochemistry, no significant group × time interaction effect was detected for total protein (F = 0.18, $p = 0.836$) (Table 5). Additionally, the influence of covariates did not affect the interaction for total protein. No statistically significant changes were detected within the PBM and placebo groups ($p > 0.05$) at any time point. The concentration of IgA did not significantly differ between the groups at any time point (Mann–Whitney U test: baseline–postintervention, $p = 0.892$; baseline–6 months, $p = 0.545$). However, a significant within-group effect was observed for IgA in the PBM group (Fr = 11.08, $p = 0.004$) and in the placebo group

Table 2 Sociodemographic and clinical characteristics

	PBM group (*n* = 16)	Placebo group (*n* = 15)	*P* value
Age (years), mean (SD)	58.38 (7.69)	62.67 (12.06)	0.24
Height (m), mean (SD)	1.66 (7.99)	1.68 (8.00)	0.60
Weight (kg), mean (SD)	82.81 (20.51)	76.07 (16.03)	0.32
Lean mass (kg), mean (SD)	30.99 (7.14)	29.73 (5.33)	0.58
Fat content (%), mean (SD)	31.33 (14.50)	28.29 (9.48)	0.50
Race, n (%)			
Caucasian	16 (100)	14 (93.3)	0.48[a]
Arabic	0 (0)	1 (6.7)	
Sex, n (%)			
Women	5 (31.3)	4 (26.7)	1.00[a]
Men	11 (68.8)	11 (73.3)	
Educational level, n (%)			
Basic	8 (50)	4 (26.7)	0.13[a]
Medium	6 (37.5)	4 (26.7)	
High	2 (12.5)	7 (46.7)	
Tobacco consumption, n (%)			
Yes	1 (6.3)	2 (13.3)	1.00[a]
No	5 (31.3)	4 (26.7)	
Ex-smoker	10 (62.5)	9 (60)	
Alcohol consumption, n (%)			
Yes	6 (37.5)	8 (53.3)	0.58[a]
No	5 (31.3)	5 (33.3)	
Ex-consumer	5 (31.3)	2 (13.3)	
Cancer stage, n (%)			
Stage I	1 (6.3)	0 (0)	0.23[a]
Stage II	2 (12.5)	2 (13.3)	
Stage III	5 (31.3)	1 (6.7)	
Stage IV	8 (50.0)	12 (80)	
Primary tumour location, n (%)			
Oral cavity	3 (18.8)	1 (6.7)	0.64[a]
Oropharynx	2 (12.5)	4 (26.7)	
Larynx	3 (18.8)	4 (26.7)	
Hypopharynx	0 (0)	1 (6.7)	
Nasal cavity and paranasal sinuses	1 (6.3)	1 (6.7)	
Salivary glands	1 (6.3)	1 (6.7)	
Nasopharynx	6 (37.5)	2 (13.3)	
Occult primary cancer	0 (0)	1 (6.7)	
Oncological treatment, n (%)			
Surgery and RT	4 (25)	2 (13.3)	0.11[a]
Chemoradiotherapy	10 (62.5)	6 (40)	
Surgery and chemoradiotherapy	2 (12.5)	7 (46.7)	
Glandular irradiation, n (%)			
One-side	3 (18.8)	1 (6.7)	0.1.00[a]
Two-sides	13 (81.3)	14 (93.3)	
Time since the end of RT (months), mean (SD)	28.25 (19.82)	38.07 (27.60)	0.26
Type of RT, n (%)			
RT3D	6 (37.5)	10 (66.7)	0.21[a]
IMRT_IGRT	1 (6.3)	0 (0)	
VMAT_IGRT	9 (56.3)	5 (33.3)	
RT dose (Gy), mean (SD)	66.62 (4.22)	67.27 (3.55)	0.65
Glandular dissection, n (%)			
Yes	3 (18.8)	3 (20.0)	1.00[a]
No	13 (81.3)	12 (80.0)	

Table 2 (continued)

	PBM group ($n=16$)	Placebo group ($n=15$)	*P* value
Xerostomia drug/product intake, n (%)			
Yes	2 (12.5)	4 (26.7)	0.39[a]
No	14 (87.5)	11 (73.3)	

Abbreviations:Gy Gray (unit of radiation dose), *IGRT* Image-guided radiation therapy, *IMRT* Intensity-Modulated Radiation Therapy, *PBM* Photobiomodulation, *RT* Radiotherapy, *RT3D* Three-Dimensional Conformal Radiation Therapy, *VMAT* Volumetric Modulated Arc Therapy

[a]Fisher exact test

Table 3 Means, standard deviations, and 95% confidence intervals for the mean within- and between-group effects for sialometry

