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Photobiomodulation During Chemoradiation for Head and Neck Cancer: Effect on Mucositis, Weight Loss, and Feeding Tube Dependence

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Scientific Article

Photobiomodulation During Chemoradiation for Head and Neck Cancer: Effect on Mucositis, Weight Loss, and Feeding Tube Dependence

Photobiomodulation during CRT for HNC

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ABSTRACT

Purpose: The standard therapeutic approach in head and neck cancer (HNC) involves multimodality therapy, including surgery, radiation (RT), or chemoradiation (CRT). Treatment complications (mucositis, weight loss, and feeding tube dependence [FTD]) can result in treatment delays, incomplete treatment, and decreased quality of life (QOL). Studies on photobiomodulation (PBM) have shown promising reductions in mucositis severity but with little quantitative supporting data. We compared complications for HNC patients receiving PBM with those in patients who did not, hypothesizing that PBM improves mucositis severity, weight loss, and FTD.

Methods: Medical records of 44 patients with HNC treated with CRT or RT from 2015 to 2021 were reviewed (22 PBM, 22 controls; median age, 63.5 y (range 45-83 y). Between-group outcomes of interest included maximum mucositis grade, weight loss, and FTD 100 d after initiation of treatment.

Results: Median RT doses were 60 Gy (PBM) and 66 Gy (control). Eleven patients treated with PBM received CRT; 11 received RT alone (median of 22 PBM sessions [range 6-32]). Sixteen control group patients received CRT; 6 received RT alone. Median maximal mucositis grades were 1 in the PBM group and 3 in the control group ($P < .0001$). The adjusted odds of higher mucositis grade were only 0.024% ($p < .0001$, 95% CI: 0.004, 0.135) in PBM, compared to the control group.

Conclusions: PBM may have a role in decreasing complications related to RT and CRT for HNC, mainly mucositis severity.

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Introduction

Treatment for head and neck cancer (HNC) often requires a combination of surgery, chemotherapy (CHT), and/or radiotherapy (RT). Nearly all patients experience short-term toxicity during their course of cancer treatment. In addition, long-term toxicities significantly impact normal organ systems years beyond successful completion of therapy.[1] Multiple studies have shown such toxicities can negatively impact subjective and objective measures of quality of life (QOL). [2–4]

Outcomes for HNC have improved dramatically in the last decades. As a result, clinicians and investigators have begun to evaluate various supportive care measures and technologies to improve toxicity without compromising oncologic outcomes.[5] One such supportive care measure is photobiomodulation (PBM) therapy. PBM, which has been studied for more than five decades[6], is a noninvasive transcutaneous or transmucosal red/near-infrared light that produces a wide range of physiologic effects when applied in human cells and tissues.[7] PBM is thought to work predominantly on a protein in the mitochondria (cytochrome c oxidase) to increase adenosine triphosphate and decrease cellular stress resulting from oxidation.[8,9] Several downstream effects, including faster tissue repair and reduced inflammation, can result in decreased pain, swelling, and inflammation. PBM use has demonstrated improvement in symptoms from several chronic inflammatory conditions and decreased side effects from medical treatments, including chemoradiotherapy (CRT).[1]

Concerns have been expressed that PBM might negatively impact cancer outcomes by increasing tumor metabolism and growth. However, this hypothesis has been tested with no compelling supporting evidence;[10,11] in fact, one study suggests improved survival in patients receiving PBM.[12]

The benefit of PBM in decreasing treatment-related dermatitis and mucositis has been well reported but not adequately quantified.[13] In addition, the impact of PBM on other important metrics, including weight loss, feeding tube dependence (FTD)hospitalization rates, and treatment delays, is not well documented. We chose to look at FTD 100 days after radiotherapy, as we believe acute toxicities

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related to RT (i.e. dysphagia) resulting in FTD should be resolved by this time point. Our study sought to examine several of these parameters in patients receiving treatment for HNC supplemented by PBM.

Materials and Methods

Patients and treatment

This retrospective, IRB-approved study was conducted at a single institution from July 2015 to January 2021. We evaluated patients with nonmetastatic, nonrecurrent HNC undergoing RT or CRT either postoperatively or definitively, who received concurrent PBM during cancer-directed therapy. Patients who underwent PBM were selected and matched 1:1 with controls based on head and neck disease subsite, age, RT fields, and RT dose. Controls were selected from a pool of all patients treated over the course of 6 years of the study.

