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Transcutaneous Versus Intraoral Photobiomodulation for the Prevention of Oral Mucositis in Head and Neck Cancer: A Randomized Clinical Trial

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Abstract

Objectives

To compare the clinical efficacy of transcutaneous (TC-PBM) versus intraoral (IO-PBM) photobiomodulation in the prevention of radiotherapy-induced oral mucositis (OM) in patients with head and neck cancer.

Methods

This was a prospective, randomized, non-inferiority clinical trial involving 72 patients undergoing radiotherapy (RT) (60–70 Gy) for head and neck cancer (HNC), allocated to TC-PBM (n = 38), treated with an 808-nm laser using the following parameters: 100 mW, 1 J/point, 10 seconds per point, and 32 points, resulting in a fluence of 34.5 J/cm² (central) and 4.3 J/cm² (lateral); or IO-PBM (n = 34), treated with a 660-nm laser using the following parameters: 100 mW, 1 J/point, 10 seconds per point, and 44 points, resulting in a fluence of 10.20 J/cm². Treatments were applied three times weekly throughout the entire course of radiotherapy, from the first to the last day of RT. The primary outcome was OM severity (WHO scale, 0–4), and secondary outcomes included OM severity (NCI-CTC v2.0), pain (NRS), cumulative incidence, and time to OM onset, all assessed at T1 (1st week of RT), T2 (2nd week of RT), T3 (3rd week of RT), T4 (4th week of RT), and T5 (final week of RT).

Results

No significant difference was found in overall OM severity between groups (p = 0.549) or in the group × time interaction (p = 0.794). Estimated marginal means for OM grade were 1.88 (95% CI: 1.48–2.29) for the TC-PBM group and 2.18 (95% CI: 1.74–2.62) for the IO-PBM group, with an estimated between-group difference of − 0.30 (95% CI: −0.90 to 0.30), demonstrating the non-inferiority of TC-PBM. No significant differences were observed in cumulative OM incidence (71.1% in the TC-PBM group vs. 70.6% in the IO-PBM group; p = 0.965), median time to lesion onset (13 sessions in both groups; p = 0.436), pain intensity, or topographic distribution of lesions.

Conclusion

TC-PBM (808 nm) demonstrated non-inferiority to IO-PBM (660 nm) with respect to radiation-induced OM severity, while maintaining pain control. It represents a non-invasive strategy with a potential operational advantage (shorter application time), particularly relevant for patients with limited mouth opening, odynophagia, or compromised intraoral access.

INTRODUCTION

Oral mucositis (OM) is one of the most frequent and debilitating complications of antineoplastic treatment in patients with head and neck cancer. During radiotherapy (RT) and, especially, chemoradiotherapy (CRT), its incidence is markedly high, reaching 90–100% in combined-modality protocols, making it virtually unavoidable in many patients irradiated in the head and neck region when preventive management is not implemented [1, 2, 3].

Clinically, OM progresses from erythema and pain to ulceration, edema, and significant functional impairment. Severe forms are associated with dysphagia, reduced oral intake, dehydration, weight loss, the need for nutritional support, increased risk of infection and hospitalization, and impaired quality of life [3, 4, 5].

Beyond its symptomatic burden, OM can compromise the oncologic treatment itself. The literature describes treatment delays, interruptions, and dose reductions related to OM, with potential detriment to locoregional control, treatment adherence, and survival [3, 4, 6].

In this context, photobiomodulation (PBM), also referred to as low-level laser therapy, has become established as the leading non-pharmacological strategy for OM prevention in selected oncologic settings. The Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) guidelines recommend PBM for OM prevention in head and neck cancer patients undergoing RT, with or without chemotherapy, provided that specific protocols with clinically validated parameters are followed [1, 7].

PBM can be delivered via two main routes in OM management: intraoral (IO) and transcutaneous (TC). In general, the IO route applies light directly to at-risk or already affected areas of the oral mucosa, whereas the TC route delivers light externally, through the skin, aiming to reach deeper tissues in a non-invasive manner [8].

IO-PBM is the more traditional approach in clinical protocols and allows targeted irradiation of the mucosa, with application at specific points within the oral cavity. In clinical studies and protocol descriptions, this approach has frequently been performed using wavelengths in the red range, particularly around 660 nm, with early initiation during radiotherapy [6, 9]. TC-PBM, in turn, represents a non-invasive and operationally simpler alternative, as it does not require direct access to intraoral surfaces. This feature has generated particular interest for patients with limited mouth opening, increased local sensitivity, or difficulty tolerating prolonged intraoral applications [8].

From a technical standpoint, both routes depend on rigorous application parameters, such as wavelength, power, fluence, time per point, and session frequency. The literature highlights that heterogeneity in these parameters continues to hinder protocol standardization and direct comparison across studies and devices [6, 10, 11].

Thus, rather than being mutually exclusive strategies, the intraoral and transcutaneous routes should be understood as distinct forms of light delivery, each with its own practical and anatomical characteristics.

IO-PBM favors greater precision over the target mucosa, whereas TC-PBM offers potential advantages in comfort and clinical feasibility, which helps justify the growing interest in comparative studies between the two [5, 8, 9].

Despite this growing interest, relevant uncertainties remain in the literature: it is unclear whether TC-PBM delivers energy to target tissues in a sufficient and homogeneous manner, given the attenuation caused by skin and subcutaneous tissue, to the point of matching the efficacy of direct mucosal application via the IO route; nor is there consensus on the optimal dose and irradiation time parameters for each route, given the heterogeneity of published protocols; and it remains largely unexplored whether the greater practicality and comfort of TC-PBM translate, in practice, into better adherence to the prophylactic protocol throughout the entire course of radiotherapy.

The objective was to compare the clinical efficacy of two PBM protocols: TC-PBM, using an 808-nm infrared laser, and IO-PBM, using a 660-nm red laser, in the prevention of radiation-induced OM in patients with head and neck cancer, testing the hypothesis that TC-PBM is non-inferior to IO-PBM with respect to OM severity (primary outcome, assessed using the World Health Organization scale), within a predefined clinically relevant non-inferiority margin.

