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Evaluation of Photo-Biomodulation Therapy (PBMT) on Salivary Flow and Composition in Head and Neck Cancer Patients Undergoing Radiation Therapy

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Abstract **Background:** Radiotherapy (RT) for head and neck cancer (HNC) commonly results in salivary gland dysfunction, leading to hyposalivation and xerostomia. Photo-biomodulation therapy (PBMT) has emerged as a potential protective intervention, but real-world evidence remains limited. This retrospective study evaluated the effects of PBMT on salivary flow and salivary composition in HNC patients undergoing RT. **Methods:** Clinical records of 78 HNC patients treated with PBMT during RT were reviewed. Unstimulated whole salivary flow (UWSF), stimulated salivary flow (SSF) and salivary biochemical parameters (pH, buffering capacity, total protein, amylase activity, electrolytes) were assessed pre- and post-PBMT. Subgroup analyses compared outcomes by PBMT frequency and RT dose distribution. **Results:** PBMT was associated with significant improvements in UWSF (0.18 to 0.22 mL/min, $p<0.001$) and SSF (0.42 to 0.63 mL/min, $p<0.001$). Salivary composition showed favorable changes, including increased pH (6.18 to 6.72), enhanced buffering capacity and higher protein and amylase levels. Patients receiving ≥2 PBMT sessions/week demonstrated greater functional gains than those receiving fewer treatments. Parotid-sparing RT further amplified improvements. **Conclusion:** PBMT was associated with clinically meaningful enhancement in salivary flow and composition among HNC patients receiving RT. These findings support PBMT may be valuable adjunctive supportive-care strategy for reducing RT-induced xerostomia. Prospective studies are needed to validate long-term durability and optimize treatment protocols.

Key Words Photo-Biomodulation Therapy, Xerostomia, Salivary Gland Dysfunction, Radiotherapy, Head and Neck Cancer, Hyposalivation, Salivary Flow Rate, Oral Supportive Care, Low-Level Laser Therapy, Salivary Composition

INTRODUCTION

Head and neck cancers (HNC) constitute a major global health burden, with an estimated 930,000 new cases and over 460,000 deaths annually worldwide [1]. Radiotherapy (RT), either as a definitive or adjuvant modality, remains a cornerstone in the management of HNC. Despite advances in conformal techniques such as intensity-modulated radiotherapy (IMRT), irradiation of adjacent normal tissues, particularly salivary glands, is often unavoidable, leading to significant functional impairment [2].

Radiation-induced salivary gland dysfunction manifests clinically as hyposalivation and xerostomia, affecting up to 80% of patients receiving glandular doses exceeding 50 Gy [3]. These complications extend beyond simple oral dryness and significantly impair mastication, swallowing, speech and overall quality of life. Furthermore, altered salivary composition characterized by reduced buffering capacity, decreased antimicrobial proteins and electrolyte imbalance predisposes patients to dental caries, oral infections and mucosal injury [4,5].

Current management strategies for RT-induced xerostomia remain suboptimal. Pharmacologic agents such as pilocarpine and cevimeline provide limited and often transient relief, while supportive measures fail to restore glandular function [6]. Consequently, there is growing interest in adjunctive therapies aimed at preserving or restoring salivary gland integrity during RT.

Photo-biomodulation therapy (PBMT), previously termed low-level laser therapy, has emerged as a promising non-invasive modality in supportive oncology. PBMT utilizes red or near-infrared light (600–900 nm) to modulate cellular activity via mitochondrial chromophore activation,

leading to increased ATP production, reduced oxidative stress and enhanced tissue repair [7]. Its clinical efficacy in preventing and managing oral mucositis is well established, with strong recommendations from the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) [8].

Beyond mucosal protection, PBMT has demonstrated potential benefits in preserving salivary gland function. Experimental and clinical studies suggest that PBMT may reduce radiation-induced apoptosis, improve microvascular circulation and maintain acinar cell integrity, thereby contributing to improved salivary flow [9]. However, existing evidence remains heterogeneous, with variability in PBMT protocols, timing and outcome measures. Importantly, while improvements in salivary flow have been reported, data on salivary biochemical composition, an essential determinant of oral homeostasis, remain limited.

In this context, retrospective clinical analyses offer valuable real-world insights by evaluating outcomes across routine oncology practice settings. Such data are particularly relevant in understanding treatment effectiveness beyond controlled trial environments and in identifying practical factors influencing therapeutic response.

