Quality assessment of PBM protocols for oral complications in head and neck cancer patients: part 2

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Abstract
Purpose To investigate the role of photobiomodulation (PBM) in patients undergoing head and neck cancer (HNC) treatment. We focused on the consequences of the main complications, such as quality of life (QoL), analgesia, functional impairment, and nutritional status, as well as on the impact on survival/recurrences, radiotherapy (RT) interruption, adherence, cost-effectiveness, safety, feasibility, and tolerability.

Methods An electronic search in PubMed and Scopus databases was performed. Full texts were carefully assessed, and data were assimilated into a tabular form for discussion and consensus among the expert panel.

Results A total of 22 papers were included. Overall, a beneficial effect of PBM was evidenced in the amelioration of QoL, nutritional status, the reduction of pain, and functional impairment. Preventive PBM may reduce the incidence and duration of RT interruptions, potentially contributing to improved cancer treatment outcomes. PBM treatments are safe and recommended for routine use, with the caveat of avoiding direct tumor exposures where feasible. However, it does not appear to impact cancer survivorship/recurrences directly. Despite additional clinical efforts involving routine PBM use, the individual and public health benefits will positively impact oncology care.

Conclusions Quality of life, pain and functional impairment, nutritional status, and survival may be effectively improved with PBM. Given its established efficacy also in reducing RT interruptions and its safety, feasibility, and tolerability, PBM should be included in the field of supportive cancer care in HNC patients. Improved understanding of PBM mechanisms and precise dose parameters is enabling the generation of more robust, safe, and reproducible protocols; thus, it is imperative to support further clinical implementation as well as both applied and basic science research in this novel field.

Keywords Photobiomodulation · Laser therapy · Quality of life · Head and neck neoplasms · Nutritional status · Pain

Introduction

Our initial literature analysis focusing on the utility of photobiomodulation (PBM) for oral mucositis (OM) management in head and neck cancer (HNC) patients highlighted the lack of emphasis on secondary outcomes that are presented here [1]. These complications such as quality of life (QoL), analgesia, functional impairment, nutritional status, survival (safety), interruption of radiotherapy (RT), adherence to PBM protocols, cost-effectiveness, feasibility, and tolerability of PBM are presented here. While these outcomes often do not receive much attention and are under-reported, we believe they deserve more attention as they can impact overall patient well-being and supportive care.
Methods

An electronic search in the PubMed and Scopus databases was conducted with the following keywords: ("photobiomodulation" OR "PBM" OR "laser therapy" OR "LLLT" OR "laser") AND ("head and neck cancer" OR "oral cancer") AND ("mucositis" OR "oral mucositis" OR "dysgeusia" OR "oedema" OR "xerostomia" OR "dermatitis" OR “trismus”) until October 2021. Papers in languages different from English, Italian, Spanish, Portuguese, and French were excluded. Only original articles and reviews were initially included, excluding short reports and case reports. Furthermore, articles not specifying laser protocols were also excluded. A global group of experts in oral medicine, oncology, radiation biology, and PBM examined and discussed this literature. A total of 148 studies were obtained after the electronic search. Two different reviewers read all abstracts. After the abstract screening, 58 were excluded, and 90 were subdivided among reviewers’ full-text analysis, performed independently by two reviewers. After the full-text screening, 35 papers were included in our first review [1]. During the first literature analysis, we realized that most of the papers also discussed secondary outcomes worth reporting separately. Consequently, a total of 23 studies were included in the present review, and individual outcomes were elaborated.

Quality-of-life (QoL) assessments

Evaluation of QoL in HNC patients includes objective evaluation and their subjective reporting that requires careful assessment. OM as a side effect of chemotherapy/radiotherapy (CT/RT) is a good example where the patients may experience additional infections, treatment interruptions, and functional difficulties [2, 3]. Several tools are used to assess QoL such as the Functional Assessment of Cancer Therapy–Head and Neck (FACT-H&N), the European Organization Research and Treatment of Cancer (EORTC–H&N35) assessment, and the University of Washington Quality-of-Life (UW-QoL) Questionnaire. Personal experience of patients during therapy can also be assessed using the Oral Mucositis Weekly Questionnaire-Head and Neck (OMWQ-HN) and the Patient-Related Oral Mucosal Symptoms (PROMS) [4]. Overall, QoL in HNC should be evaluated at baseline (before RT start) and weekly or biweekly during RT until at least a few weeks after the end of treatment. It is demonstrated that QoL tends to decline immediately after the beginning of therapy, but that patients subjected to PBM therapy have a higher score over the entire course of RT. This is attributable to the reduced incidence of oral complications following PBM treatments [5].

Pain control and functional impairment

Most studies dealing with complications of HNC treatment refer to pain. The most used assessment scales for pain are the Visual Analogue Scale (VAS) and the Numeric Rating Scale (NRS), whereas the World Health Organization (WHO) analgesic ladder [6] is used to monitor the type and quantity of analgesics taken by the patients. Pain is frequently associated with functional impairments, such as difficulty chewing or swallowing, termed dysphagia.

Nutritional status

Malnutrition has been reported in 10% and 80% of cancer patients that elevates the risk of severe toxicity and infections, causing death in up to 20% of cases and increasing healthcare cost [7]. Both body weight and body mass index (BMI) are important surveillance tool during and after HNC treatments [8, 9]. Progression of oral complications or acute toxicity of the aerodigestive tract leads to weight loss and requires total parenteral nutrition (TPN). This is frequently, accompanied by suspension of RT, decreased treatment response, decreased QoL, and ultimately reduced survival [10].

Other secondary measures

We also analyzed other secondary outcomes such as treatment interruptions, survival and recurrence of cancer, adherence to treatment, cost-effectiveness, feasibility, and tolerability, and clinical protocols were assessed.

Results and discussion

Study characteristics

Overall, 7 papers dealt with QoL outcomes; 10 with pain control and functional impairment; 10 with nutritional status; 9 with interruption of RT; 6 with survival/recurrence of cancer; 4 with adherence, feasibility, and tolerability; and 1 with cost-effectiveness of PBM therapy (Table 1). Often, more than one topic was discussed in the same article. Detailed characteristics of PBM protocols employed in the studies included in this literature review for both approaches are summarized (Table 2).