MATERIALS AND METHODS

This study presents the final clinical results of a prospective, randomized, non-inferiority clinical trial, whose detailed protocol was previously published [12]. Although the original protocol had planned a pilot sample of 54 patients (27 per group), enrollment was expanded to 85 participants to compensate for potential radiotherapy treatment discontinuations and follow-up losses inherent to the oncologic population, ensuring adequate statistical power for the final analysis of the primary outcome in completers. In brief, adult patients diagnosed with head and neck cancer, candidates for radiotherapy with curative intent (alone or combined with chemotherapy), were recruited. Patients with severe or uncontrolled periodontal disease, or concomitant use of topical oral medication that could interfere with mucosal assessment, were excluded. Eligible patients were randomized by electronic allocation (1:1) by one of the study investigators, stored and controlled in a restricted electronic spreadsheet for sequential allocation of participants upon protocol inclusion, into two groups: intraoral photobiomodulation (IO-PBM, red wavelength, 660 nm) or transcutaneous photobiomodulation (TC-PBM, infrared wavelength, 808 nm), applied three times weekly from the first to the last day of RT. The study was approved by the Research Ethics Committee (approval no. 7.072.369) and registered in the Brazilian Clinical Trials Registry (RBR-9brv7dd). All participants signed an Informed Consent Form (ICF) prior to inclusion. Eligibility criteria, randomization and blinding methods, sample size calculation, and the complete dosimetric parameters of each PBM protocol are described in detail in the protocol publication [12].

The primary outcome, OM severity assessed using the World Health Organization (WHO) scale (grades 0–4), and the secondary outcomes, severity according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC v2.0), grades 0–4; pain intensity by the Numeric Rating Scale (NRS), 0–10; and

incidence and time to OM onset, were assessed weekly by the examiners, at five time points throughout radiotherapy (T1 to T5: T1 (week 1, days 1–6), T2 (week 2, days 7–12), T3 (week 3, days 13–20), T4 (week 4, days 21–26), and T5 (final week, days 27–33). The study was designed to test the non-inferiority of TC-PBM relative to IO-PBM, with a pre-specified non-inferiority margin of 0.5 grade on the WHO scale, based on references from the literature [12].

STATISTICAL ANALYSIS

Complete methodological details, including the sample size calculation, the non-inferiority margin (Δ = 0.5 on the WHO score), and the statistical model design, were previously described in the study protocol [12]. Briefly, the primary outcome (OM severity, WHO scale) was analyzed longitudinally using a Cumulative Link Mixed Model (CLMM), an ordinal logistic mixed-effects regression, with treatment group, assessment time point, and the group × time interaction as fixed effects, patient as a random effect, and concomitant chemotherapy as a covariate. The protocol had also planned to adjust the model for total radiotherapy dose and tumor site; however, these covariates showed incomplete records in part of the sample, which would have required the additional exclusion of patients from the model if included, further reducing the statistical power already limited by the heterogeneity of the population. For this reason, only concomitant chemotherapy was retained as a covariate in the final model, as it had no relevant missing data across the entire sample. Non-inferiority was assessed by comparing the 95% confidence interval of the difference between estimated marginal means with the pre-specified margin of 0.5 grade.

Descriptive between-group comparisons at each assessment time point (severity by the WHO and NCI-CTC v2.0 scales, pain by the NRS) were performed using the Mann-Whitney U test. Cumulative OM incidence and baseline categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate for the expected frequencies. Time to OM onset was analyzed using the Kaplan-Meier method, with between-group comparison by the log-rank test. Predictors of OM (smoking status, PBM group) were evaluated by binomial logistic regression. The effect of chemotherapy regimen and treatment modality on OM severity at peak toxicity was assessed by the Kruskal-Wallis test, and the topographic distribution of lesions was compared using Fisher's exact test.

A significance level of 5% (α = 0.05) was adopted for two-tailed analyses. Analyses were performed using Jamovi software (version 2.7.38.0), considering the population of participants with available data (completers, n = 72); a per-protocol (PP) sensitivity analysis included only participants with ≥ 80% adherence to PBM sessions.

RESULTS

A total of 85 patients were randomized between November 2024 and May 2026. Thirteen patients were excluded during treatment (TC = 8, IO = 5). Seventy-two patients completed study participation and were included in the analysis (TC = 38, IO = 34). Reasons for exclusion are described in the flowchart in Fig. 1.

This is, therefore, a completers (available-case) analysis rather than a classic intention-to-treat (ITT), as the 13 participants excluded after randomization were not retained in the final analysis. The results of the PP analysis are presented throughout this section alongside those of the completers analysis, showing convergent conclusions of non-inferiority between groups.

Sample characteristics and treatment modalities are presented in Table 1. Most patients in both groups were male (68.1% vs. 31.9%), aged over 50 years (90.3%).

Regarding smoking and alcohol consumption history, 25% and 48.7% of patients reported use during the study period, respectively, and 47.2% self-identified as former smokers. Patients who continued smoking after diagnosis (n = 18) consumed, on average, 11.2 cigarettes/day (SD = 8.74; median = 8.5), a lower value than that reported by former smokers during the period in which they smoked, with a mean of 18.9 cigarettes/day (SD = 14.6; median = 20). The mean smoking duration among active smokers was 41 years (SD = 10; median = 40; range 17–53 years), while former smokers reported a mean smoking duration of 35.4 years (SD = 16.3; median = 40; range 2–60 years) before cessation. Among former smokers, time since smoking cessation showed considerable variability, with a median of 6.0 months (mean = 98.7 months; SD = 157), ranging from 0 to 600 months (50 years), reflecting the heterogeneity in time elapsed since habit discontinuation among patients. Of the total sample (n = 72), 12 patients (16.7%) presented combined abstinence, characterized by smoking cessation associated with absence of alcohol consumption, while 10 patients (13.9%) maintained both habits, being active smokers and alcohol consumers (socially or frequently).

The most frequent tumor type was squamous cell carcinoma (SCC) (93.1%). The oropharynx was the most common site (n = 17, 23.6%), followed by the larynx (n = 15, 20.8%) and tongue (n = 15, 20.8%), followed by other sites (n = 25, 34.8%). Most tumors showed invasion of adjacent structures (23.6%) and lymph node involvement (N2 in 22.2%), while 43.1% of cases had no distant metastasis. Regarding histological profile, 30.6% of tumors were classified as moderately differentiated. It should be noted that, in most of the medical records analyzed, information regarding staging (TNM classification: T = 29.2%; N = 36.1%; M = 43%) and histopathological grade of differentiation (59.7%) was incomplete or missing, having been recorded exclusively by the medical team.

Regarding oncologic treatment, 26.4% of patients underwent RT alone, 26.4% RT and surgery, 25% chemotherapy and RT, and 22.2% received a combination of modalities (RT + CT+surgery). Intensity-Modulated Radiation Therapy (IMRT) was used in 98.64% of patients, while 1.36% received the 3D technique. The most common chemotherapy regimen was cisplatin (37.5%), followed by capecitabine, carboplatin, and docetaxel+cisplatin+fluorouracil (DCF), each corresponding to 1.4%. Missing data: 5.6%.

Demographic and clinical characteristics were descriptively similar between the TC-PBM and IO-PBM groups (sex, age, race, skin phototype, tumor type, smoking status, alcohol consumption, tumor site, TNM staging, and histopathological grade of differentiation), without the use of significance testing for this comparison, as recommended by CONSORT for randomized trials (Table 1).