	PBM group $n=16$	Placebo group $n=15$	*Between-group effect*
SFR (ml/min)			
Baseline	0.24 ± 0.37 [0.12, 0.36]	0.19 ± 0.25 [0.05, 0.33]	
Postintervention	0.45 ± 0.31 [0.29, 0.62]	0.23 ± 0.23 [0.11, 0.36]	
6-month follow-up	0.37 ± 0.31 [0.20, 0.53]	0.26 ± 0.31 [0.08, 0.43]	
Within-Group Effect			
Baseline-postintervention	0.22 ± 0.29 [0.06, 0.37]*	0.05 ± 0.15 [−0.04, 0.13]	0.17 [−0.001, 0.34]†
Baseline-6 months	0.13 ± 0.20 [0.02, 0.24]	0.07 ± 0.34 [−0.12, 0.26]	0.06 [−0.14, 0.27]
Salivary volume (µl)			
Baseline	702.70 ± 664.60 [348.56, 1056.84]	570 ± 757.14 [150.71, 989.29]	
Postintervention	1090.00 ± 702.83 [715.49, 1464.51]	823.13 ± 598.29 [491.81, 1154.45]	
6-month follow-up	1168.44 ± 738.09 [775.14, 1561.74]	693.91 ± 736.55 [286.02, 1101.80]	
Within-Group Effect			
Baseline-postintervention	387.30 ± 351.54 [199.98, 574.62]	253.13 ± 656.51 [−110.43, 616.69]	134.17 [−249.18, 517.52]
Baseline-6 months	465.74 ± 460.69 [220.26, 711.23]	123.91 ± 951.07 [−402.78, 650.60]	341.83 [−201.54, 885.20]

Data are presented as mean ± standard deviation [95% confidence interval for the mean] at baseline, after the 12-week intervention, at the 6-month follow-up, and as mean differences [95% confidence interval for the difference] for within- and between-group effects. Pairwise comparisons were adjusted using Bonferroni

Abbreviations:PBM Photobiomodulation, *SFR* Salivary Flow Rate

*$P < 0.05$

†near-significant $p < 0.10$

(Fr = 6.53, $p = 0.038$), as determined by the Friedman test. Wilcoxon signed-rank tests were subsequently conducted to identify where there were such within-group effects (baseline–postintervention and/or baseline–6 months), but no significant mean differences were found (all p values: $p > 0.05$).

No significant time × group interaction effect was observed for global health (F = 0.16, $p = 0.857$) or physical function (F = 0.08, $p = 0.925$) measured using the EORTC QLQ-C30. The influence of covariates had no effect on the interaction. In addition, no statistically significant changes were detected within the groups at any time point (p > 0.05) (Table 6).

With respect to the EORTC QLQ-H&N35, a near-significant time × group interaction effect was found for dry mouth (F = 3.24, $p = 0.054$). The interaction effect was influenced by cancer stage and RT dose ($p < 0.05$). Bonferroni post hoc ANCOVA revealed that the PBM group had a significantly smaller reduction in dry mouth sensation than the placebo group did (−11.05 ± 26.30 vs. −33.27 ± 21.87, $p = 0.016$) after the intervention. The ES for between-group differences after intervention was large (d = 0.91, 95% CI 0.17, 1.65). After the follow-up period, the previously noted disparity favouring the placebo group was no longer evident. Within the placebo group, a significant decrease in dry mouth occurred (−33.27 ± 21.87, $p < 0.001$) after the intervention. No statistically significant changes were detected within the PBM group at any time point ($p > 0.05$) (Table 7).

A significant time × group interaction effect was found for sticky saliva (F = 3.91, $p = 0.032$). The interaction was influenced by age, time since the end of RT, and type of RT ($p > 0.05$). Bonferroni post hoc ANCOVA revealed a significant improvement in sticky saliva in the placebo group compared with the PBM group (−33.67 ± 21.96 vs. −9.48 ± 32.98, $p = 0.024$) after the 6-month follow-up. The ES for between-group differences after follow-up was large (d = 0.86, 95% CI 0.11, 1.59). A significant decrease in sticky saliva was observed within the placebo group (−33.67 ± 21.96, $p < 0.001$) after follow-up. No statistically significant changes were detected within the PBM group at any time point ($p > 0.05$) (Table 7). No significant group × time interaction effect was observed for swallowing (F = 2.08, $p = 0.144$). The influence of covariates had no effect on the interaction. Bonferroni post hoc ANCOVA did not reveal any improvement in swallowing