Quality-of-life (QoL) outcomes

Lima et al. evaluated QoL at the beginning and the end of RT via the Quality-of-Life Questionnaire C30 (QLQC30) and Quality-of-Life Questionnaire for Head and Neck
| Paper                        | Sample size                                                                 | Type of study                                      | Topics                                      | Assessment tool       | Synthesis of main results                                                                                                                                 |
|-----------------------------|------------------------------------------------------------------------------|---------------------------------------------------|---------------------------------------------|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antunes H. S. (2017) [11]   | PBM group: 47 patients (M, F) Placebo group: 47 patients                   | Retrospective, using data from prospective, randomized, double-blind, placebo (SHAM)-controlled, phase 3 trial Preventive PBM | Survival and recurrence Cost-effectiveness | Cost analysis         | Higher costs in the placebo group for opioid use ($L_G = US $9.07; PG = US $44.26), gastrostomy ($L_G = US $50.50; PG = US $129.86), and hospitalization ($PG = US $77.03) Higher costs in the PBM group for laser therapy only (US $180.57) Lower morbidity in the PBM group PBM more cost-effective than placebo up to a threshold of at least US $5000 per oral mucositis case prevented |
| Arora H. (2008) [12]        | PBM group: 11 patients Control group: 13 patients Age range: 55–59 years Gender ratio: M:F = 1:1 | Single-center, prospective, controlled study Preventive PBM | Oral mucositis Pain control and functional impairment Nutritional status | 1) NRS: pain 2) Steps 1, 2, 3 analgesic (WHO), Analgesic ladder: required analgesics | 1) Pain increased gradually and was greatest at the end of 7 weeks. Significantly worst pain in PBM than controls Maximum functional impairment at the third week RT, greater for controls. No tube feeding during PBM 2) No significant difference for analgesics |
| Bensadoun R. J. (1999) [13] | PBM group: 15 patients Placebo group: 15 patients Mean age: 60.4 (36–78) years | Multi-center double-blind randomized controlled trial Preventive PBM | Oral mucositis Pain control and functional impairment Nutritional status | 1) VAS: pain 2) Functional impairment: swallowing function | PBM well tolerated, no side effects. PBM significantly reduced pain ($p = 0.025$). Swallowing ability less compromised in PBM ($p < 0.01$) |
| Bensadoun R. J. (2022) [14] | Seventy-two patients (A1: 17 M, 5 F; A2: 8 M, 1 F) Median age: 61.4 years | Multicentric, prospective, non-comparative study Preventive and therapeutic PBM | Oral mucositis Dermatitis Adherence/feasibility/tolerability | Device-related adverse events and NCI CTCAE v4 | CareMin650 is feasible, safe, and well tolerated for preventive or curative treatment of OM and RD in cancer patients treated with RT. No device-related adverse event relating to local pain, irritation, or unpleasant feelings has been reported during 1312 sessions. Only 3 patients (4.7%) declared that the application was rather painful and provoked discomfort |
Table 1 (continued)

| Paper                              | Sample size                      | Type of study                  | Topics                           | Assessment tool | Synthesis of main results                                                                 |
|------------------------------------|----------------------------------|--------------------------------|----------------------------------|-----------------|--------------------------------------------------------------------------------------------|
| Bourbonne V. (2019) [15]           | PBM group: 31 M, 9 F<br>Median age: 61 (45–76) years | Prospective not controlled study<br>Therapeutic PBM | Oral mucositis<br>RT interruption | RT interruption | The surface laser applied trans-cutaneously seems to allow patients to tolerate treatment without interruption and to develop low mucosal toxicity rates |
| da Costa J. D. R. (2021) [16]      | PBM group: 30 patients (23 M, 7 F)<br>Mean age: 55.97 ± 3.5 years | Cross-sectional study<br>Preventive PBM | Adherence/feasibility/toleration<br>Number of missed sessions |                | Adherence was moderate: 50% did not miss any treatment session, 20% missed one session, 16.6% missed 2 or 3 sessions, 13.3% missed > 4 sessions<br>Worst degree of OM was related to the individuals’ attendance to the scheduled sessions. Main reasons for absences: occurrence of technical problems, lack of patience to wait, systemic complications or side effects, depression |
Table 1 (continued)

| Paper                                | Sample size                                                                 | Type of study                                                                 | Topics                              | Assessment tool                                                                 | Synthesis of main results                                                                                                                                                                                                 |
|--------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|-------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| de Pauli Paglioni M. (2021) [17]     | PBM group: 107 M (73.8%), 38 F (26.2%)                                       | Retrospective, cohort study Preventive PBM                                   | Oral mucositis                      | 1) NRS: pain                                                                   | 1) At the end of the first week of treatment, no patients required analgesics. At the end of the third week, 95 (65.5%) patients did not report OM-related pain, 23 (16%) patients were using level 1 analgesics, 21 (14.5%) used level 2 analgesics, and 6 (4%) used level 3 analgesics. By the end of RT, 54 (37.2%) patients did not report OM-related pain, 21 (14.5%) patients used level 1, 50 (34.5%) patients level 2, and 20 (13.8%) patients required level 3 analgesics. 3) On the first day of RT, 51 (35.2%) patients had unrestricted diet, 76 (52.4%) had restricted diet (soft or liquid intake only), and 18 (12.4%) by enteral diet (nasogastric tube or gastrostomy). At completion of treatment, 24 (16.5%) of the patients had an unrestricted diet, 83 (57.3%) had restricted diet (soft or liquid intake only), and 38 (26.2%) were fed by enteral diet (nasogastric tube or gastrostomy). There were no significant differences regarding OM prevalence or any of the investigated outcomes between patients who undergo RT alone or combined with CT |
|                                      | Mean age: 58.9 ± 10.19 years                                                 |                                                                              | Pain control and functional impairment | 2) Steps 1, 2, 3 analgesic (WHO). Analgesic ladder: required analgesics          |                                                                                                                                                                                                                           |
|                                      |                                                                              |                                                                              | Nutritional status                  | 3) Nutritional status: diet                                                   |                                                                                                                                                                                                                           |
Table 1 (continued)