Therefore, the present study aims to evaluate the effects of PBMT on both salivary flow rates and salivary biochemical composition in HNC patients undergoing RT. By analyzing routinely collected clinical data, this study seeks to provide clinically meaningful evidence on the role of PBMT as a supportive intervention in mitigating RT-induced salivary gland dysfunction.

Radiation-induced salivary gland injury is a complex, multifactorial process involving acinar cell apoptosis, microvascular damage and inflammatory cascades, ultimately leading to irreversible glandular hypofunction [10]. The severity of dysfunction is dose-dependent, with parotid glands being particularly sensitive to radiation exposure.

PBMT has gained increasing attention due to its biological effects at the cellular level. By stimulating mitochondrial respiratory chain activity, PBMT enhances ATP synthesis and promotes cellular repair mechanisms. Additionally, it exerts anti-inflammatory effects by reducing pro-inflammatory cytokines and oxidative stress, which are critical mediators of radiation-induced tissue injury [7].

Clinical studies have demonstrated that PBMT can improve salivary flow rates in patients undergoing RT, although the magnitude of benefit varies depending on treatment protocols and timing. Randomized controlled trials have reported improvements in both unstimulated and stimulated salivary secretion, suggesting a protective effect on glandular function [8]. Moreover, systematic reviews and clinical guidelines support the use of PBMT in managing oral complications associated with cancer therapy, particularly mucositis, with emerging evidence for xerostomia management.

In addition to quantitative improvements, qualitative changes in saliva are equally important. Salivary pH, buffering capacity, protein concentration and enzymatic activity are essential for maintaining oral health and preventing infection. However, limited studies have evaluated the impact of PBMT on these biochemical parameters, representing a significant gap in current literature.

Given these considerations, further investigation into both functional and compositional salivary changes is necessary to better understand the full therapeutic potential of PBMT in HNC patients undergoing RT.

Objectives

- To evaluate the effect of PBMT on unstimulated whole salivary flow (UWSF) in HNC patients undergoing RT
- To assess changes in stimulated salivary flow (SSF) following PBMT
- To analyze alterations in salivary biochemical parameters (pH, buffering capacity, protein, amylase, electrolytes)
- To compare outcomes based on PBMT treatment frequency
- To evaluate the influence of radiation dose distribution (parotid-sparing vs high-dose exposure) on salivary outcomes

METHODS

Study Design

This retrospective observational study analyzed clinical records of head and neck cancer patients who received PBMT during curative radiotherapy at a tertiary oncology center. Ethical approval was obtained from the institutional review board and the study adhered to the Declaration of Helsinki guidelines. Only anonymized data were used.

Patient Selection

Inclusion criteria were:

- adults ≥18 years;
- diagnosis of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx;
- definitive or adjuvant RT with or without concurrent chemotherapy;
- availability of documented PBMT records;
- documented salivary flow measurements before and after PBMT during RT

Patients were excluded if they had: previous salivary gland surgery; recurrent disease; prior RT to the head and neck region; systemic conditions affecting salivary secretion (e.g., Sjögren's syndrome, uncontrolled diabetes); or incomplete salivary data.

As a retrospective study, selection bias cannot be completely excluded.

PBMT Protocol

PBMT was administered using a diode laser system emitting red (660 nm) and/or near-infrared (808–830 nm)

wavelengths. The protocol followed MASCC/ISOO supportive care guidelines when applicable. Laser parameters were standardized where possible:

- Power output: 100 mW
- Spot size: 0.04–0.5 cm²
- Energy density: 2–4 J/cm² per point
- Application time: 20–40 seconds per point
- Frequency: 2–3 sessions per week during RT

Light was applied intraorally and extra-orally over major salivary glands (parotid and submandibular). All sessions were performed by trained clinicians.

Salivary Flow Assessment

Unstimulated whole salivary flow (UWSF) and stimulated salivary flow (SSF) were measured using standardized sialometry. For UWSF, patients expectorated into a pre-weighed sterile container over 5 minutes. For SSF, citric-acid stimulation was used. Values were recorded as mL/min. Baseline measurements were taken before PBMT initiation and follow-up measurements were recorded during the final week of RT.

Salivary Composition Analysis

Saliva samples were evaluated for pH, buffering capacity, total protein content, amylase activity and electrolyte concentrations (Na^+, K^+, Cl^- in mmol/L). Analyses were conducted in the institutional biochemistry laboratory using standard enzymatic and ion-selective electrode methods.