RT utilized volumetric-modulated arc therapy and was delivered 5 d/wk over 5-7 weeks at 1.7– 2 Gy/fraction in the majority of cases. Patients in the PBM group received 2–5 sessions per week starting the first wk of RT, with PBM session frequency at the treating physician's discretion. PBM continued until 2 wk after completion of treatment or longer when toxicity persisted. Both patient groups received standard oral hygiene education per institutional standards, which included dietary and dental consultation pre-treatment, education on oral hygiene, and instruction on performing salt and soda rinses at least three times per day.

PBM therapy was delivered utilizing the Pointer Pulse, emitting light in the red visible spectrum (650 nm). Light measurement was completed using the Power meter (Thoralabs, USA). Clinically relevant treatment points were determined prior to starting RT at the discretion of the treating physician based on areas anticipated to receive the highest dose of RT. Each point was treated with a power of 5 mW and an irradiation time of 120 seconds per acupoint. Beam area was 3.14 mm2 (fluence 19.2J/cm2, power density 0.16 W/cm2, total dose = 0.6 J).

Study endpoints

Weight loss was calculated as each patient's pretreatment body weight in kilograms minus his or her weight 1 mo after completion of treatment, expressed as a percentage.

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FT utilization was first evaluated by looking at the number of patients in either group who required FT placement during cancer treatment. Second, we evaluated the number of patients who were FT dependent 100 d (FT100) after the final day of treatment. The time point of 100 d post treatment was chosen as the authors believe that at this time point, acute toxicities related to RT should have subsided by this time point.

Physician-reported mucositis severity was graded based on Common Terminology Criteria for Adverse Events v5.0 for oral mucositis (G1, asymptomatic or mild symptoms, intervention not indicated; G2, moderate pain or ulcer not interfering with oral intake, modified diet indicated; G3, severe pain, interfering with oral intake; G4, life-threatening consequences, urgent intervention indicated; G5, death). The time to maximum mucositis was also calculated in number of days from the start of treatment to the day of maximum mucositis experienced by the patient as documented by the treating physician.

For the purposes of the study, a hospitalization was defined as any emergent or medical clinic visit resulting in admission of ≥1 night during the patients' course of cancer treatment. If a patient was admitted for ≥1 night on 2 separate occasions, this was considered as 2 hospitalizations.

Treatment delay was calculated based on the initial RT prescription and the projected number of total fractions. For example, if a patient was prescribed a 30-fraction course of RT, then the anticipated number of days to complete the RT course would be 42 to account for both treatment days and weekends. Due to transportation difficulties, external conflicts, or mild illness, missed treatments are not uncommon. For this reason, a predefined number of >2 d was considered to be a delay outside of normal expectations. The median treatment delay (number of days) as well as number of delays >2 d were evaluated.

Statistical analysis

Patients' baseline demographics, tumor characteristics, and primary study endpoints were compared between groups using Wilcoxon rank sum tests for continuous variables. The χ^2 test (or Fisher exact test when necessary) was conducted for categorical variables. To investigate the association between mucositis and FT placement requirement during treatment and group status (PBM vs control), both univariable and multivariable regression analyses were performed. In the multivariable analysis

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where in addition to group status, age, gender and smoking status, T stage, RT dose, and use of chemotherapy and/or surgery were accounted for. Baseline swallow function was not able to be accounted for due to the lack of pre-treatment information in the chart review. Because mucositis grade is ordinal in nature, a proportional odds model was employed (a regression model generalization of the Wilcoxon rank sum test (Harrell, 2022)). A logistic regression model was employed for FT placement requirement. All statistical analyses were performed using R 4..2.1 (R Core Team; Vienna Austria) and the "*rms*" (v6.3-0) package.

Results

Of the 44 patients evaluated in this study, 22 received PBM and 22 were matched historic controls based on age, smoking status, dose, and use of concurrent chemotherapy. **Table 1** shows baseline demographic and histopathologic characteristics, which were well balanced between the 2 groups. The median age was 63 y (IQR 54–66.5 y), and 74% of patients in each group had squamous cell carcinoma. Forty-six percent and 32% of patients in the control and PBM groups, respectively, were active smokers during treatment.

Table 2 includes treatment characteristics, again similar for the 2 groups. The majority of patients underwent upfront resection for their HNC, whereas only 18% and 14% of patients in the control and PBM groups, respectively, were treated with definitive CRT. Only 9% of patients in each group received RT alone. Postoperative CRT was administered for 55% and 36% in the control and PBM groups, respectively, with corresponding percentages of 18% and 55% for postoperative RT alone. Cisplatin was the most commonly administered systemic therapy, in 81% and 72% of patients in the control and PBM groups, respectively. Median prescribed RT doses were 60 Gy (range, 41.4–70 Gy) in the PBM and 66 Gy (range, 50–70 Gy) in the control groups.