| Paper | Sample size | Type of study | Topics | Assessment tool | Synthesis of main results |
|-------|-------------|---------------|--------|----------------|--------------------------|
| Elgohary H. M. (2018) [18] | Group A (LIUS and TET): 11 M, 9 F; 61.00 ± 6.16 years Group B (LLLT and TET): 10 M, 10 F; 60.75 ± 5.09 years Group C (TET): 12 M, 8 F; 62.85 ± 5.77 years | Original study TET versus LLLT and LIUS Therapeutic PBM | Pain and trismus Quality of life | QoL: UW-QOL | At the end of the treatment, the three groups showed noteworthy statistical differences using ANOVA test and the post hoc test in favor of group A ($p < 0.05$) for UW-QOL questionnaire |
| Fischlechner R. (2021) [19] | PBM group: 126 patients Control group: 126 patients Median age: 59.5 (30–85) years | Original retrospective study with matched control Therapeutic PBM | Survival and recurrence | CT scans head and neck, chest, abdomen and biopsy with endoscopy of primary tumor site at 8–10 weeks and 2 years from end of treatment | Overall survival of LLLT patients and controls did not differ significantly. The hazard ratio for survival was close to 1 with a 95% confidence interval of 0.7 to 1.4. These results suggest that LLLT, with the exposure parameters used, does not worsen patient survival even when the primary tumor or cervical lymph nodes are within the external LLLT radiation field. Overall survival of LLLT patients and controls did not differ significantly |
| Gautam A. P. (2012) [20] (Radiotherapy and oncology) | PBM group: 111 patients (97 M, 14 F) Mean age: 55.18 ± 11.70 years Placebo group: 110 patients (92 M, 18 F) Mean age: 55.95 ± 11.61 years | Prospective, single-centered, triple blinded, randomized controlled trial | Oral mucositis Xerostomia Pain control and functional impairment Nutritional status RT interruption | 1) VAS: pain 2) Nutritional status: TPN and weight loss 3) Systemic analgesia: opioid analgesics use | 1) Less severe pain in PBM than controls 2) Mean duration of TPN required was also less in laser (14.05 ± 12.96 days) than placebo (17.95 ± 13.80 days) group. Weight loss was significantly less in laser than placebo group patients. 3) Incidence of opioid analgesics use in laser and placebo group patients was 7% and 21%, respectively ($p < 0.001$) |
| Paper | Sample size | Type of study | Topics | Assessment tool | Synthesis of main results |
|-------|-------------|---------------|--------|-----------------|---------------------------|
| Gautam A. P. (2012) [21] (Oral Oncology) | PBM group: 55 patients (50 M, 5 F)  Mean age: 51.71 ± 11.94 years  Placebo group: 55 patients (48 M, 7 F)  Mean age: 52.60 ± 12.51 years | Prospective, unicentric, double-blinded, randomized controlled trial  Preventive and therapeutic PBM | Oral mucositis  Nutritional status  Pain control and functional impairment  RT interruption | 1) Need for supplemental analgesics using WHO analgesic ladder  2) Dysphagia using need for TPN  3) Weekly weight loss  4) Any unplanned treatment interruptions | 5) 1) Comparing laser vs placebo group. Various steps of analgesics required were step 1 (29% vs 32%), step 2 (22% vs 31%), and step 3 (9% vs 26%). Also, mean duration of step 3 analgesia required was significantly lower (p < 0.001) in laser (3.2 ± 1.4 days) than placebo (6.7 ± 2.6 days) group  6) 2) PBM patients required less TPN and for less time  7) 3) Significant reduction in mean weight in both the groups (p < 0.05), statistically significant (F = 87.56, df = 8876, p < 0.0001) between the laser and placebo groups. Less unplanned treatment interruption in laser (3) than placebo (8) group due to severe OM |
| Gautam A. P. (2013) [22] | PBM group: 97 M (88%); 13 F (12%)  Mean age: 55 ± 11.52 years  Control group: 92 M (84%); 18 F (16%)  Mean age: 56 ± 11.80 years | PBM versus placebo Therapeutic PBM | Oral mucositis  Pain control and functional impairment  Quality of life  RT interruption | QoL: OMWQ-HN and FACT-HN | Overall mean OMWQ-HN and FACT-HN scores were consistently lower in the laser than the placebo group throughout the course of CRT |
| Gautam A. P. (2015) [23] | PBM group: 22 patients (20 M, 2 F)  Mean age: 71.57 ± 7.27 years  Placebo group: 24 patients (19 M, 5 F)  Mean age: 69.67 ± 8.68 years | A randomized, double-blinded, placebo-controlled trial  Therapeutic PBM | Oral mucositis  Nutritional status  Pain control and functional impairment  RT interruption | 1) Pain: VAS, morphine analgesics  2) Nutritional status: weight loss, enteral nutrition  3) RT interruption | 1) PBM significantly less severe oral pain and lesser opioids (8.3% versus 35.7% in controls  2) Less TPN in PBM (swallowing difficulty) (p = 0.677) and shorter duration (12.5 days) than placebo (14.3 days). Less weight loss in PBM (2.58 kg) than the placebo (5.57 kg) (p = 0.004 over time)  3) No RT interruption PBM versus 14.3% placebo group |
Table 1 (continued)

| Paper                                                        | Sample size                                                                 | Type of study                          | Topics                                | Assessment tool                        | Synthesis of main results                                                                 |
|--------------------------------------------------------------|------------------------------------------------------------------------------|----------------------------------------|---------------------------------------|----------------------------------------|-------------------------------------------------------------------------------------------|
| Genot-Klastersky M. T. (2020) [24]                           | PBM group: 222 patients (163 M, 59 F) Control group: 139 patients (107 M, 32 F) Median age: 59 ± 11 years | Retrospective case control Therapeutic PBM | Survival and recurrence                | Overall survival, time to local recurrence, progression-free survival Median follow-up 9.3 years | No different prognosis between PBM vs no PBM in overall survival, time to local recurrence, and progression-free survival Not recognized harmful effects |
| Gobbo M. (2014) [25]                                         | PBM group: 29 M, 13 F Control group: 14 M, 7 F Mean age: 65.4 ± 10.3 (43–89) years | Case-control retrospective Therapeutic PBM | Oral mucositis                         | Nutritional status: BMI                 | BMI reduction was greater in the control group as compared to the laser group (p < 0.001), with crucial role of PBM application at the regression analysis |
| González-Arriagada W. A. (2018) [26]                         | PBM group: 87 M, 21 F Control group: 86 M, 22 F                             | Case-control study Therapeutic PBM      | Oral mucositis Xerostomia Pain and trismus Dermatitis Nutritional status RT interruption | RT interruption                       | Patients of the PBM group had less interruption of the oncologic therapy because of mucositis (p = 0.030) and the introduction of TPN (p = 0.027) |
| Gouvêa de Lima A. (2012)*                                   | PBM: 27 M, 10 F Mean age: 53.1 ± 9.4 years Placebo: 30 M, 8 F Mean age: 53.2 ± 10.3 years | Phase 3, randomized, double-blind study Preventive PBM | Xerostomia Pain control and functional impairment Nutritional status RT interruption Survival and recurrence | 1) Dysphagia: TPN 2) Analgesia: drugs and opioids use 3) Nutritional status: weight loss 4) Unplanned RT interruption | 1) Significantly higher dysphagia in PBM group only at 4th week RT (p = 0.04). Similar use of drugs including opioids in PBM patients and controls 2) No differences in weight loss and TPN 3) 0% RT interruption in PBM group and 16% in controls (p = 0.02) 4) No recurrences, no side effects, no differences for overall survival between groups |
| Guedes CDCFV. (2018) [28]                                   | PBM group: 58 patients (88% M, 12% F) Median age: 59.5 (30–85) years         | Prospective cohort study Therapeutic PBM | Oral mucositis Survival and recurrence Adherence/feasibility/tolerability | 2-year follow-up                      | Tumoral recurrence was found in 14 cases (24%) and did not vary significantly between the groups Mild to moderate pain when the laser tip was placed in contact with ulcerated lesions |
| Paper | Sample size | Type of study | Topics | Assessment tool | Synthesis of main results |
|-------|-------------|---------------|--------|----------------|--------------------------|
| Legouté F. (2019) [29] | PBM group: 37 M, 5 F  Mean age: 58 (53–62) years  Placebo group: 38 M, 3 F  Mean age: 58 (53–68) years | Prospective randomized study Preventive PBM | Oral mucositis  Pain control and functional impairment  Nutritional status  Quality of life  Adherence/feasibility/tolerability | 1) Nutritional status: weight loss  2) QoL: non-specified questionnaire | No difference between groups for nutritional assessment ($p = 0.39$), analgesia (NS, $p = 0.27$), and quality of life (NS) |
| Lima A. G. (2010) [30] | PBM group: 12 patients  AH: 13 patients  Mean age: 55.82 (33–80) years  Male 90.91%, female 9.08% | PBM versus AH Preventive PBM | Oral mucositis  Quality of life  Pain control and functional impairment | 1) VAS: pain  2) QoL: EORTC’s questionnaires (QLQ-C30 and QLQ-H&N35)  3) Functional impairment: swallowing function | 1) Lower pain scores in PBM patients  2) Dry mouth, sticky saliva, and painkillers worse index for both groups but better scores for PBM (NS). Coughing, sense, and speech problems worse index for both groups but better scores for AH patients  3) Severe grades (3 and 4) of dysphagia were found in approximately 33% of the LLLT group versus 50% of the AH group |
| Martins A. F.L. (2021) [31] | PBM group: 25 (20 M, 5 F)  Control group: 23 (21 M, 2 F)  Mean age: 59.75 ($\pm 11.69$) years | Double-blind randomized clinical trial Preventive PBM | Oral mucositis  Quality of life | QoL: PROMS and OHIP-14 | OHRQoL worse in the control group compared to the PBM group at the 21st RT session ($p = 0.029$) and the 30th RT session ($p = 0.006$). Tendency for higher increase of PROMS in controls, although difference was not statistically significant ($p = 0.060$) |
Table 1 (continued)