Table 1
— Baseline demographic, clinical, pathological, and treatment characteristics of the study sample.

Characteristics	TC PBM (n = 38)	IO PBM (n = 34)	p
Sex			
Male	26 (36,1%)	23 (31,9%)	**> 0,05**
Female	12 (16,7%)	11 (15,3%)	
Age			
≤ 50 years	5 (6.9%)	2 (2,8%)	**> 0,05**
> 50 years	33 (45,8%)	32 (44,4%)	
Race			
White	31 (43,1%)	27 (37,5%)	**> 0,05**
Mixed race	7 (9,7%)	6 (8,3%)	
Asian	0	1 (1,4%)	
Skin phototype			
Very fair skin	5 (6,9%)	6 (8,3%)	**> 0,05**
Fair skin	19 (26,4%)	16 (22,2%)	
Light brown skin	8 (11,1%)	10 (13,9%)	
Dark brown skin	6 (8,3%)	2 (2,8%)	
Smoking status			
Current smoker	9 (12,5%)	9 (12,5%)	**> 0,05**
Former smoker	14 (19,4%)	20 (27,8%)	
Non-smoker	15 (20,8%)	5 (6,9%)	
Alcohol consumption			
Frequent	5 (6,9%)	8 (11,1%)	**> 0,05**
Social	10 (13,9%)	12 (16,7%)	
None	23 (31,9%)	14 (19,4%)	
Tumor type			
SCC	35 (48,6%)	32 (44,4%)	**> 0,05**
Osteosarcoma	0	1 (1,4%)	

Characteristics	TC PBM (n = 38)	IO PBM (n = 34)	p
Sex			
Melanoma	1 (1,4%)	0	
Pleomorphic adenocarcinoma	1 (1,4%)	0	
Acinic cell carcinoma	0	1 (1.4%)	
Myoepithelial carcinoma	1 (1,4%)	0	
Staging – T			
T0	0	1 (1,4%)	**> 0,05**
T1	4 (5,6%)	2 (2,8%)	
T2	5 (6,9%)	7 (9,7%)	
T3	8 (11,1%)	7 (9,7%)	
T4	10 (13,9%)	7 (9,7%)	
Missing data	11 (15,3%)	10 (13,9%)	
Staging – N	9 (12,5%)	8 (11,1%)	**> 0,05**
N0	7 (9,7%)	3 (4,2%)	
N1	6 (8,3%)	10 (13,9%)	
N2	2 (2,8%)	1 (1,4%)	
N3	14 (19,4%)	12 (16,7%)	
Missing data			
Staging – M	2 (2,8%)	6 (8,3%)	**> 0,05**
MX	20 (27,8%)	11 (15,3%)	
M0	1 (1,4%)	1 (1,4%)	
M1	15 (20,8%)	16 (22,2%)	
Missing data			
Histopathological grade	3 (4,2%)	1 (1,4%)	**> 0,05**
G1 – Well differentiated	8 (11,1%)	14 (19,4%)	
G2 – Moderately differentiated	1 (1,4%)	1 (1,4%)	
G3 – Poorly differentiated	25 (34,7%)	18 (25%)	
Missing data			

Characteristics	TC PBM (n = 38)	IO PBM (n = 34)	p
Sex			
Treatment modality	11 (15,3%)	8 (11,1%)	**> 0,05**
RT	12 (16,7%)	7 (9,7%)	
RT+surgery	6 (8,3%)	12 (16,7%)	
RT + CT	9 (12,5%)	7 (9,7%)	
RT + CT+surgery			

To assess the primary outcome, OM severity was compared between groups over the course of radiotherapy using an ordinal logistic mixed-effects regression model (Cumulative Link Mixed Model – CLMM), considering treatment group, time, and concomitant chemotherapy as fixed effects, and patient as a random effect, given the repeated-measures structure (five assessment time points).

The model showed no statistically significant difference in overall OM severity between groups (Exp(β) [TC vs. IO] = 0.62; 95% CI: 0.13–2.93; p = 0.549), nor in the group × time interaction (p = 0.794). OM severity increased significantly over the course of RT in both groups (p < 0.001) (Table 2 – Part A; Fig. 2). Estimated marginal means for OM grade were 1.88 (95% CI: 1.48–2.29) for the TC-PBM group and 2.18 (95% CI: 1.74–2.62) for the IO-PBM group, with an estimated between-group difference of − 0.30 (95% CI: −0.90 to 0.30, calculated by normal approximation from the standard errors of the model-estimated marginal means). Given that the upper bound of this confidence interval (0.30) did not exceed the pre-specified clinically relevant non-inferiority margin of 0.5 grade on the WHO scale, the non-inferiority of TC-PBM relative to IO-PBM was statistically demonstrated.

As a sensitivity analysis complementary to the completers analysis above, the per-protocol (PP) population was defined as participants with ≥ 80% adherence to PBM sessions, totaling 62 patients (33 in the TC-PBM group and 29 in the IO-PBM group), with no difference in the proportion of eligibility between groups ($\chi^2 = 0.036$; p = 0.850). Peak OM severity (highest grade reached during follow-up) was compared between groups in this population: the median peak was grade 2 in the TC-PBM group and grade 3 in the IO-PBM group, with no statistically significant difference (Mann-Whitney test; U = 399; p = 0.343), corroborating the non-inferiority conclusion obtained in the main completers analysis (n = 72).

Cumulative OM incidence, considering any grade on the WHO scale (grade 1 to 4) throughout the entire course of RT, was 70.8% in the total sample. No statistically significant difference was detected between groups: 71.1% in the TC-PBM group and 70.6% in the IO-PBM group ($\chi^2 = 0.002$; df = 1; p = 0.965) (Table 2 – Part B).

The descriptive analysis of OM severity across the five assessment time points showed no statistically significant difference between groups at any time point (Mann-Whitney test; T1: p = 0.648; T2: p = 0.946; T3: p = 0.494; T4: p = 0.726; T5: p = 0.225). At T1, both groups presented minimal to absent mucositis

(TC-PBM: 0.01; IO-PBM: 0.01 on the marginal means scale), consistent with the absence of cumulative radiation dose at this early stage, and the median OM grade remained at 0 during the first two weeks (T1 and T2) in both groups. From T3 onward, severity progressed differently between protocols: in the IO-PBM group, the median reached grade 2 already in the third week, remaining at this level through T5; in the TC-PBM group, progression was more gradual, with a median of 1.5 at T3 and grade 2 from the fourth week (T4) onward, reflecting the expected pattern of cumulative worsening of radiation-induced mucosal toxicity and corroborating the significant effect of the "Time" factor already reported in the CLMM model (Table 2 – Part B). This pattern is illustrated in Fig. 2, which presents the estimated marginal means: between T3 and T5, the TC-PBM group ranged between 1.24 and 1.42, and the IO-PBM group between 1.68 and 2.02, with overlapping confidence intervals at all time points. Worsening over time was statistically significant in the model (Time effect: $\chi^2 = 79.60$; df = 4; $p < 0.001$), while the effects of group ($\chi^2 = 0.359$; df = 1; $p = 0.549$) and the group × time interaction ($\chi^2 = 1.60$; df = 4; $p = 0.794$) were not, indicating that transcutaneous and intraoral photobiomodulation produced comparable trajectories of oral mucositis severity throughout radiotherapy (Table 2 – Part A; Fig. 2).