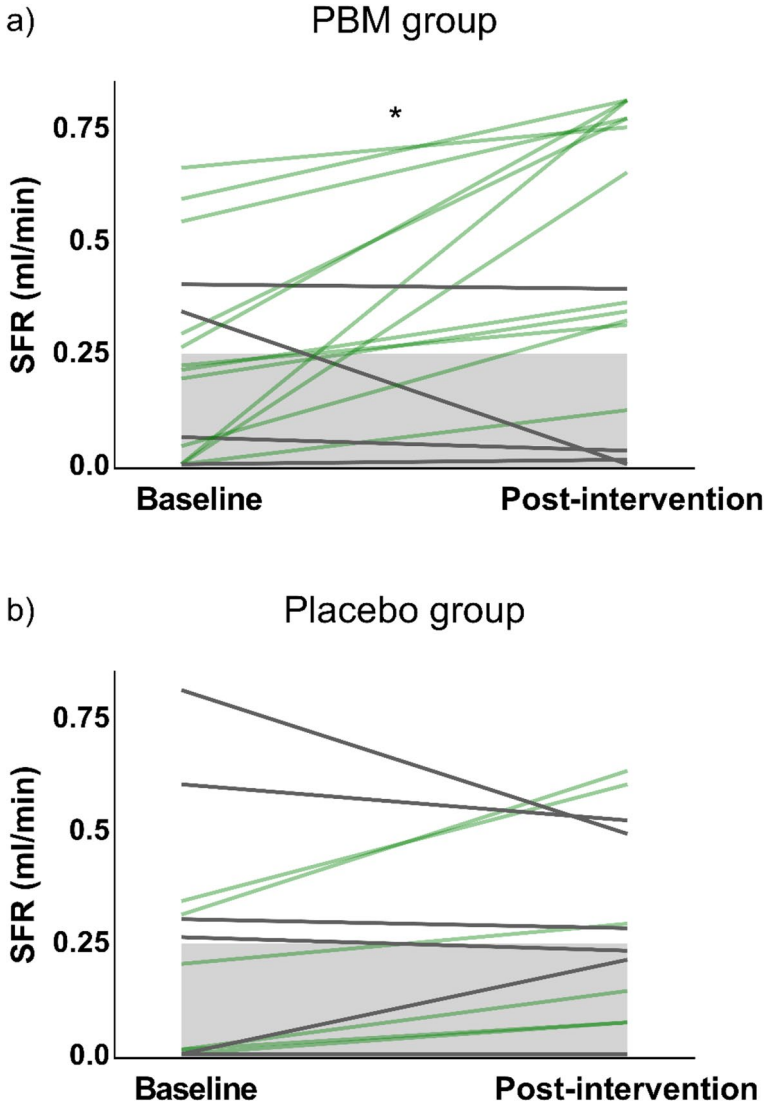

Fig. 3 Within-group changes in the SFR postintervention for the PBM group (**a**) and for the placebo group (**b**). Abbreviations: PBM: photobiomodulation, SFR: salivary flow rate. **P* value < 0.05. The grey area represents the cut-off of 0.25 ml/min, which is used to determine the presence or absence of hyposalivation. The green lines denote improvements above 0.25 ml/min, whereas the grey lines indicate cases where there was no improvement or deterioration in saliva production

Table 4 Estimation of SFR among study groups before and after PBM therapy

	PBM group ***n*** **= 16**				**Placebo group** ***n*** **= 15**			
	Normal SFR		**Hyposalivation**		**Normal SFR**		**Hyposalivation**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Baseline	7	43.8	9	56.3	6	40	9	60
Postintervention	12*	75	4*	25	6	40	9	60
Baseline-postintervention	+5		−5		0		0	

Abbreviations:PBM Photobiomodulation, *SFR* Salivary Flow Rate

*Statistical significance was assessed using the Chi-square test (*P* < 0.05)

in the PBM group compared with the placebo group (Table 7), either after the intervention ($p = 0.931$) or after follow-up ($p = 0.156$). Within-group analysis revealed a decrease in the swallowing domain in the placebo group (-12.37 ± 18.76, $p = 0.023$) after the 6-month follow-up. However, the PBM group did not change significantly within groups at any time point ($p > 0.05$). Finally, no significant time × group interaction effect was observed for

Table 5 Means, standard deviations, and 95% confidence intervals for the mean within- and between-group effects for sialochemistry