| Paper                     | Sample size                                      | Type of study   | Topics                        | Assessment tool | Synthesis of main results                                                                 |
|---------------------------|--------------------------------------------------|-----------------|-------------------------------|-----------------|-------------------------------------------------------------------------------------------|
| Morais M. O. (2020) [32] | PBM group: 49 M (80.3%); 22 F (19.7%) Mean age: 58.6 ± 9.9 years | Original prospective study Preventive PBM | Oral mucositis Xerostomia Quality of life RT interruption Survival and recurrence | 1) QoL: PROMS and OHIP-14 2) Adverse events 3) RT interruption | 1) Both PROMS and OHIP-14 showed an overall decrease in QoL 2) No adverse events, and overall survival rate was 77% (mean survival of 35.0 months; 95% CI = 21.2–48.7), while disease-free survival was 73.8% (mean = 42.2 months; 95% CI = 29.2–55.2) 3) Interruption of RT occurred in 55 participants (90.2%) due to several reasons (5% OM) |
| Oton-Leite A. F. (2012) [33] | PBM group: 22 M, 8 F Placebo group: 27 M, 3 F Median age: 55.6 (30–80) years | Therapeutic PBM | Oral mucositis Quality of life RT interruption | 1) QoL: UW-QoL 2) RT interruption | 1) Remarkable reduction in QOL scores placebo vs PBM (p < 0.001) (all domains) 2) Less RT interruptions in PBM group |