Data Collection and Statistical Analysis

Parametric or non-parametric tests were selected based on normality of data distribution. Demographic variables, tumor site, RT dose distribution, chemotherapy use, PBMT parameters and salivary outcomes were extracted from electronic medical records. Statistical analysis included paired t-tests or Wilcoxon signed-rank tests to compare pre- and post-PBMT salivary parameters. Subgroup analyses evaluated differences by RT dose and PBMT frequency. A p-value <0.05 was considered statistically significant. Data were analyzed using SPSS (version 26.0).

RESULTS

A total of 78 head-and-neck cancer patients who received PBMT during radiotherapy met the inclusion criteria. The median age was 57.4 years, with a male predominance (71.8%). Most patients had oropharyngeal (41%) or oral cavity cancers (32%). Table 1 summarizes the demographic and baseline clinical characteristics.

Salivary Flow Changes

At baseline, unstimulated whole salivary flow (UWSF) was markedly reduced (mean 0.18 mL/min). After PBMT, UWSF significantly increased to 0.22mL/min (p <0.001). Likewise, stimulated salivary flow (SSF) improved from 0.42 mL/min to 0.63 mL/min (p <0.001). (Table 2).

Table 1: Baseline Characteristics of the Study Population (n=78)

Variable	Value
Age, Mean±SD	57.4±9.8 years
Sex, n (%)	Male 56 (71.8%), Female 22 (28.2%)
Primary tumor site	Oropharynx 32 (41%), Oral cavity 25 (32%), Hypopharynx 11 (14%), Larynx 10 (13%)
RT modality	IMRT 68 (87%), 3D-CRT 10 (13%)
Concurrent chemotherapy	47 (60%)
Baseline UWSF	0.18±0.07 mL/min
Baseline SSF	0.42±0.16 mL/min

Table 2: Effect of PBMT on Salivary Flow Rates

Parameter	Pre-PBMT (Mean±SD)	Post-PBMT (Mean±SD)	p-value
Unstimulated whole saliva (mL/min)	0.18±0.07	0.22± 0.11	<0.001
Stimulated saliva (mL/min)	0.42±0.16	0.63±0.19	<0.001
Percentage improvement (UWSF)		+72%	
Percentage improvement (SSF)		+50%	

Table 3: Changes in Salivary Biochemical Composition After PBMT

Parameter	Pre-PBMT	Post-PBMT	p-value
pH	6.18±0.34	6.72±0.40	0.008
Buffering capacity (mEq/L)	3.1±1.2	3.85±1.4	0.012
Total protein (mg/mL)	0.84±0.26	1.12±0.31	0.004
Amylase activity (U/mL)	52.3±21.6	74.8±28.4	0.001
Sodium (mmol/L)	12.4±4.3	10.8±3.7	0.041
Potassium (mmol/L)	18.6±6.1	17.1±5.4	0.078
Chloride (mmol/L)	18.2±6.9	16.4±6.1	0.095

Table 4: Subgroup analysis; Outcomes by PBMT frequency and radiation dose

Subgroup	UWSF Improvement (mL/min)	SSF Improvement (mL/min)	Notes
PBMT ≥2 sessions/week (n = 54)	+0.17±0.06	+0.24±0.08	Significantly greater improvement
PBMT <2 sessions/week (n = 24)	+0.08±0.05	+0.13±0.06	Less pronounced gains
Parotid-sparing RT (n = 40)	+0.16±0.07	+0.25±0.09	Better gland preservation
Parotid dose >50 Gy (n = 38)	+0.10±0.05	+0.16±0.07	Reduced improvement

Salivary Composition Changes

PBMT was associated with changes notable improvements in biochemical parameters. Salivary pH increased from acidic (6.18) to near-neutral (6.72), while buffering capacity increased by approximately 24% (p <0.01). Total protein concentration and amylase activity also increased, indicating enhanced glandular functional output. Electrolyte concentrations showed moderate normalization post-therapy. Detailed biochemical comparisons are provided in Table 3.

Subgroup Analysis by Radiation Dose and PBMT Frequency

Patients who received PBMT ≥2 sessions/week showed greater improvements in UWSF (+0.17 mL/min) compared to those with <2 sessions/week (+0.08 mL/min). Similarly, patients receiving parotid-sparing RT experienced larger increases in SSF compared to those receiving higher gland doses (>50 Gy). These subgroup outcomes are summarized in Table 4.

DISCUSSION

This retrospective analysis demonstrates that photo-biomodulation therapy (PBMT) was associated with measurable differences in head and neck cancer (HNC) patients undergoing radiotherapy (RT). The significant improvements observed in both unstimulated whole salivary flow (UWSF) and stimulated salivary flow (SSF) after PBMT support its potential role as a complementary supportive care modality. These findings align with emerging evidence indicating that PBMT protects glandular tissue from RT-induced oxidative and inflammatory damage [11]. The observed improvements are particularly relevant given that RT-associated xerostomia remains one of the most debilitating complications affecting survivors' long-term oral health and quality of life.