	PBM group ***n*** **= 16**	**Placebo group** ***n*** **= 15**	***Between-group effect***
Total protein (μg/ml)			
Baseline	1724.13 ± 2075.95 [617.93, 2830.33]	1586.18 ± 1001.58 [1031.53, 2140.84]	
Postintervention	888.96 ± 468.55 [639.29, 1138.63]	1279.48 ± 1097.43 [671.74, 1887.22]	
6-month follow-up	783.16 ± 483.54 [525.50, 1040.83]	1074.42 ± 1026.68 [505.86, 1642.97]	
Within-Group Effect			
Baseline-postintervention	−835.17 ± 1923.70 [−1860.23, 189.90]	−306.70 ± 1312.09 [−1033.31, 419.91]	−528.46 [−1746.35, 689.42]
Baseline-6 months	−940.97 ± 2013.80 [−2014.04, 132.11]	−511.77 ± 1132.71 [−1139.04, 115.50]	−429.20 [−1640.81, 782.41]
IgA (μg/ml)			
Baseline	69.24 ± 17.32 [60.01, 78.47]	65.55 ± 20.51 [54.20, 76.91]	
Postintervention	75.01 ± 12.40 [68.41, 81.62]	75.46 ± 7.82 [71.13, 79.79]	
6-month follow-up	65.50 ± 16.03 [56.96, 74.04]	64.72 ± 15.77 [55.98, 73.45]	
Within-Group Effect			
Baseline-postintervention	5.77 ± 15.04 [−2.24, 13.79][a]	9.91 ± 21.21 [−1.83, 21.66][a]	−4.14 [−17.57, 9.30][b]
Baseline-6 months	−3.74 ± 16.66 [−12.62, 5.14][a]	−0.84 ± 27.38 [−16.00, 14.33][a]	−2.90 [−19.43, 13.62][b]

Data are presented as mean ± standard deviation [95% confidence interval for the mean] at baseline, after the 12-week intervention, at the 6-month-follow-up, and as mean differences [95% confidence interval for the difference] for within- and between-group effects. Pairwise comparisons were adjusted using Bonferroni

Abbreviations:IgA Immunoglobulin A, *PBM* Photobiomodulation

[a]no parametric Friedman test

[b]no parametric U Mann Whitney test

The square root transformation was applied to total protein, affecting only the *p*-values

Table 6 Means, standard deviations, and 95% confidence intervals for the mean within- and between-group effects for quality of life

	PBM group ***n*** **= 16**	**Placebo group** ***n*** **= 15**	***Between-group effect***
EORTC QLQ-C30			
Global health			
Baseline	65.62 ± 26.85 [51.31, 79.93]	61.11 ± 16.57 [51.93, 70.28]	
Postintervention	74.40 ± 23.86 [61.69, 87.11]	68.29 ± 17.24 [58.74, 77.84]	
6-month follow-up	72.06 ± 18.96 [61.96, 82.16]	69.78 ± 17.46 [60.11, 79.45]	
Within-Group Effect			
Baseline-postintervention	8.78 ± 21.56 [−2.71, 20.26]	7.18 ± 16.13 [−1.75, 16.11]	1.60 [−12.47, 15.66]
Baseline-6 months	6.43 ± 25.81 [−7.32, 20.19]	8.67 ± 14.97 [0.38, 16.96]	−2.24 [−17.88, 13.41]
Physical function			
Baseline	88.33 ± 22.11 [76.55, 100.11]	84.89 ± 16.99 [75.48, 94.30]	
Postintervention	89.19 ± 14.78 [81.32, 97.07]	87.05 ± 12.52 [80.12, 93.98]	
6-month follow-up	89.42 ± 9.37 [84.42, 94.41]	86.06 ± 12.90 [78.92, 93.21]	
Within-Group Effect			
Baseline-postintervention	0.86 ± 12.84 [−5.98, 7.70]	2.16 ± 17.85 [−7.73, 12.05]	−1.30 [−12.67, 10.07]
Baseline-6 months	1.08 ± 19.32 [−9.21, 11.38]	1.17 ± 12.85 [−5.94, 8.29]	−0.09 [−12.23, 12.05]

Data are presented as mean ± standard deviation [95% confidence interval for the mean] at baseline, after the 12-week intervention, at the 6-month-follow-up, and as mean differences [95% confidence interval for the difference] for within- and between-group effects. Pairwise comparisons were adjusted using Bonferroni

Abbreviations:EORTC QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, *PBM* Photobiomodulation

The square root transformation was applied to physical function, affecting only the p-values

the remaining EORTC QLQ-H&N35 domain, i.e., mouth opening (F = 1.34, $p = 0.278$). The influence of covariates had no effect on the interaction. No statistically significant changes were detected within the groups at any time point ($p > 0.05$) (Table 7).

No significant time × group interaction effect was observed for the severity of xerostomia measured with the XI (F = 0.20, $p = 0.818$). The median values for the XI were 32.40 for the PBM group and 39.00 for the placebo group at the baseline assessment. After the intervention, these values were 30.50 and 34.24, respectively, and at follow-up, they were 33.28 for the PBM group and 34.09 for the placebo group. Similarly, no significant time × group interaction effect was observed for dysphagia evaluated with the EAT-10 (F = 0.13, $p = 0.879$) or mouth opening (F = 0.33, $p = 0.723$) measured with ROM. The influence of covariates had no effect on the interaction of any of these outcome measures. In addition, no statistically

Table 7 Means, standard deviations, and 95% confidence intervals for the mean within- and between-group effects for specific module of quality of life