The prevalence of severe OM (grades 3 and 4) according to the WHO scale did not differ between groups at any assessed time point, ranging from 0–9.4% at T1–T2 to a peak of 34.2% (TC-PBM) and 29% (IO-PBM) at T3 ($p = 0.654$), remaining without significant difference through T5 (36.4% vs. 41.4%; $p = 0.694$) (Table 2 – Part B). A similar result was observed when severity was defined by the NCI-CTC v2.0 criteria, with a prevalence of severe OM at T5 of 18.2% and 27.6% in TC-PBM and IO-PBM, respectively ($p = 0.386$) (Table 2 – Part B). The concordance between the two grading scales reinforces the finding of consistent results between protocols.

Table 2
— Efficacy outcomes of transcutaneous versus intraoral photobiomodulation for the prevention of oral mucositis.

Part A – Primary outcome model					
Effect	**Estimate**	**95% CI**		**Exp (β)**	**p**
GROUP (TC vs. IO)	-0.47	-7.56 to -0,34		0,62	.549
Time (progression)*					**< .001**
T2 - T1	3.92	12.02–214.27		50.75	< .001
T3 - T1	6.07	92.65–2041.67		434.94	< .001
T4 - T1	6.24	107.53–2453.15		513.60	< .001
T5 - T1	6.56	141.98–3513.51		706.31	< .001
CHEMOTHERAPY (Yes vs. No)	0.49	0.36–7.49		1.64	.521
Group × Time Interaction*					.794
Part B – Descriptive outcomes across radiotherapy time points					
Time	**Median WHO (TC/IO)**	**Moderate-severe WHO % (TC/IO)**	**Moderate-severe NCI % (TC/IO)**	**Moderate-severe pain % (TC/IO)**	**p**
T1	0(0–2)/0(0–3)	0/0	0/0	0/0	.648
T2	0(0–4)/0(0–3)	7.9/9.4	2.6/3.1	0/8.8	.946
T3	1.5(0–4)/2(0–4)	34.2/29	7.9/12.9	21.1/32.3	.494
T4	2(0–4)/2(0–4)	27/36.6	16.2/13.3	43.9/44.1	.726
T5	2(0–4)/2.5(0–4)	36.4/41.4	18.2/27.6	39.5/41.2	.225

Model fit: marginal R^2 = 0.343; conditional R^2 = 0.825; ICC = 0.734. The terms "Time (progression)" and "Group × Time Interaction" refer to the omnibus tests (F test) of the main and interaction effects in the mixed model. As these represent joint tests of multiple coefficients (comparisons of time levels relative to the reference category), they do not have a single associated estimate (β) or confidence interval. β:

estimated regression coefficient; 95% CI: 95% Confidence Interval; Exp(β): Odds Ratio. The model adopted Time 1 (T1) as the reference category for evaluating the main effect of time. The p-value presented in Table B refers to the TC vs. IO comparison for the median WHO score (Mann-Whitney test) at each time point. Between-group comparisons for severe OM (grades 3–4), on both the WHO and NCI-CTC v2.0 scales, did not reach statistical significance at any assessed time point (all $p > 0.05$).

Kaplan-Meier survival analysis, considering the development of OM of any grade as the event, showed no significant difference in time to event between groups (log-rank $\chi^2 = 0.607$; df = 1; $p = 0.436$). The median time to OM onset was 13 radiotherapy sessions in both groups (TC-PBM: 95% CI 12.0–26.0; IO-PBM: 95% CI 11.0–15.0) (Fig. 3A), coinciding with the transition observed in Table 2 – Part B, in which the median severity in the IO-PBM group shifted from grade 0 to grade 2 between T2 and T3, whereas in the TC-PBM group this progression occurred more gradually, reaching grade 2 only at T4.

Pain intensity was assessed using the Numeric Rating Scale (NRS), with scores categorized as: no pain (NRS = 0), mild pain (NRS 1–3), moderate pain (NRS 4–6), and severe pain (NRS 7–10). Regarding pain intensity, no difference was observed between groups at any time point in the study (Mann-Whitney test; T2: $p = 0.125$; T3: $p = 0.185$; T4: $p = 0.938$; T5: $p = 0.961$). At T1, all participants reported no pain (NRS = 0), which precluded statistical comparison at this time point. From T3 onward, an increase in the proportion of patients with moderate to severe pain (NRS 4–10) was observed in both groups, in parallel with the worsening of OM described in Table 2 – Part B, with no difference in this progression between the photobiomodulation protocols (Table 2 – Part B).

Concomitant chemotherapy was not associated with greater OM severity in the ordinal logistic mixed-effects regression model ($p = 0.521$). To specifically investigate the effect of chemotherapy regimen, the peak severity time point (T5) was isolated and compared across three categories (no chemotherapy, platinum-based agents, and other regimens) using the Kruskal-Wallis test, with no statistically significant difference ($\chi^2 = 2.99$; df = 2; $p = 0.224$). It should be noted that the "capecitabine" and "DCF" categories were grouped into the "other regimens" category due to the limited number of patients in each (n = 1 per group), which limits the power of the analysis to detect differences between specific regimens.

Similarly, the overall oncologic treatment modality (RT alone, RT+surgery, CT + RT, or the combination of all three modalities) did not influence OM severity at the peak toxicity time point ($\chi^2 = 1.56$; df = 3; $p = 0.669$), showing that OM intensity behaved similarly regardless of the associated oncologic treatment.

In the binomial logistic regression adjusted for smoking status and photobiomodulation group, neither smoking status (current smoker: OR = 0.87 [0.20–3.68]; 95% CI; $p = 0.846$; former smoker: OR = 0.70 [0.20–2.41]; 95% CI; $p = 0.569$) nor PBM group (TC vs. IO: OR = 0.94 [0.32–2.70]; 95% CI; $p = 0.902$) were independent predictors of OM incidence (Table 3). The low McFadden's R^2 value (0.004) indicates limited explanatory power of the model, suggesting that other factors not included may carry greater weight in determining OM risk (Table 3).