Our findings are consistent with the randomized placebo-controlled trial by Lopez-Garzon *et al.*, which demonstrated that PBMT has been reported to be associated with restoration of salivary flow in head and neck cancer patients following radiotherapy [12]. The underlying mechanisms are likely multifactorial. PBMT has been shown to modulate mitochondrial activity, enhance ATP synthesis and attenuate apoptosis in salivary acinar cells exposed to radiation stress [13]. Additionally, PBMT improves microcirculation, promoting tissue oxygenation and facilitating cellular recovery factors that collectively contribute to enhanced glandular secretion [14].

The results demonstrate notable enhancements in salivary biochemical composition, including increased pH, buffering capacity, total protein and amylase activity. These findings are clinically important because qualitative salivary changes are as detrimental as quantitative loss. Acidification and reduced buffering capacity increase susceptibility to dental caries and mucosal infections, while diminished enzymatic activity compromises digestion and antimicrobial protection [15]. PBMT's ability to partially restore these parameters suggests that its benefits extend beyond flow restoration to more comprehensive preservation of glandular function.

Previous studies have also reported PBMT-induced changes in biomolecular markers, including reductions in pro-inflammatory cytokines such as TNF-α and IL-6 and increased expression of tissue-repair mediators [16]. While our study did not measure inflammatory biomarkers, the biochemical improvements observed likely reflect underlying anti- inflammatory and cytoprotective effects. These biochemical improvements may also play a role in ameliorating xerostomia-related symptoms, although patient-reported outcomes were not included in this retrospective analysis.

A key finding from our subgroup analysis is that PBMT frequency appears to influence treatment outcomes. Patients receiving ≥2 PBMT sessions per week exhibited greater improvements in UWSF and SSF than those receiving fewer sessions. This dose-response relationship supports recommendations proposed by professional societies suggesting that PBMT should be administered multiple times weekly for optimal effect [17-20]. The superior outcomes in patients undergoing parotid-sparing RT further highlight the cumulative importance of both technological and supportive interventions in mitigating xerostomia risk.

CONCLUSIONS

This retrospective study demonstrates that PBMT was associated with improved salivary gland function and increased salivary flow. PBMT not only was seen to enhance unstimulated and stimulated salivary flow rates but also improved key biochemical parameters, indicating better qualitative glandular performance. The observed benefits were more pronounced in patients receiving more frequent PBMT sessions and in those treated with parotid-sparing radiation techniques. These findings support PBMT may be a valuable adjunctive approach for mitigating the severity of radiation-induced xerostomia, one of the most impactful toxicities experienced by this patient population. Although additional prospective studies are needed to confirm long-term benefits and to standardize treatment parameters, the present results underscore PBMT's potential role in comprehensive supportive care, contributing to improved oral health and overall treatment tolerability.

Limitations

This study has several limitations that should be considered while interpreting the findings. First, the retrospective design inherently limits the ability to establish causality and is subject to potential selection bias, as only patients with complete clinical records and salivary assessments were included. Second, the study was conducted at a single center with a relatively modest sample size (n=78), which may limit the generalizability of the results to broader and more diverse patient populations. Third, although PBMT parameters were standardized as per institutional protocol, minor variations in application technique, operator handling and patient compliance could have influenced treatment outcomes. Fourth, the assessment was restricted to short-term changes observed during the course of radiotherapy and long-term durability of salivary gland recovery was not evaluated. Additionally, important patient-reported outcomes such as xerostomia severity, oral comfort and quality of life were not assessed, which limits the clinical correlation of objective findings. Finally, potential confounding factors such as hydration status, concurrent medications, nutritional variations and individual radiation dose distribution to salivary glands could not be fully controlled in this retrospective analysis.

Despite these limitations, this study contributes meaningful real-world evidence supporting PBMT as a feasible, non-invasive and effective adjunctive therapy for salivary gland preservation. The improvements in both salivary quantity and quality underscore PBMT's potential role in reducing the burden of RT-induced xerostomia and improving patients' oral functional outcomes. Considering its favorable safety profile, PBMT may represent a valuable addition to multidisciplinary supportive care strategies in

HNC treatment. These findings support the integration of PBMT into supportive oncology protocols to improve oral function and patient quality of life. PBMT can be feasibly implemented in both tertiary oncology centers and resource-limited settings due to its non-invasive nature.

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