Table 3 compares toxicity outcomes. No significant between-group differences were noted in weight loss during cancer treatment, FT placement or dependence, number of hospitalizations, number of treatment delays, or number of days to maximum toxicity between. To further quantify the association between FT placement requirement during treatment and group status, logistic regression analyses were

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run. The results revealed that FT placement requirement during treatment was not significantly associated with group status. In particular, in the univariable analysis where only group status was used as the predictor, the odds of FT placement requirement during treatment in PBM are 0.463 times the odds of FT placement requirement during treatment in the control group, although it is important to note that this value was not statistically significant (p = 0.3496, 95% CI: 0.092, 2.324). Although in **Table 1**, there was no significant difference in age and distribution of sex between the two groups, age, sex, smoking status, and radiotherapy dose were still used in the multivariable regression analysis as they were deemed as important factors influencing the association between group status and FT placement requirement. The results revealed that the odds of FT placement requirement during treatment in PBM are 0.412 times the odds of FT placement requirement in the control group, however once again this was not statistically significant (p = 0.3081, 95% CI: 0.075, 2.267).

To further quantify association between mucositis and group status, regression analyses using proportional odds models were conducted. For univariable analysis where only group status was used as the predictor, the results revealed that PBM was significantly associated with lower mucositis grade (p <.0001). In particular, the odds of higher grade of mucositis in PBM are only 0.0283 times the odds of higher grade of mucositis in the control group (p <.0001, 95% CI: 0.005, 0.155). In other words, higher grade of mucositis are less likely to appear in PBM. Although in **Table 1**, there was no significant difference in age and distribution of sex between the two groups, we included these factors in the multivariate analysis in addition to smoking status, T stage, RT dose (as the median dose in each group differed), and use of upfront surgery and/or chemotherapy in the multivariate analysis as they were deemed by the authors as important factors influencing the association between group status and mucositis grade according to a review of the available literature.[14,15] The results revealed that PBM was significantly associated with lower grade of mucositis (p <.0001). In particular, the odds of higher grade of mucositis in PBM are only 0.037 times the odds of higher grade of mucositis in the control group (p <.0001, 95% CI: 0.007, 0.145). In other words, higher grades of mucositis are less likely to appear in patients receiving PBM.

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Discussion

Standard of care treatment for HNC often requires multimodal therapy, including oncologic resection, RT, and/or CHT. Although outcomes are often favorable, these therapies present serious challenges in terms of toxicity and QOL months to years after treatment. The impact of PBM on mucosal toxicity grade, FTD, weight loss, and treatment delays during RT for HNC has not previously been well quantified. While we observed numerically less weight loss, fewer feeding tubes placed, less hospitalizations, and fewer treatment delays in patients receiving PBM treatment, no statistically significant differences in these variables were noted between groups. The use of PBM during RT for HNC in this study was associated with a significantly lower mucositis toxicity grade, with fewer patients experiencing grade 2+ and only 1 patient reporting grade 3+ toxicities. The control group included 14 patients with grade 3 and 1 patient with grade 4 toxicities. Our findings suggest that PBM may be an effective therapy to reduce the severity of mucositis during treatment for HNC.

Reducing toxicity from HNC treatment is important for several reasons. It helps patients' complete treatment in a timely, uninterrupted manner, thereby avoiding compromised outcomes and results in faster recovery, restored functionality, and possibly improved QOL although this was not explored in this study. Decreasing toxicity rates could help patients avoid unnecessary medical procedures and complications, however further studies are needed to evaluate this.

Strategies to mitigate toxicity, including de-escalation of treatment in low-risk patients[16–19] or oral or topical medications/treatments to decrease side effects, are under active evaluation.[20] PBM has demonstrated promising improvements in CRT-related mucositis by decreasing inflammation and pain severity and by promoting mucosal healing.[7] PBM is simple to administer and can be executed as frequently as needed within the constraints of time. In contrast to oral pain medications and prophylactic agents, PBM has few to no reported side effects.[1,12,21–23]

Future studies with a larger number of patients and improved study design could expand on the utility of observations documented here. The retrospective nature of this study limits conclusions based on both comparisons and findings, as does the relatively small number of patients included. In addition,

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the authors recognize that the 1:1 match design of this study poses several limitations to final study results. This design is inefficient, leaving the study statistically underpowered due to detect differences between the groups. In future studies, additional matches in the control group would certainly be beneficial. Regression-based covariate adjustment using the broader range of available data from a higher number of controls would permit possible reproof of other coefficients aside from PBM.