	PBM group *n* = 16	Placebo group *n* = 15	*Between-group effect*
EORTC QLQ-H&N35			
Dry mouth			
Baseline	68.75 ± 30.96 [52.25, 85.25]	82.22 ± 21.33 [70.41, 94.04]	
Postintervention	57.70 ± 28.46 [42.53, 72.86]	48.95 ± 14.80 [40.76, 57.15]	
6-months-follow-up	52.59 ± 22.49 [40.61, 64.57]	57.06 ± 25.68 [42.84, 71.28]	
Within-Group Effect			
Baseline-postintervention	−11.05 ± 26.30 [−25.06, 2.96]	−33.27 ± 21.87 [−45.38, −21.16]*	22.22 [4.39, 40.05]*
Baseline-6-months	−16.16 ± 31.55 [−32.97, 0.65]	−25.16 ± 21.86 [−37.27, −13.06]	9.00 [−11.07, 29.08]
Sticky saliva			
Baseline	47.92 ± 38.43 [27.44, 68.39]	66.67 ± 28.17 [51.07, 82.27]	
Postintervention	34.04 ± 27.36 [19.46, 48.62]	43.17 ± 23.20 [30.32, 56.01]	
6-months-follow-up	38.43 ± 20.58 [27.47, 49.40]	33.00 ± 25.25 [19.02, 46.98]	
Within-Group Effect			
Baseline-postintervention	−13.87 ± 41.87 [−36.18, 8.43]	−23.50 ± 28.43 [−39.24, −7.76]	9.63 [−16.84, 36.10]
Baseline-6-months	−9.48 ± 32.98 [−27.05, 8.09]	−33.67 ± 21.96 [−45.83, −21.51]*	24.19 [3.63, 44.74]*
Mouth opening			
Baseline	35.42 ± 35.42 [16.54, 54.29]	35.55 ± 34.43 [16.49, 54.62]	
Postintervention	20.10 ± 23.73 [7.46, 32.75]	32.17 ± 12.79 [25.08, 39.25]	
6-months-follow-up	24.81 ± 21.53 [13.33, 36.28]	24.78 ± 22.47 [12.33, 37.22]	
Within-Group Effect			
Baseline-postintervention	−15.32 ± 30.37 [−31.50, 0.87]	−3.39 ± 34.43 [−22.45, 15.68]	−11.93 [−35.74, 11.88]
Baseline-6-months	−10.61 ± 30.51 [−26.86, 5.65]	−10.78 ± 30.68 [−27.77, 6.21]	0.17 [−22.32, 22.65]
Swallowing			
Baseline	21.87 ± 19.22 [11.63, 32.11]	31.67 ± 20.70 [20.20, 43.13]	
Postintervention	15.97 ± 14.00 [8.51, 23.43]	26.30 ± 13.83 [18.64, 33.95]	
6-months-follow-up	19.56 ± 14.21 [11.99, 27.13]	19.30 ± 9.58 [14.00, 24.60]	
Within-Group Effect			
Baseline-postintervention	−5.90 ± 15.28 [−14.05, 2.24]	−5.37 ± 18.61 [−15.68, 4.94]	−0.53 [−13.01, 11.94]
Baseline-6-months	−2.31 ± 19.59 [−12.75, 8.12]	−12.37 ± 18.76 [−22.76, −1.98]	10.05 [−4.05, 24.16]

Data are presented as mean ± standard deviation [95% confidence interval for the mean] at baseline, after the 12-week intervention, at the 6-month-follow-up, and as mean differences [95% confidence interval for the difference] for within- and between-group effects. Pairwise comparisons were adjusted using Bonferroni

Abbreviations:EORTC QLQ-H&N35 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module 35, *PBM* Photobiomodulation

*$P < 0.05$

significant changes were detected within the groups at any time point ($p > 0.05$) (Table 8).

Upon reviewing the results regarding AEs, no cases were documented according to the CTCAE. The satisfaction results suggest similarity between the two groups ($p = 0.205$), implying that the placebo group did not distinguish its membership in the sham intervention. Table 9 shows the results of satisfaction after the intervention. In addition, the mean level of satisfaction in the PBM group was 8.84 ± 1.24 (95% CI 8.18, 9.50), whereas that in the placebo group was 8.12 ± 1.83 (95% CI 7.10, 9.13). Finally, the adherence rate in the PBM group was 19.69 ± 5.24 (95% CI 16.90, 22.48), whereas that in the placebo group was 17.13 ± 9.15 (95% CI 12.07, 22.20). In this sense, there were no significant differences in the number of sessions attended in either group ($p = 0.355$).