When specifically analyzing the association between smoking status and the presence of ulcerative OM (grade ≥ 2) during the periods of greatest radiotherapy-related toxicity, no significant association was observed either at T4 (current smoker: 65%; former smoker: 65.8%; non-smoker: 51.7%; χ^2 p = 0.835) or at T5 (current smoker: 58.8%; former smoker: 68.8%; non-smoker: 58.6%; χ^2 p = 0.967). No independent association between smoking status and ulcerative OM (grade ≥ 2) was identified in this sample (Table 3).

The topographic distribution of OM lesions did not differ between groups, either for ulcerative lesions of grade ≥ 2 (p = 0.979) or for grade 1 lesions (p = 0.196) (Table 3; Figs. 3B and 3C). In both protocols, the sites most frequently affected by ulcerative lesions were the tongue and multiple simultaneous sites, whereas the buccal/labial mucosa predominated among erythematous lesions, with no apparent relationship between the photobiomodulation delivery route (TC vs. IO) and the anatomical location of lesions.

Regarding treatment safety, both photobiomodulation protocols were well tolerated, and no adverse effects or local complications related to laser application (such as burns, abnormal cutaneous erythema, pain during application, or excessive discomfort) were observed in either group throughout the entire study period.

Table 3
— Exploratory analyses of clinical predictors and subgroup factors associated with oral mucositis severity.

Part A - Logistic regression			
Analysis	**Comparison**	**Statistic**	**p**
Logistic regression (ref: never smoked):	Active smoker: OR 0,87 (0,20–3,68)	--	.846
	Former smoker: OR 0,70 (0,20–2,41)		.569
Logistic regression - PBM group	TC vs IO: OR 0,94 (0,32–2,70)	-	.902
Part B - Bivariate tests (χ^2/Fisher)			
Analysis	**Comparison**	**Statistic**	**p**
Smoking status × OM grade ≥ 2 (T4)	Active smoker/former smoker vs never smoked	χ^2	.835
Smoking status × OM grade ≥2 (T5)	Active smoker/former smoker vs never smoked	χ^2	.967
Chemotherapy regimen × OM (T5)	Cisplatin/capecitabine vs. carboplatin/DCF	χ^2=2,99	.224
Treatment modality × OM (T5)		χ^2 =1,56	.669
Topographic distribution (grade ≥ 2)	TC vs IO	Fisher	.979
Topographic distribution (grade 1)	TC vs IO	Fisher	.196

DISCUSSION

The hypothesis of this study was that transcutaneous photobiomodulation (TC-PBM) would be clinically non-inferior to intraoral photobiomodulation (IO-PBM) in the prevention of radiotherapy- or chemoradiotherapy-induced oral mucositis (OM) in patients with head and neck cancer. The findings supported this hypothesis, demonstrating that TC-PBM achieved clinical outcomes comparable to those of IO-PBM. The groups showed similar patterns of OM development, particularly up to the 13th radiotherapy session, with no statistically significant differences in overall severity according to the WHO scale, cumulative incidence, time to lesion onset, anatomical distribution of lesions, or pain intensity. No significant group-by-time interaction was observed. To our knowledge, this study is among the first non-inferiority randomized trials to directly compare these two PBM delivery routes in this clinical setting. Its relevance, therefore, goes beyond confirming the already established benefits of PBM in reducing the incidence, severity, and pain associated with OM [1, 5, 13]. Rather, it addresses an important and still insufficiently explored question: whether TC-PBM application can offer clinical efficacy comparable to that of IO-PBM while providing a potentially more feasible treatment delivery approach. This is particularly relevant because it shifts the discussion away from the overall efficacy of PBM already established and recommended by MASCC/ISOO guidelines for mucositis prevention in head and neck

radiotherapy, toward a question that remains largely unresolved in the literature: whether the transcutaneous route can achieve the clinical efficacy of intraoral application while offering greater delivery feasibility [1, 4].

Our results converge with the multicenter trial by Klein et al. (2025) [9], which included 58 patients, compared intraoral application at 660 nm with extraoral application at 810/980 nm, and found no difference between groups for any mucositis grade by the WHO or NCI scales, nor for time to ulcerative mucositis. This finding is also consistent with an earlier multicenter study by the same group, in which transcutaneous PBM was as effective as intraoral PBM in the course of mucositis during radiotherapy, with a possible additional functional benefit on dysphagia [15]. Taken together, these data suggest that clinical non-inferiority between light delivery routes is beginning to emerge consistently in the literature, albeit still on a limited empirical basis.

This convergence gains practical relevance when considering that intraoral protocols at 632.8–660 nm remain the best-studied historical foundation, with reductions in pain, delayed mucositis onset, and lower severity during radiotherapy [1, 16]. However, IO application, while effective, may be uncomfortable or logistically challenging in patients with severe odynophagia, trismus, nausea, pain, or extensive lesions. In this context, the TC route emerges as a non-invasive and more feasible alternative for routine hospital use [8], which is consistent with reviews describing PBM as a well-accepted and safe intervention that specifically facilitates adherence to oncologic treatment and quality of life [17, 18].

To understand how the TC route may reproduce a clinical effect non-inferior to that of direct application, it is necessary to consider both the pathophysiology of the lesion and the optics of the tissues involved. Radiation-induced OM arises from complex inflammatory cascades mediated by reactive oxygen species, pro-inflammatory signaling, and progressive basal mucosal damage. PBM acts on the processes of inflammation, analgesia, and tissue repair, without necessarily fully preventing the cumulative damage induced by radiation [19, 20, 21]. From a physical standpoint, the biological plausibility of TC-PBM depends on the penetration of infrared light into tissues. Although red light (660 nm) is widely effective for superficial mucosal lesions, due to high absorption by cytochromes in the epidermal layers, its power density attenuates exponentially as it passes through deeper soft tissues. In contrast, the infrared wavelength (808 nm) lies within the tissue "optical window," with lower scattering and absorption coefficients by hemoglobin and water, allowing photons to traverse the skin and muscle layers to reach the basal layer of the oral mucosa [22]. It is therefore biologically plausible that the energy density delivered transcutaneously, despite partial attenuation by extraoral tissues, was sufficient to stimulate the mitochondrial chain and suppress pro-inflammatory cytokine cascades in a manner comparable to direct intraoral light administration. Nonetheless, our study design focused on clinical outcomes and did not directly measure these biochemical interactions.

The longitudinal trajectory of OM in our study follows the classic pathophysiological model of radiation-induced mucosal injury, in which fractionated radiotherapy produces cumulative daily damage, overlapping with already activated inflammatory and repair pathways, leading to clinical worsening after

the first weeks of treatment [23]. The statistically significant progression of scores from T3 onward is consistent with the literature, which places the initial signs of OM around 20–30 Gy, with substantial worsening after approximately 2–3 weeks and severe OM occurring around day 35, or a median cumulative dose of 37.7 Gy [23, 24, 25]. This temporal behavior is biologically plausible: ionizing radiation induces the generation of reactive oxygen species, DNA damage, and double-strand breaks in epithelial cells and mucosal stem cells, promoting apoptosis, loss of basal renewal, ulceration, and inflammatory amplification [26, 27, 28].