In conclusion, our study indicates that patients receiving PBM during RT for HNC are less likely to develop severe mucositis than patients who do not. PBM is a promising newer strategy which could improve toxicity outcomes for patients with HNC undergoing cancer-directed therapy, and future studies are needed to further refine its role for this patient population.

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Table 1. Baseline patient characteristics

	Control	PBM	*P**
	n = 22	*n* = 22	
Patient age in y			
Median (IQR)	63 (54–66.5)	63.5 (54–66.5)	0.698
Patient sex			
Men	17 (77.3%)	17 (77.3%)	0.999
Women	5 (22.7%)	5 (22.7%)	
Active smoker during treatment			
Yes	10 (45.5%)	7 (31.8%)	0.536
No	12 (54.5%)	15 (68.2%)	
Primary tumor site			
Oral cavity	10 (45.5%)	10 (45.5%)	
Larynx	5 (22.7%)	5 (22.7%)	
Oropharynx	4 (18.2%)	5 (22.7%)	0.893
Hypopharynx	1 (4.5%)	0	
Other	2 (9.1%)	2 (9.1%)	
Tumor histology			
Squamous cell carcinoma	19 (74.3%)	19 (74.3%)	0.999
Other	3 (21.3%)	3 (21.3%)	
P16 status			
Positive	4 (18.2%)	2 (9.1%)	
Negative	5 (22.7%)	10 (45.5%)	0.319
Unknown	13 (59.1%)	10 (45.5%)	
T stage			
T0–2	7 (31.8%)	6 (27.3%)	
T3–4	15 (68.2%)	16 (72.7%)	0.999
T unknown	0	0	
N Stage			
N0–1	9 (40.9%)	8 (36.4%)	
N2–3	13 (59.1%)	13 (59.1%)	0.589
N unknown	0	1 (4.5%)	
Karnofsky performance status			
90–100	10 (45.5%)	11 (50%)	
70–80	11 (50%)	11 (50%)	0.592
<70	1 (4.5%)	0	

Abbreviations: PBM = photobiomodulation; IQR = interquartile range.

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Table 2. Patient treatment characteristics

	Control	PBM	*P**
	n = 22	*n* = 22	
Upfront surgery			
Yes	16 (72.7%)	17 (77.3%)	0.999
No	6 (27.3%)	5 (22.7%)	
Treatment characteristics			
Definitive CRT	4 (18.2%)	3 (13.6%)	
Definitive RT alone	2 (9.1%)	2 (9.1%)	
Postoperative (adjuvant) CRT	12 (54.5%)	8 (36.4%)	0.437
Postoperative (adjuvant) RT alone	4 (18.2%)	12 (54.5%)	
Systemic agents used			
Cisplatin	13 (81.3%)	8 (72.3%)	
Carbotaxol	1 (6.3%)	3 (27.3%)	0.318
Cetuximab	2 (12.5%)	0	
Median maximum RT dose			
Median, Gy (IQR)	66 (6)	60 (6)	0.275
Range, Gy	30–70	41.4–70	
Number of PBM treatments			
Days (IQR)	NA	22 (17.25–24)	NA

Abbreviations: PBM = photobiomodulation; CRT = chemoradiation therapy; RT = radiation therapy; IQR = interquartile range.

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Table 3. Comparison of outcomes per group

	Control	PBM	*P**
Weight loss (kg)			
25%/median/75%	3.2/7.8/13.3	2.5/5.9/9.8	0.342
Feeding tube			
FT100: *n* (%)	14 (63.6)	10 (90.9)	0.212
FT during RT: *n* (%)	9 (64.3)	4 (45.5)	0.435
Mucositis grade			
25%/median/75%	2/3/3	1/1/2	**<0.0001**
Patients hospitalized			
n (%)	4 (18.2)	2 (9.1)	0.664
Treatment delay (d)			
25%/median/75%	2.0/3.0/4.75	0.25/2.0/4.0	0.186
Delay >2 d: *n* (%)	15 (68.2)	10 (45.5)	0.223
Range	0–51	0–26	NA
Days to max toxicity			
25%/median/75%	38/43/49	36.25/42.5/48.3	0.817

Abbreviations: PBM = photobiomodulation; FT100 = patients with feeding tube 100 d after completion of treatment; FT = feeding tube; RT =radiation therapy.

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