Discussion

The findings revealed that PBM therapy with an 830 nm diode significantly enhanced hyposalivation (SFR) in patients with HNC after RT. Our results, in terms of the unstimulated SFR (sialometry), surpassed those reported in a recent meta-analysis in favour of PBM therapy (0.09 ml/min; 95% CI 0.05, 0.12), although they did not exceed the between-group effect (0.51 ml/min 95% CI 0.16, 0.86) [20]. The intervention in the PBM group resulted in a significant increase in the SFR, reaching + 87.50% compared with that in the control group, which was only + 21.05%. This aligns with the expected positive response to PBM only within the active group, which strongly suggests the potential benefit of this therapy. The intervention was also found to be both safe and well accepted by our patients, demonstrating its feasibility as a potential standard of care. In contrast to

Table 8 Means, standard deviations, and 95% confidence intervals for the mean within- and between-group effects for xerostomia, dysphagia and mouth opening

	PBM group *n* = 16	Placebo group *n* = 15	*Between-group effect*
XI			
Baseline	34.75 ± 8.96 [29.97, 39.53]	37.60 ± 7.75 [33.31, 41.89]	
Postintervention	31.68 ± 7.45 [27.72, 35.65]	35.04 ± 6.13 [31.64, 38.43]	
6-months-follow-up	32.92 ± 7.38 [28.99, 36.85]	35.17 ± 8.96 [30.21, 40.13]	
Within-Group Effect			
Baseline-postintervention	−3.07 ± 5.92 [−6.22, 0.09]	−2.56 ± 6.68 [−6.26, 1.14]	−0.50 [−5.13, 4.13]
Baseline-6-months	−1.83 ± 4.61 [−4.28, 0.63]	−2.43 ± 6.77 [−6.18, 1.31]	0.60 [−3.62, 4.83]
EAT-10			
Baseline	12.25 ± 11.86 [5.93, 18.57]	15.67 ± 8.49 [10.96, 20.37]	
Postintervention	9.47 ± 9.64 [4.33, 14.60]	12.11 ± 5.59 [9.02, 15.21]	
6-months-follow-up	10.52 ± 8.86 [5.80, 15.24]	12.64 ± 7.60 [8.44, 16.85]	
Within-Group Effect			
Baseline-postintervention	−2.78 ± 5.72 [−5.83, 0.27]	−3.55 ± 7.67 [−7.80, 0.70]	0.77 [−4.18, 5.72]
Baseline-6-months	−1.73 ± 7.81 [−5.89, 2.43]	−3.02 ± 5.97 [−6.33, 0.28]	1.29 [−3.84, 6.43]
ROM (cm)			
Baseline	3.48 ± 0.93 [2.98, 3.98]	3.33 ± 1.21 [2.65, 3.99]	
Postintervention	3.57 ± 1.03 [3.02, 4.12]	3.66 ± 0.69 [3.27, 4.04]	
6-months-follow-up	3.57 ± 0.86 [3.11, 4.03]	3.65 ± 0.92 [3.15, 4.16]	
Within-Group Effect			
Baseline-postintervention	0.09 ± 0.44 [−0.15, 0.32]	0.33 ± 1.12 [−0.29, 0.95]	−0.24 [−0.86, 0.38]
Baseline-6-months	0.08 ± 0.78 [−0.33, 0.50]	0.33 ± 1.27 [−0.38, 1.03]	−0.24 [−1.01, 0.53]

Data are presented as mean ± standard deviation [95% confidence interval for the mean] at baseline, after the 12-week intervention, at the 6-month-follow-up, and as mean differences [95% confidence interval for the difference] for within- and between-group effects. Pairwise comparisons were adjusted using Bonferroni

Abbreviation:EAT-10 Eating Assessment Tool-10, *PBM* Photobiomodulation, *ROM* Range of Motion, *XI* Xerostomia Inventory

Table 9 Responses in satisfaction questionnaire after intervention

	PBM group *n* = 14				Placebo group *n* = 11			
	Yes		No		Yes		No	
	n	%	n	%	n	%	n	%
1. Do you trust the positive effects of the PBM treatment received for xerostomia and hyposalivation that you suffer from after head and neck cancer?	14	100	0	0	10	90.9	1	9.1
2. Would you recommend PBM treatment to other individuals suffering from similar issues (xerostomia)?	14	100	0	0	11	100	0	0
3. Do you intend to continue with the PBM treatment once the study is completed?	13	92.9	1	7.1	6	54.5	5	45.5
4. Has the PBM treatment been bothersome for you during any of the sessions received?	2	14.3	12	85.7	0	0	11	100
5. Do you agree with the frequency of sessions received (2 sessions per week)?	13	92.9	1	7.1	11	100	0	0

Abbreviations:PBM Photobiomodulation

the present favourable unstimulated SFR outcome measure, previous investigations have revealed no difference between groups; a recent randomised controlled clinical trial [48], in which the authors investigated the effect of PBM on improving hyposalivation caused by antihypertensive medications, did not find a significant difference (baseline–postintervention change) when comparing study groups and only observed a significant difference within the PBM group ($p = 0.0007$) for the unstimulated SFR. In another study where preventive PBM therapy was administered during RT [49], no difference was found between groups in relation to the unstimulated SFR. Hence, all the above findings suggest that a larger sample size may be needed to obtain definitive results regarding the efficacy of PBM therapy in both nononcological and oncological patients.