Topics in **bold** characters: theme discussed in the present review: *PBM*, photobiomodulation; *M*, male; *F*, female; *LG*, laser group; *PG*, placebo group; *NRS*, numeric rating scale; *WHO*, World Health Organization; *RT*, radiotherapy; *CT*, chemotherapy; *OM*, oral mucositis; *VAS*, visual analogue scale; *QoL*, quality of life; *BMI*, body mass index; *NCI CTCAE*, National Cancer Institute Common Toxicity Criteria for Adverse Events Version Four; *RD*, radiodermatitis; *LIUS*, low-intensity ultrasound; *TET*, traditional exercise therapy; *LLLT*, low-level laser therapy; *UW-QoL*, University of Washington Quality-of-Life Questionnaire; *TPN*, total parenteral nutrition; *OMWQ-HN*, oral mucositis weekly questionnaire-head and neck cancer; *FACT-HN*, functional assessment of cancer therapy scales; *NS*, nonsignificant; *AH*, aluminum hydroxide; *EORTC*, European Organization for Research and Treatment of Cancer; *QLQ-C30*, quality-of-life questionnaire C30; *QLQ-H&N35*, quality-of-life questionnaire for head and neck module 35; *PROMS*, patient-reported outcome measures; *OHIP-14*, Oral Health Impact Profile-14; *OHRQoL*, Oral Health-Related Quality of Life; *Lack of reported benefits after PBM therapy.*
| Paper                      | Type brand                                                                 | Wavelength (nm) | Mode (CW/pulse) | Format (fiber, array) | Contact or distance | Power output (mW) | Irradiance (mW/cm²) | Spots/area | Time/site | Time/session | Repetitions | Fluence/site (J/cm²) | Fluence/session | Total fluence |
|----------------------------|-----------------------------------------------------------------------------|-----------------|-----------------|----------------------|---------------------|-------------------|-------------------|-------------|-----------|---------------|-------------|----------------------|-----------------|---------------|
| Antunes H. S. (2017) [11]  | InGaAlP diode laser (DMC, São Carlos, São Paulo, Brazil)                     | 660             | CW              | Fiber                | Contact            | 100               | 416.67            | 0.24 cm²   | 10 s      | 720 s         | 5 days/week  | 72 J                 | NS              | NS            |
| Arora H. (2008) [12]      | He-Ne laser (Electro Care Ltd., Laser 2001, Chennai, India)                  | 632.8           | Pulse (10 Hz) for 8 days and then CW for 25 days | Scanner for 8 days, fiber for the following 25 days | Distance           | 10                | NS               | NS          | 5 min/site | 60 s          | Thirty-three sessions | 1.8             | NS            |
| Bensadoun R. J. (1999) [13]| Low-energy He-Ne laser (Fradama Geneva, Switzerland)                         | 632.8           | CW              | Fiber                | 0.5-mm distance    | 60                | NS               | 1 cm²/point: 9 points | 33 s per spot (Nice and Mar- | 5 min/session (Nice and Mar- | 5 days/week (Monday to Friday) for 7 consecutive weeks | 2           | 18 J       | 3 J/cm²       |
| Bensadoun R. J. (2021) [14]| Caremin 650                                                                 | 650             | CW              | Array                | Contact            | NS               | NS               | NS          | NS        | NS            | NS          | 3 J/cm² (prophylactic) | 6 J/cm² (curative) | NS            |
| Paper                          | Type brand                                                                                     | Wavelength (nm) | Mode (CW/pulse) | Contact or distance | Power output (mW) | Irradiance (mW/cm²) | Spots/area | Time/site | Time/session | Repetitions | Fluence/site (J/cm²) | Fluence/session | Total fluence |
|-------------------------------|----------------------------------------------------------------------------------------------|-----------------|-----------------|---------------------|-------------------|---------------------|-------------|------------|----------------|-------------|---------------------|----------------|--------------|
| Bourbonne V. (2019) [15]      | Laser Heltschl FL 3500 ME-TL 10 000 SK (Schlüßberg, Austria)                                 | 660             | CW              | Array, noncontact   | External: 350     | External: 2 points | NS          | External: | NS            | 3 times/week | 6 J/cm²             | 6 J/cm²        | 252 J        |
| da Costa J. D. R. (2021) [16] | Semiconductor diode, gallium aluminum arsenide laser device (AsGaAl) Twin Flex® (MM Optics, São Carlos, Brazil) | 660             | CW              | Fiber, contact      | 86.7              | 0.1256 cm²         | 10 s        | External: | NS            | 3 times/week | 20 J/cm²            | 20 J/cm²       | 56 J         |
| de Pauli Paglioni M. (2021) [17] | Diode laser (Twin Flex, MM Optics Equipment, São Paulo, Brazil)                               | 660             | CW              | Fiber, contact      | 40                | 0.04 cm²           | NS          | Preventive: Treatment: | 60 J/cm² | 600 J/cm²            | NS             | 60 J/cm²     |
| Guedes C. D. C. F. V. (2018) [28] | InGaAlP Twin Flex Evolution (MM Optics Ltda, São Carlos, São Paulo, Brazil) and Laser Duo (MM Optics Ltda, São Carlos, São Paulo, Brazil) | 660             | CW              | Fiber, contact      | 25                | 625 4 mm²          | 10 s/point  | 280 s     | NS            | 3 times/week | 6.3 J/cm²            | 7 J/session    | 28 J/session |
| Paper                  | Type brand                                                                 | Wavelength (nm) | Mode (CW/pulse) | Format (fiber, array) | Contact or distance | Power output (mW) | Irradiance (mW/cm²) | Spots/area | Time/site | Time/session | Repetitions | Fluence/site (J/cm²) | Fluence/session | Total fluence |
|-----------------------|-----------------------------------------------------------------------------|-----------------|-----------------|-----------------------|---------------------|-------------------|---------------------|-------------|------------|---------------|-------------|----------------------|-----------------|---------------|
| Elghohary H. M. (2018) [18] | Laser equipment (Electro Medical Supplies, Greenham Ltd., Wantage, Oxfordshire, UK) | 950             | Pulsed 80% Fiber | NS                    | 15                  | NS                | NS                  | 360 s       | NS         | 5 times/week for 4 consecutive weeks | NS          | 4.3                  | 86 J            |              |
| Fischlechner R. (2021) [19] | InGaAs semiconductor laser diode (FL 3500, Heltschl GmbH Medizintechnik, Schlüsselberg, Austria) | 660 ± 3         | CW (external and intraoral) | Array with 7 emitters | 5 cm distance | External: 350 | Intraoral: 70 | NS          | NS         | 1–2 times/day, average 6 sessions | Extraoral: 12 (grades 1–2) | 420 J        | NS          |              |
| Gautam A. P. (2012) [20] (Radiotherapy and oncology) | He-Ne laser (Technomed Electronics, Advanced Laser Therapy 1000, Chennai, India) | 632.8           | CW Fiber | Noncontact (< 1 cm) | 24                  | 24                | 1 cm²               | 150–200 s 6 points | 900–1200 s 45 sessions | 5 sessions/week prior to RT for 45 days | 3 J/point | 36–40 J/session | 1620–1800 J/cm² |              |
| Gautam A. P. (2012) [21] (Oral Oncology) | He-Ne laser (Technomed Electronics, Advanced Laser Therapy 1000, Chennai, India) | 632.8           | CW Fiber | Noncontact (< 1 cm) | 24                  | 24                | 0.6 mm Spot size 1 cm² 6 sites | 145 s       | 870 s      | Daily for 6.5 weeks | NS          | NS                   | 3.5 J/cm²       |              |
| Paper | Type brand | Wavelength (nm) | Mode (CW/pulse) | Format (fiber, array) | Contact or distance | Power output (mW) | Irradiance (mW/cm²) | Spots/area | Time/site | Time/session | Repetitions | Fluence/site (J/cm²) | Fluence/session | Total fluence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gautam A. P. (2013) [22] | He-Ne laser (Technomed Electronics Advanced Laser Therapy 1000) | 632.8 | NS | Fiber | ns | 24 | 24 | 1 cm² | 6 sites | 125 s | 750 s/session | 5 times/week | 3 J/cm² | 18 J/session | NS |
| Gautam A. P. (2015) [23] | He-Ne laser (Technomed Electronics, Advanced Laser Therapy 1000, Chennai, India) | 632.8 | CW | Fiber | Non-contact (< 1 cm) | NS | 0.024 | 0.6 mm Spot size 1 cm² | 125 s | 12 sites | NS | 5 times/week | 3 J/point | 36 J/session | NS |
| Genot-Klaster-sky M. T. (2020) [24] | Biophoton Travelers Oncolase TW scanning laser | 630 | CW | Fiber | 5–10 mm distance | 100 | 100 | 1 cm² | 33 s | 360 s | 3 times/week for 1 month | 2–3 | NS | NS |
| Gobbo M. (2014) [25] | GaAlAs diode laser Eltech K-Laser Srl Treviso (Italy) | 970 | Pulsed 2 Hz 50% duty cycle | Fiber | Distance | 5000 | NS | 1 cm² | 9 sites | 26 s/site on 9 sites | 234 s | 2 times/day for 4 consecutive days | NS | NS | NS |
| González-Arriaga W. A. (2018) [26] | Diode InGaAlP Photon Lase III (DMC Odontológica, São Carlos, Brazil) | 660 | NS | Fiber | NS | 100 | NS | NS | 10 s | 27 points | 270 s | 3 times/week since the first day up to the end of RT | 60 | NS | NS |
| Gouvêa de Lima A. (2012) [30] | GaAlAr diode laser (Twin Flex, MMOptics, São Carlos, Brazil) | 660 | CW | Fiber | NS | 10 | 2.5 | 4 mm² | 10 s/point | 90 s | 5 consecutive days (Monday to Friday) during all RT sessions | 0.1 J | 0.9 J | 2.5 J/cm² |
| Paper | Type brand | Wavelength (nm) | Mode (CW/pulse) | Format (fiber, array) | Contact or distance | Power output (mW) | Irradiance (mW/cm²) | Spots/area | Time/site | Time/session | Repetitions | Fluence/site (J/cm²) | Fluence/session | Total fluence |
|-------|------------|-----------------|-----------------|----------------------|---------------------|-------------------|-------------------|------------|-----------|-------------|------------|-------------------|-----------------|--------------|
| Legouté F. (2019) [28] | He-Ne laser HETSCHL® | 658 | Pulsed (50 Hz) | Fiber | 0.5 mm | 100 | 100 | 1 cm² per application | 40 s/cm² | NS | 1 session/day, 5 sessions/week from day of OM grade 2 until the resolution of OM | 4 J | NS | 4 J/cm² |
| Lima A. G. (2010) [29] | Diode laser (Laser Unit KM 3000; DMC, São Carlos, SP, Brazil) | 830 | CW | Fiber | NS | Nominal: 60 effective: 15 | 75 | 0.2 cm² | 160 s | 12 sites | Daily session (Monday to Friday) since the first day up to the end of RT | 12 | 28.8 J/session | NS |
| Martins A. F. L. (2021) [31] | InGaAIP laser (Twin Flex Evolution, MMOptics Ltd., São Paulo, Brazil) | 660 | NS | Fiber | Contact | 25 | 625 | 0.028 cm² | 19 points | 10 s | 610 s | 5 days/week | 6.2 | | 15.25 J | 533.75 J |
| Morais M. O. (2020) [32] | InGaAIP laser (Twin Flex Evolution, MMOptics Ltd., São Paulo, Brazil) | 660 | CW | Fiber | 1-cm distance | 25 | NS | 0.04 mm² | 62 spots | 10 s/site | 620 s/session | 5 days/week | 6.2 | | 14.88 J/day | 446.4 J |
| Oton-Leite A. F. (2012) [33] | InGaAIP diode laser (Thera Lase; DMC Equipments Ltda, Sao Carlos, Brazil) | 685 | CW | Fiber | Contact | 35 | NS | Fifty-nine sites | NS | NS | 1 time/day for 5 consecutive days (1 week before the beginning of RT/CT until the end of the treatment) | 2 | NS | NS |