In this context, our study shows that PBM does not completely eliminate toxicity but flattens the severity curve, which is consistent with evidence that PBM reduces incidence, pain, and severe mucositis from weeks 2–3 onward, without necessarily abolishing all events, although some protocols show a lower frequency of high grades and even the absence of grade 4 [5, 29, 30]. This pattern is consistent with a meta-analysis of 14 evaluated trials, in which PBM reduced OM incidence from the second week and severe OM from the third week, without completely eliminating toxicity [5]. These data help explain why, even with PBM, OM still occurs in a substantial proportion of patients: the intervention modulates lesion intensity but does not fully block the cumulative damage caused by RT/CRT [5, 17]. The same pattern appears in individual studies, such as that of Marín-Conde et al. (2019) [29], in which significant differences emerged from week 5 onward, with 72.7% normal mucosa in the laser group versus 20.0% in the control group, and 40.0% of controls presenting grade 2 OM.

The maintenance of a median WHO grade of 2 and the prevention of grade 4 peaks in our study also converge with prospective studies in which prophylactic PBM kept average toxicity at moderate levels, peaking around week 7, with a lower incidence of severe OM compared to other studies [21, 31]. The role of concomitant chemotherapy is relevant in part of the literature, but is not uniform across cohorts and regimens [24, 32, 33], making it plausible that it did not retain significance in our adjusted model.

The fact that nearly our entire sample was treated with IMRT reinforces the external relevance of the study, as contemporary literature emphasizes that much of the historical OM data originated in the era of 3D conformal radiotherapy, while modern practice is dominated by IMRT [34]. Nevertheless, IMRT does not eliminate OM: in the prospective study by Iovoli et al. (2023) [34], 98.6% of patients developed some grade of OM and 62.5% developed severe OM by the end of treatment, which helps contextualize why our groups still presented relevant toxicity despite PBM and the use of a modern technique. In this same regard, the absence of a significant association between concomitant chemotherapy and greater severity in our model should be interpreted with caution, and not as evidence of an absence of effect: PBM trials and reviews in head and neck cancer generally include patients undergoing RT with or without chemotherapy, and show PBM benefit in both scenarios [1, 35, 36]. It is plausible that, in a comparative sample between two active arms such as ours, the temporal and dosimetric effect of radiotherapy predominated over the effect of chemotherapy in explaining the observed variance.

The pain results are also consistent with the literature. The absence of difference between the two application routes does not contradict previous studies, as studies with different wavelengths have

observed pain reduction without difference between groups [35]. On the other hand, when PBM is compared to placebo or control, the predominant trend is analgesic benefit: Shen et al. (2024) [5] found pain improvement with a weighted mean difference of − 1.09, and Ameri et al. (2026) [21] reported pain reduction already in the first week, with lesion improvement from the third week onward. In a therapeutic trial involving grade 3–4 mucositis, Barati et al. (2025) [37] also observed significant pain reduction and improved quality of life in the PBM group.

The absence of an independent association between active smoking and greater mucositis severity in our final model should also be interpreted with caution, as the recent literature is heterogeneous: reviews and observational studies identify smoking as a risk factor for the occurrence or severity of radiation-induced OM [38, 39, 40], while other findings show inconsistent behavior, including later OM onset in patients with a smoking history [24]. This discrepancy makes it plausible that, in our sample, factors such as underreporting of exposure, recent cessation during treatment, and the predominance of dosimetric determinants reduced the statistical effect of smoking, since OM severity tracks dose and irradiated volume more consistently than isolated clinical variables [24, 38, 40]. The hypothesis of partial compensation by PBM is also consistent with the literature, given that PBM reduces mucositis incidence, modulates pro-inflammatory cytokines, increases anti-inflammatory mediators, improves oxidative balance, and favors tissue repair, angiogenesis, re-epithelialization, and collagen deposition, although the overall strength of this evidence remains limited by methodological heterogeneity across reviews and protocols [2, 4, 41].

The anatomical distribution of the observed lesions also reflects this dosimetric logic: the higher frequency at the tongue borders, soft palate, and buccal mucosa is consistent with OM occurring preferentially in non-keratinized mucosa overlying the high-dose fields used for tumors of the oral cavity and oropharynx. Studies show that OM severity is related to dose-volume parameters of the oral mucosa, reinforcing that lesion topography largely reflects the geometry of the irradiated target volumes [4, 42].

A plausible interpretation for the predominance of grade 1 lesions in the labial and buccal mucosa, with no topographic difference between TC and IO, is that these sites receive greater relative photoprotection, as they are more directly irradiated by the laser and routinely covered in both treatment protocols [14]. At the same time, the literature does not support that this protection is complete: the lateral tongue, multiple sites, and deeper areas remain more resistant to protection, likely due to less favorable geometry, greater tissue thickness along the light path, and limitations in light coverage [14, 22, 43]. In summary, there is experimental, anatomical, and clinical grounding to discuss that the labial and buccal mucosa may receive greater laser photoprotection, particularly due to accessibility and direct coverage.

This study has limitations that warrant joint discussion. First, complete operator blinding during PBM application proved unfeasible, given the evident visual and procedural differences between TC and IO applications. Since the same team applied PBM and assessed mucositis, the possibility of assessment bias cannot be ruled out, as the severity outcomes (WHO, NCI-CTC v2.0) and pain have components

dependent on clinical or patient-reported evaluation; future studies could employ centralized, independent, blinded assessment of intraoral photographs for at least part of the morphological outcomes. Second, some clinical variables, such as detailed TNM staging and histological classification, were collected retrospectively from medical records, resulting in a small amount of missing data, which did not interfere with the adjusted models. Third, there was no PBM-free arm, a limitation shared by much of the recent literature in this area, as well as by the logistical challenges inherent to the clinical implementation of repeated protocols [8, 44]. Finally, the literature highlights heterogeneity in parameters across studies, wavelengths ranging from 635 to 980 nm, TC and IO applications, and wide dose variation, which limits direct comparisons and protocol standardization [45]. Future multicenter studies with larger cohorts are needed to validate these findings across different radiotherapy techniques and to assess long-term patient-reported quality of life. Nevertheless, a strength of this study lies in offering a direct comparison between two PBM delivery routes still scarcely investigated together, consolidating evidence that the transcutaneous route contributes to OM control in a manner non-inferior to the intraoral route, already classically recognized as effective in preventing radiation-induced mucositis.