This study also assessed sialochemistry (total protein and IgA), broadening the understanding beyond flow. First, an increase during RT is expected due to the greater permeability of the glandular parenchyma caused by radiation, which damages the acini. Therefore, a decrease in total protein concentration would be anticipated after the application of PBM therapy [48, 49]. Our results align with those of Louzeiro et al., who could also not demonstrate significant between-group effects after PBM therapy in oncological patients. However, noteworthy distinctions, at least in absolute values, were observed in our study, with a greater reduction in total protein

concentration in the active group (PBM) than in the placebo group (−835.17 vs. −306.70, respectively); however, it is unclear whether this reduction might be influenced by the increase in the SFR, which could result in greater dilution of this biomarker [48]. Therefore, future studies are recommended to perform a net total protein analysis. Although the potential of PBM therapy to increase the SFR has already been demonstrated according to our results, antimicrobial properties were not improved, as evidenced by the lack of increased IgA levels in our cohort [50].

With respect to QoL (patient-reported outcome measures, PROMs), a significant between-group effect was not observed after PBM therapy or at follow-up. However, notably, the active group maintained a global health status above the cut-off point (> 71) [51] after the intervention and at the 6-month follow-up, whereas the placebo group remained below this threshold. With respect to physical function, both groups remained below the cut-off point (< 97), although with high values [51]. A randomised controlled trial after RT led by Saleh et al. [52] reported an improvement in QoL; however, in both study groups (PBM vs. placebo), a different PROM called the Oral Health Impact Profile was used. With respect to the head and neck module, the placebo group showed greater significant improvement than did the PBM group in terms of dry mouth after the intervention and in terms of sticky saliva at the 6-month follow-up (although both groups demonstrated clinical improvement ≥ -10%) [53]. These results may be partially explained by the mucosal hydration and oral hygiene recommendations provided to both groups [52], which may have reduced their perception of symptoms, as reflected in the EORTC QLQ-H&N35, but not in a more comprehensive PROM such as the XI, which is why we have considered them with caution. Nor did they correlate with the objective increase in quantity of saliva detected (SFR). As shown in previous research, the association between objective outcome measures and PROMs (for instance, the EORTC QLQ-H&N35) was weak in patients with HNC [54].

The remaining outcome measures (PROMs and range of motion) did not show significant between-group effects after PBM therapy or at follow-up. According to the baseline scores in the XI, both groups reported a clinical problem (median score > 25: PBM = 32.4 vs. placebo = 39) [55], although our PBM parameters did not seem to influence this perception. Additionally, both groups maintained swallowing difficulties throughout the study (> 3) [41], although mouth opening was preserved within the normal range (> 3.5 cm) [56].

Despite the overall lack of results at the 6-month follow-up, few authors have considered comparable or larger long-term follow-up [13]. However, there seems to be a consensus that the effects of PBM therapy are likely to diminish after several months, as concluded by Golež et al. in their review [20]. Others, however, declare that it would be intriguing to see whether occasional PBM therapy would maintain constant salivation [15].

The intervention parameters used are consistent with those recommended in previous studies. Clinical trials involving oncological patients who receive only extra-oral stimulation of the salivary glands have shown better results with parameters quite similar to ours, including wavelengths between 630–830 nm, energy density of 2–10 J/cm^2, and session frequencies of 2–3 per week, as concluded in the review by Oliveira et al. [19]. Indeed, Saleh et al. [52] did not find a significant between-group effect when parameters such as a much higher energy density (71 J/cm^2) were applied after RT, whereas the preliminary single-arm study by Palma et al. [29], which also used parameters similar to those described here, revealed significant improvement in terms of the SFR after RT. The only difference with the latter was that they were stricter regarding the time since the end of RT (90% of their sample 3–24 months vs. 100% of our sample > 28 months on average).

In this context, several of the aforementioned articles highlight the importance of the time elapsed since the end of RT in preserving residual capacity in the salivary glands. It is estimated that upon completing RT, salivary secretion levels rarely return to baseline, even five years after the last dose [57]. Another important aspect of this study is that 100% of patients received a mean irradiation dose greater than 60 Gy. Although there is no consensus in the scientific literature regarding the exact radiation dose threshold for salivary gland dysfunction, some studies suggest that damage can start at doses smaller than the 10–15 Gy mean dose [58], with doses above 60 Gy causing degenerative changes in the parenchyma [19]. Consequently, the likelihood of normal glandular function recovery in our cohort was reduced. In addition, many patients in both groups received three-dimensional conformal radiation therapy (RT3D), or conventional RT, which is presumed to be more aggressive in terms of fibrosis and acinar damage [59]. While the trends in our results do not suggest irreversible effects, these RT-related factors may have contributed to the absence of more definitive results. All these arguments contrast with those of an uncontrolled study [29], which reported significant increases in both stimulated and unstimulated SFR in patients with chronic xerostomia after high-dose RT3D (total radiation dose: 50–69 Gy, 55%; 70 Gy, 45%).