InGaAlP, indium gallium aluminum phosphorus; He-Ne, helium-neon; AsGaAl, arsenide gallium aluminum; InGaAsP, indium gallium arsenide phosphorus; InGaAs, indium gallium arsenide; GaAlAs, gallium aluminum arsenide; GaAlAr, gallium aluminum arsenide; CW, continuous wave; RT, radiotherapy; OM, oral mucositis; CT, chemotherapy.
Module 35 (QLQ-H&N35) in two cohorts of 12 and 13 patients, respectively, subjected to either PBM therapy or to aluminum hydroxide (AH) mouthwash to treat OM [30]. They observed higher pain grades in the AH group, but the worsening QoL was similar in both groups during the completion of RT. Dry mouth, sticky saliva, and painkillers consumption had better scores, although not statistically significant, in the PBM group. The EORTC questionnaire noted AH presented higher efficacy than PBM in coughing control, speech problems, sensory issues, and reduced trouble with social contact. The authors assert that oral suspension has a direct contact with the esophagus triggering beneficial effects. The study limitation included its small sample and non-randomized design with PBM group having more hypopharyngeal or laryngeal disease suggesting selection bias. Elgohary et al. used UW-QOL in randomly allocated participants subjected to three different protocols, namely Low Intensity UltraSound (LIUS) plus Traditional Exercise treatment (TET) program that included stretching exercises, passive and active range of motion exercises, and strengthening exercises (group A), PBM therapy plus TET (group B), and only TET (group C) [18]. They used the UW-QOL, which is defined as a simple and accurate tool [34, 35]. Despite equivocal QoL scores in the three groups at the beginning and at the end of the treatment, the three groups showed statistical differences using ANOVA and post hoc test in favor of group A (p < 0.05). This study limitations included a small sample size and lack of a control group.

Gautam et al. noted significantly (p < 0.001) reduced Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (OMWQ-HN) in PBM-treated group compared to placebo group throughout chemoradiotherapy (CRT) [22]. Moreover, the control group experienced more functional limitations (swallowing, drinking, eating, sleeping, and brushing) and had lower physical and emotional scores than the PBM group. However, social well-being scores did not differ significantly between the two groups. Legoutè et al. assessed QoL weekly with a multi-scale questionnaire in 50 patients who underwent PBM with OM ≥ grade 2 [29]. There were no differences between PBM therapy and placebo arms for 17 parameters. However, one factor, sticky saliva, favored the placebo arm (p = 0.004). As the data for “swallowing” and “dry mouth” were inconclusive, the authors suggest interpreting these results with caution. Martins et al. [31] evaluated the QoL of HNC patients subjected to PBM therapy for RT using Oral Health-related Quality of Life (OHRQoL) and PROMS. Despite the low subject numbers, a general decrease in OHRQoL was observed in both the PBM group and placebo but with a statistically significant (p < 0.001) in PBM in the final phases of RT. Conversely, OM-related symptoms increased in both groups but more markedly in the control group. Morais et al. prospectively observed a cohort of HNC patients subjected to RT, and preventive PBM evaluated OHRQoL with OHIP-14 (Oral Health Impact Profile-14) and PROMS [32]. They observed a progressive increase in severity until the 14th RT session that remained stable until the completion of RT. Oton-Leite et al. administered the UW-QOL to the 60 HNC patients with placebo or daily PBM sessions starting 1 week before CRT and ending of oncotherapy [8, 33]. Overall, QoL scores were significantly (p < 0.001) lower in controls than in the PBM group. Appearance, activity, recreation, speech, and taste were greatly more affected in the control group during the intermediary period. Pain (p = 0.03), chewing (p = 0.004), and saliva (p < 0.001) were also more affected in the final period for the placebo group. These studies confirm that PBM therapy improves QoL in cancer patients receiving oncotherapy.