Even considering these limitations, the study brings a relevant clinical implication: TC-PBM emerges as a feasible and well-tolerated alternative for OM prevention in irradiated head and neck cancer patients, particularly when the IO route is uncomfortable or logistically difficult [9, 45]. This is relevant because sessions related to intraoral PBM, although simple, are time-consuming and sometimes uncomfortable, requiring dedicated resources and a care workflow [44]. In summary, the results support that the 808-nm transcutaneous protocol evaluated may expand PBM implementation without a detectable loss of clinical efficacy relative to the 660-nm intraoral protocol tested, in line with the need for more pragmatic protocols in supportive oncology.

CONCLUSION

Transcutaneous photobiomodulation (808 nm) is non-inferior to intraoral photobiomodulation (660 nm) in controlling the severity of radiation-induced oral mucositis in patients with head and neck cancer. TC-PBM is a non-invasive and operationally advantageous alternative (shorter application time) for clinical practice, particularly in patients with severe or intense trismus, or with compromised oral access.

Declarations

Human Research Ethics Committee This study was approved by an accredited Human Research Ethics Committee (HREC), in accordance with national ethical guidelines for research involving human subjects (Resolutions No. 466/12 and No. 510/2016 of the National Health Council). All participants signed the Informed Consent Form (ICF) before participating in the study.

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Author Contribution

WTK: participated from the beginning of the project's development, carried out patient recruitment, material collection, and photobiomodulation in patients. Wrote the text.GLKR:participated from the beginning of the project's development, carried out patient recruitment, material collection, and photobiomodulation in patients.Collaborated on the writing and reviewed the text.IBS: carried out patient recruitment, material collection, and photobiomodulation in patients. Collaborated on the writing and reviewed the text.MLFC:carried out patient recruitment, material collection, and photobiomodulation in patients. Collaborated on the writing and reviewed the text.LMS: assisted in patient recruitment, assisted in patient care, and provided the physical structure for patient care. Collaborated on the writing and reviewed the text. LAL: collaborated on the definition of dosimetric parameters for the protocols, provided equipment for the research.Collaborated on the writing and reviewed the text.MRA: participated from the beginning of the project's development, coordinated patient recruitment, material collection, and photobiomodulation in patients. He collaborated on the writing and performed the revision of the text.

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DATA AVAILABILITY

No datasets were generated or analysed during the current study.

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Figures

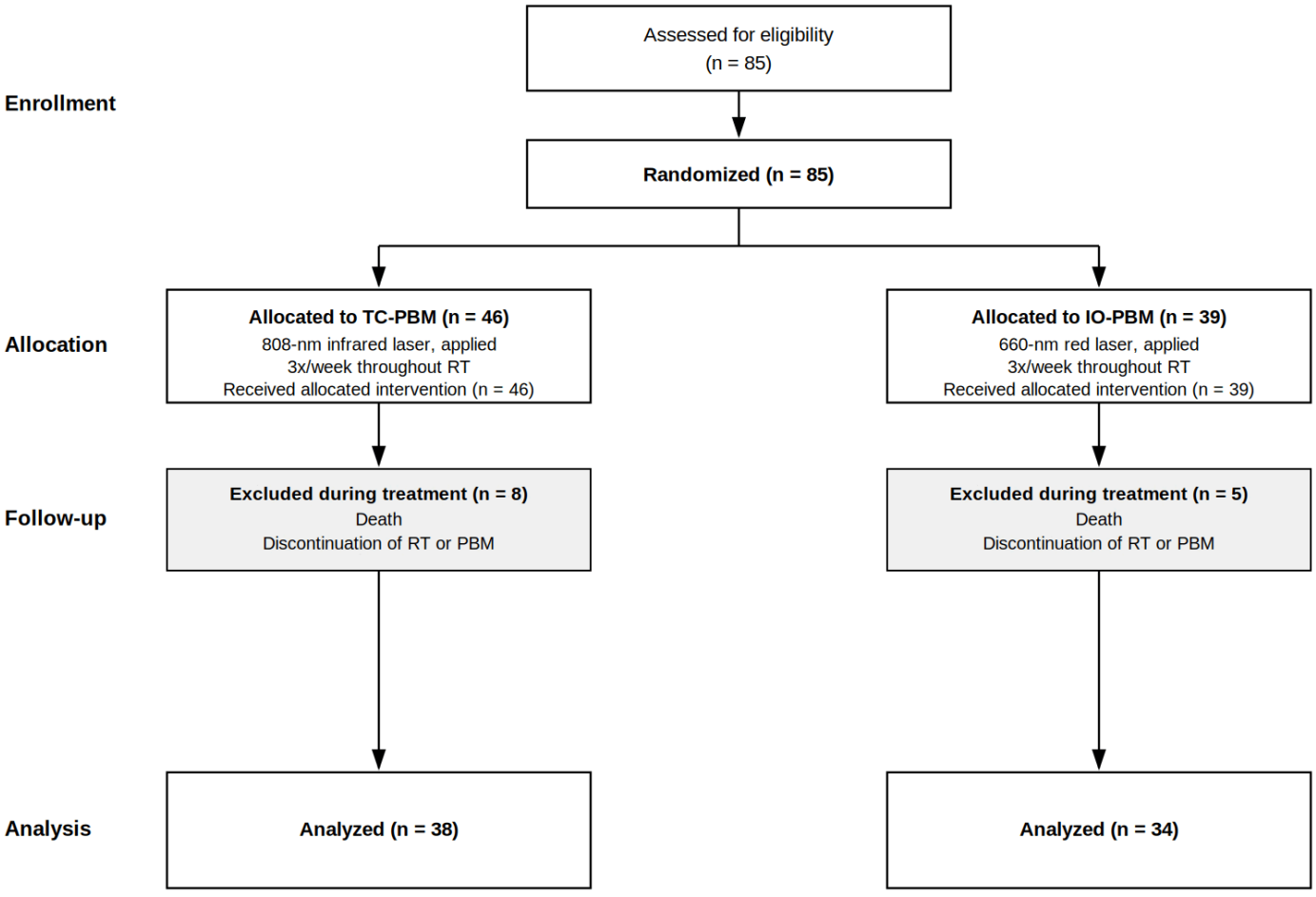


Figure 1

CONSORT flow diagram of patient randomization, allocation, and analysis.