As previously explained, a wide range of conditions affect salivary secretion, and their impact on recovery should be discussed. Sjögren's syndrome or RT, which results in more harmful damage to the parenchyma, might make PBM therapy less effective. For example, the salivary glands have a limited mitotic response but are

highly radiosensitive, which seems to result in damage with limited recovery potential [60]. Therefore, the effect of PBM therapy may be partially determined by the aetiology of hyposalivation/xerostomia.

Finally, considering the therapeutic application of PBM defended in this study, if this capacity in the salivary glands is minimal or nonexistent after RT, the outcome measures tend to be poorer. Nonetheless, this application seems safer because it is not applied to an active tumour [61], and patients are more suitable for therapy, as they do not present other side effects, such as mucositis or radiodermatitis, which could limit adherence to therapy itself.

This study has several limitations that may impact the interpretation of its findings. First, the sample size calculation was based on the ES reported in a previous study [26]; however, the resulting statistical Power was only 76%, and we recognise that this level is below the more conventional 80–90% range. Nonetheless, given the inclusion criteria, the logistical complexities of following this oncological population, and the preliminary nature of this trial [62], we opted to maintain a manageable sample size that still allowed us to explore the potential efficacy of PBM therapy under rigorous conditions (randomisation, placebo control, and double-blinding). Additionally, the lack of calibration of the device's Power could have led to underdosing of the active therapy. The absence of a follow-up period extending beyond 6 months further limits the ability to assess long-term outcome measures. Furthermore, the eligibility criteria were not sufficiently strict, particularly concerning the time since the end of RT, which may have introduced variability in patient responses. The assessment of the SFR by the pipetted volume, rather than the sputum weight, could also affect accuracy. Importantly, while the initial plan was to implement a double-blind design across all outcome measures, resource limitations restricted this to sialometry and sialochemistry only.

Despite these limitations, the study has several strengths that enhance its validity. Notably, objective outcome measures were analysed with evaluators blinded to group allocation. Additionally, the randomised design, which included a placebo group, provides a robust framework for comparison. Finally, by using parameters that align with current scientific evidence, the reliability of the findings is supported.

Conclusion

PBM therapy demonstrated potential positive benefits on hyposalivation in patients with HNC after RT. Our results revealed a clinically significant increase in the SFR and suggest that PBM therapy has modulatory and regenerative effects on the salivary glands. All RT-related factors (time elapsed since the end of RT, dose and type) and non-RT factors (therapeutic application of PBM and sample size) discussed above may have contributed to a lower chance of reverting to improved hyposalivation/xerostomia. Future studies with larger samples and greater statistical power will be essential to confirm and expand upon our preliminary results.

Abbreviations

AE	Adverse event
AJCC/UICC	American Joint Committee on Cancer/Union for International Cancer Control
ANCOVA	Analysis of covariance
BSA	Bovine serum albumin
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
EAT-10	Eating Assessment Tool-10
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-H&N35	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck Module 35
ES	Effect size
HNC	Head and neck cancer
ICC	Intraclass correlation coefficient
IgA	Immunoglobulin A
IGRT	Image-guided radiation therapy
IMRT	Intensity-modulated radiation therapy
NCCN	National Comprehensive Cancer Network
PBM	Photobiomodulation
PROM	Patient-reported outcome measure
QoL	Quality of life
ROM	Range of motion
RT	Radiotherapy
RT3D	Three-dimensional conformal radiation therapy
SFR	Salivary flow rate
VMAT	Volumetric modulated arc therapy
XI	Xerostomia Inventory

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Authors' contributions

NGC contributed to the conception of this trial and was the trial coordinator. EIPS was in charge of recruiting patients. NGC was responsible for patient evaluations over time. MLL and FAC were responsible for the assessment of salivary flow, the analysis of biochemical biomarkers and the collection of samples. Data analysis was performed by MLG and MCPP. NGC was responsible for patient treatment. All authors drafted the manuscript and critically reviewed and approved the final manuscript as submitted.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Andalusian Biomedical Research Ethics Portal (1552-N-18 CEIM/CEI Provincial de Granada) according to the Declaration of Helsinki for Biomedical Research and was registered with Clinicaltrials.gov (NCT05614843). All patients received verbal and written information about the

study and signed an informed consent form before participating. At all times, patients were able to withdraw or decline their participation.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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