Pain control and functional impairment

The PBM analgesic effect is known to be mediated by the selective inhibition of nociceptors and pain conduction blockade [36]. Repeated PBM sessions modulate synaptic connection via reduced tonic peripheral nociceptive afferent inputs and decreased central sensitization accompanied by increased endorphin synthesis [37]. Lima et al. evaluated the functional capacity worsening throughout RT via assessment of subjective swallowing function and found no amelioration in the PBM group compared to controls [30]. Severe grades (3 and 4) of dysphagia were found in approximately 33% of the PBM group versus 50% of the AH group (p < 0.05). Both groups worsen in coughing, sense, and speech problems throughout RT, but the impairment was less evident in the PBM group (p = 0.05). Gautam et al. performed several studies on HNC subjects with PBM therapy [20, 21, 23]. It is unclear if there were patient overlaps across these studies. In 2012, they monitored the analgesics used during RT and noted 40% of PBM-treated patients versus 11% of controls did not require analgesics, whereas less (9%) of PBM-treated patients than controls (26%) required step 3 analgesics at some point of oncological treatment (p < 0.001) [20]. In the same year, they also demonstrated a lower incidence and duration of severe pain with VAS in PBM (5.3 ± 6.4 days) versus placebo (9.9 ± 6.1 days) group. Furthermore, the opioids use was significantly lower (7% versus 21%, p < 0.001) in these groups [21]. A follow-up study obtained similar results [22]. They also performed a randomized controlled trial on opioid use in HNC patients undergoing CRT and noted more patients experienced severe oral pain (VAS > 7, p = 0.023), longer duration (16.5 versus 10 days), and increased opioid use (35.7% versus 8.3%) in the placebo compared to PBM-treated group at the end of RT [23].

Similarly, Arora et al. used the NRS and WHO analgesic ladder to monitor pain and the use of opioids [12]. Although both PBM-treated and control groups showed a progressive
increase in pain scores throughout RT, the control group felt significantly worse ($p = 0.019$) and experienced swallowing difficulties, and TPN was needed in one case. None of the PBM group patients used opioids. Besandoun et al. demonstrated PBM therapy aided recovery from swallowing difficulties ($4.9 \pm 1.3$ versus $6 \pm 0.8$ weeks, $p < 0.01$) compared to controls. Severe pain (grade 3) lasted longer (25 versus 2 weeks, $p < 0.001$) with more patients (11 versus 5) taking morphine in the control versus PBM group [13].

De Pauli Paglioni et al. monitored pain scores (VAS) and analgesics intake (WHO analgesic ladder) weekly and throughout CRT in 145 HNC patients subjected to preventive PBM therapy [17]. They noted PBM reduced pain related to OM from the third week onwards, and only $4\%$ and $13.8\%$ need opioids at 3 weeks and end of RT. The authors noted that the mean pain ratings were significantly lower than in other studies, with the highest mean value reported at 6 weeks of treatment ($VAS = 2.69$) [38]. They discuss the importance of including the tongue dorsum, retromolar trigone, and hard palate in PBM treatment applications as high-risk areas in OM associated with pain. The retrospective design and the absence of a control group were limitations of this study. A study by Gouvea de Lima et al. noted no significant differences between pain scores or concomitant analgesic medication ($54\%$ versus $50\%$ for NSAIDAs, $8\%$ versus $8\%$ for opioids) between PBM and control groups [27]. Similarly, Legoutè et al. found that more patients in the PBM treatment arm took major painkillers than the controls, but the differences were not statistically significant [29].

While more studies are needed, PBM therapy appears to have significant utility as an adjunct in managing pain during cancer therapy.

**Nutritional status**

Weight loss represents an early sign of malnutrition, and it has been well established that early recognition and mitigation of this problem provide remarkable benefits to patients [7]. Despite the frequency of the problem, nutritional assessment of patients is not part of the routine practice in HNC subjects, and there are few studies investigating the role of malnutrition. Legouté et al. examined patients at the end of RT and noted $54.1\%$ ($5\%$) and $17.6\%$ ($10\%$) weight loss but with no significant differences between PBM and control groups [29]. Similarly, at the end of CRT, 37 patients ($59.7\%$) moved to a liquid diet or enteral feeding (TPN) with no difference ($p = 0.39$) between the two groups for nutritional assessment. De Pauli Paglioni et al. observed a lower number of patients with restricted diet or TPN on the first versus last day of RT ($52.4\%$ versus $57.3\%$ and $12.4\%$ versus $26.2\%$, respectively), irrespective of their treatment regimen (RT alone or CRT) [17]. Their results are lower than those reported in the literature, where $35\%$ of patients needed TPN [39]. Gautam et al. obtained similar results in terms of TPN need ($p = 0.9$) and weight loss ($p = 0.1$) in the third week of CRT, comparing PBM and placebo subjects. At the end of RT, TPN was significantly less in the PBM than in the placebo group. The mean duration of TPN required was also less in the PBM ($14 \pm 13$ days) than in the placebo ($17.9 \pm 13.8$ days) group. Also, weight loss was significantly lower in the PBM than in the placebo group [21].

Gautam et al. proved that PBM-treated subjects experienced a significantly ($p < 0.0001$) lower weight loss and increased TPN requirement ($65.5\%$ vs $45\%$) in the control compared to PBM group [20]. Similarly, Besandoun et al. obtained a shorter duration of TPN and swallowing difficulty with PBM-treated ($4.9 \pm 1.3$ weeks) than the placebo ($6 \pm 0.8$ weeks) group [13]. Gobbo et al. retrospectively analyzed 42 subjects subjected to PBM versus 21 controls during RT for HNC to examine if the application of PBM therapy could affect the nutritional status [25]. They demonstrated that BMI reduction was significantly ($p < 0.001$) greater in the control group as compared to the PBM group with lower scores for RT + surgery and higher scores for RT + CT ($p < 0.05$). On the contrary, the weight loss was similar between the groups or among the therapies, with no significant differences. However, multiple regression analysis noted the PBM group was associated with a lower BMI reduction. Arora et al. monitored the severity of dysphagia using the Functional Impairment Scale (FIS) and noted a maximum grade in third week of RT in controls compared to PBM group [12]. Moreover, none of the patients in the PBM group required TPN, versus three in the control group. Similarly, another study by Gouvea de Lima et al. noted no significant differences in the amount of weight loss between PBM and control groups during RT, but TPN was needed in 13 patients ($35\%$) in the PBM group versus 11 patients ($29\%$; $p = ns$) in the placebo group [27]. The TPN placement was done at a mean of five fractions later for the PBM-treated patients (RT fraction number 22 vs. 17, $p = 0.01$). Gonzalez-Arrigada et al. noted a significant ($p = 0.027$) reduction in the need for TPN in preventive PBM-treated groups ($5.5\%$) versus control groups ($15.74\%$) in CRT-treated patients [26]. Gautam et al. noted a lower number of patients requiring TPN support in PBM-treated groups than placebos with a decreased mean duration of TPN ($12.5$ versus $14.3$ days respectively, $p = 0.461$) [23]. While both groups experienced weight loss, it was significantly ($p = 0.004$) lower in PBM ($2.58$ kg) than in the placebo ($5.57$ kg) group. The data obtained by our literature review support the role of PBM therapy in improving the overall nutritional status of HNC patients.