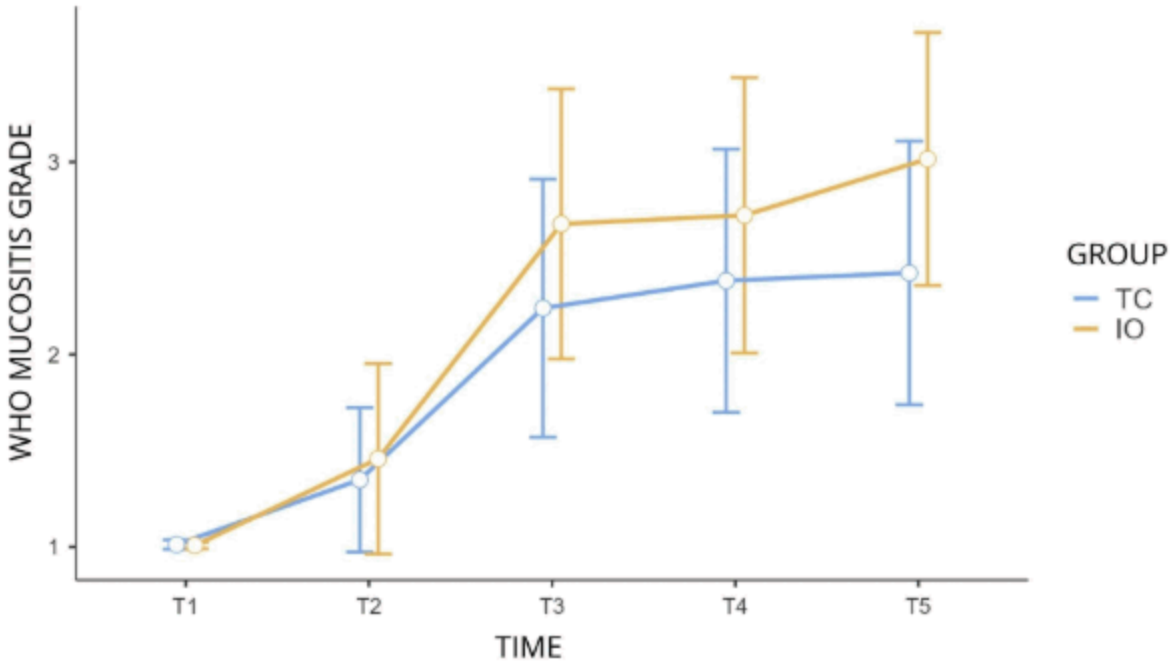


Figure 2

Estimated marginal means of oral mucositis (OM) severity across treatment groups and radiotherapy time points.

TC: transcutaneous photobiomodulation; IO: intraoral photobiomodulation. OM grade follows the WHO scale (0–4). Time points: T1 (week 1, days 1–6), T2 (week 2, days 7–12), T3 (week 3, days 13–20), T4 (week 4, days 21–26), and T5 (final week, days 27–33). Error bars represent 95% confidence intervals (CI) around the estimated marginal means.

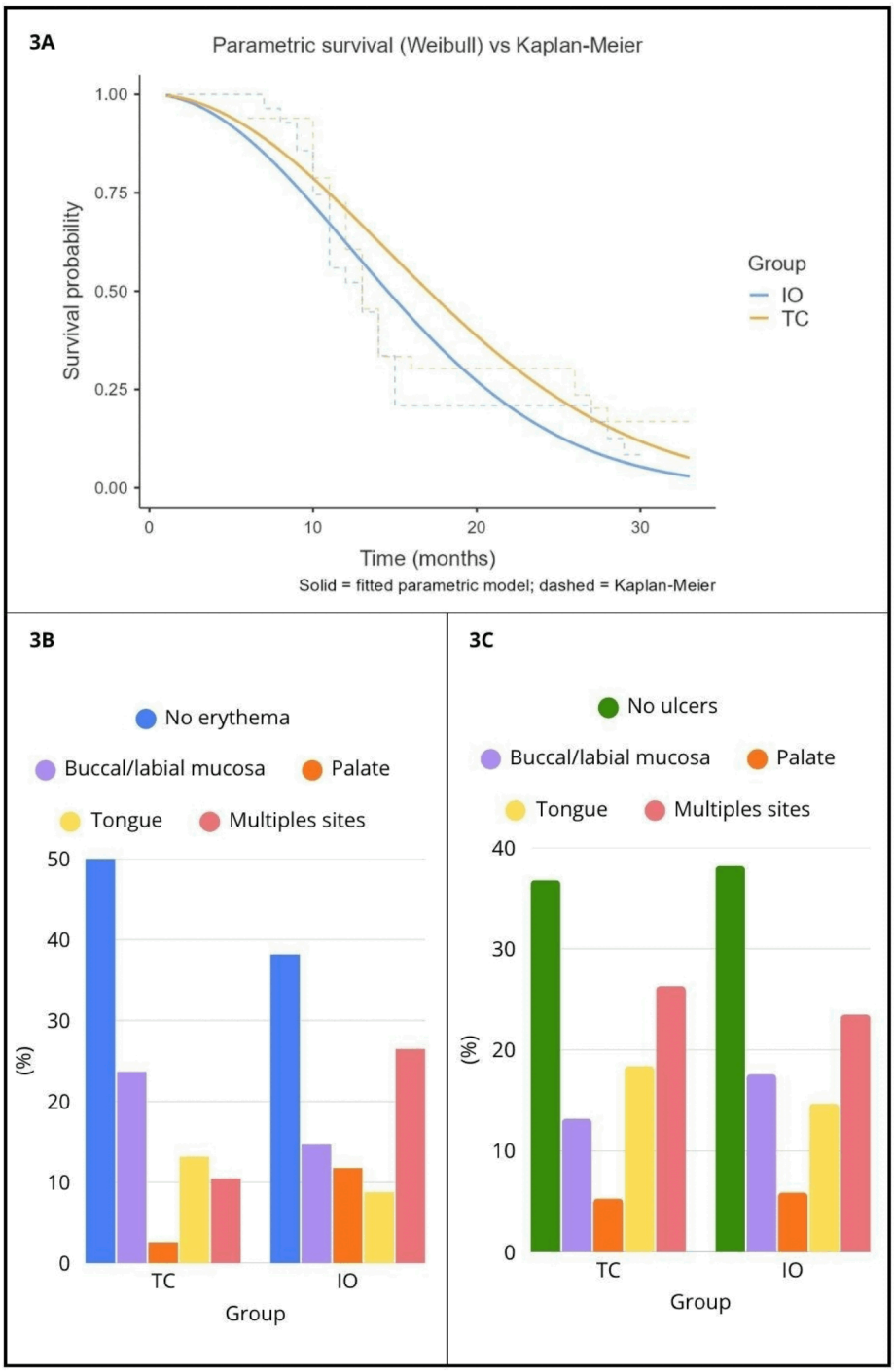


Figure 3

Time to onset and topographic distribution of oral mucositis by grade and treatment group.

3A: Kaplan-Meier survival curves comparing time to grade ≥2 oral mucositis (OM) between the transcutaneous (TC) and intraoral (IO) photobiomodulation (PBM) groups (log-rank p = 0.549). The dashed line indicates the median survival time. **3B:**Topographic distribution of grade 1 OM lesions in the

TC-PBM and IO-PBM groups. **3C:** Topographic distribution of grade ≥2 OM lesions in the TC-PBM and IO-PBM groups. Values are expressed as percentages (%) of affected sites.