**Treatment interruptions**

The severity of side effects in HNC-treated subjects may lead to unwanted treatment interruption ($80\%$ of patients)
correlated to a nearly 1% survival rate reduction for each
day of RT suspension [40]. Many studies have shown that
the incidence of severe OM is proportional to the risk of
RT interruptions [41]. Bourbonne et al. applied PBM treat-
ments to a cohort of subjects they defined as “high risk”
of OM due to concomitant CRT treatments and accelerated-
RT regimen [15]. Gautam et al. conducted several studies
demonstrating that unexpected RT interruptions were more
frequent in controls than in PBM-treated groups [20, 22].
In one study, no patients in the PBM-treated group required
CRT break compared to 9% of patients in the placebo group
due to severe OM [21]. Again, they found that RT break
due to severe OM was not required for patients in the PBM
group, while 14.3% of patients were in the placebo group
[23]. Gonzalez-Arrigada et al. reported that PBM treatments
(11%) significantly (p = 0.03) reduced the suspension of RT
compared to control (25%) due to toxicity [26]. Similarly,
the studies by Gouvea de Lima et al. and by Oton-Leite et al.
observed significant (p = 0.02 and p < 0.001, respectively)
unplanned RT interruptions due to severe OM were neces-
sary for more patients in the placebo arm [27, 33]. Interes-
tingly, Morais et al. monitored the interruption of RT for any
rate. It occurred in 55 participants (90.2%) overall but
just in three patients (5%) due to OM and for a maximum
duration of 10 days [32]. The authors monitored the reasons
for interruptions and demonstrated that technical mainte-
nance of the RT equipment corresponded to 46.7% of all
RT interruption events. Similar results were reported; the
leading causes of RT interruption were calendar holidays
and maintenance of the RT apparatus [42]. These observa-
tions indicate preventive PBM treatments can reduce the
incidence, duration, and treatment outcomes.

Survival and recurrence of cancer

The role of PBM safety and potential synergistic improve-
ments to conventional oncotherapy affecting the recurrence
of cancer and patients’ survival has been hotly debated [43].
The biological PBM mechanisms capable of promoting cell
proliferation have conversely raised concerns on the possi-
bilities of enhancing tumor cells [44]. Several reports have
indicated PBM as a supportive care technique is not harm-
ful or does not induce tumor proliferation [45]. Besides its
lack of direct carcinogenic potential, recent studies suggest
that PBM treatments may sensitize cancer cells to radiation
and promote apoptosis [46, 47]. Antunes et al. performed
a randomized clinical trial in HNC patients treated with
CRT using a preventive PBM therapy and median follow-
up of 41 months. They noted better overall survival (p = 0.9),
improved progression-free survival (p = 0.03), and
a significantly (p = 0.013) higher complete response rate
in patients receiving PBM treatments [11]. It is prudent to
emphasize the tumor sites were excluded from direct PBM
treatments. Fischnecher et al. investigated the survival/recur-
rence rate after HNC in patients (n = 126) treated with six
or more PBM sessions versus matched controls (n = 126)
[19]. Extraoral PBM treatments included the primary tumor
site and intraoral application of circumscribed lesions. The
authors noted that PBM treatments did not impact patient
survival, even when the primary tumor or cervical lymph
nodes were within the irradiation fields. Median survival in
PBM-treated patients (48 months, 95% CI 34 to 62 months)
versus controls (58 months, 95% CI 23 to 93 months) was
not statistically significant (p = 0.91). Furthermore, median
survival in patients was 49 months (95% CI 33 to 65 months)
versus 79 months (35 to 123; p = 0.92) based on 6 or more
PBM treatment sessions. Gouvea de Lima et al. found no
difference either disease control or survival between the two
arms at a median follow-up of 2 years [27].

Morais et al. treated 71 subjects with preventive PBM
and found an overall survival rate of 77% (mean survival
35.0 months; 95% CI 21.2 to 48.7 months) and disease-
free survival of 73.8% (mean survival 42.2 months; 95% CI
29.2 to 55.2 months) [32]. Shorter survival was observed
for patients with no response to RT (disease-free survival of
31.3%; p < 0.01 and overall survival rate of 31.3%; p
< 0.01). No significant associations were found for other
clinicopathological factors, such as time from diagnosis to
surgical treatment, the histological grade of malignancy,
regional metastasis, and the number of RT interruptions.
Guedes et al. followed up 58 patients subdued to PBM for
RT-OM and investigated the tumoral recurrences every 3
months for 2 years, finding out a 24% of recurrences. The
authors concluded that PBM does not significantly increase
the risk of tumor recurrence [28].

Genot-Klastersky [24] retrospectively investigated
361 patients charts, among which 222 patients (62%) had
received PBM treatments for the prevention or management
of OM due to HNC therapies. Even after adjusting data for
known prognostic factors, the authors found no statistical
evidence that PBM treatments were related to improvements
in overall survival, progression-free survival, or local recur-
rence. This study was limited by the retrospective study
design and limited subjects. In summary, these studies affirm
PBM treatments are safe and recommended for routine use,
with the caveat to avoid direct tumor exposures where fea-
sible. However, it does not appear to directly impact cancer
survivorship or recurrences.

Adherence, feasibility, and tolerability

Da Costa et al. evaluated the adherence of patients with
HNC who underwent RT/CRT combined with preventive
PBM therapy in a public health service [16]. It was found
that 50% did not miss any treatment session, 20% missed
one session, 16.6% did not attend two or three sessions, and
13.3% missed four or more visits. The three most reported reasons included the occurrence of technical problems in the RT service (12%), the lack of patience to wait for dental care (25%), and systemic complications resulting from cancer treatment (45%). Among the 15 patients who missed at least one PBM session, 72.7% attributed such absence to psychological problems, mainly depression. Interestingly, the authors noted a positive correlation between the number of absent PBM sessions with increased severity of OM incidences. Bensadoun et al. analyzed the safety profile in HNC patients with RT using a PBM device (CareMin 650) in over 1312 sessions [14]. Nine patients reported 14 adverse events, none of which was correlated to the PBM, while 81.3% noted the treatments were not burdensome or discomfort (76.6%) and acceptable duration (68.8%). Only five patients complained about tolerable pain, and three about unbearable pain during the application, attributing it to provoking pain or irritation in preexisting lesions. The PBM operators noted the device was easy to use and satisfactory (> 90% for both groups), demonstrating that device’s choice can influence the technique’s applicability, and that the technique is easy and feasible. Guedes et al reported that the only complaint reported by oncological patients subdued to PBM for OM was mild to moderate pain when the laser tip was placed in contact with ulcerated lesions, without causing session’s interruption [28].

Legouté et al. stated that treatment tolerance was excellent in PBM sessions for 91% of patients, and only 4.5% had a moderate level of discomfort [29]. Although PBM has demonstrated efficacy and feasibility in several randomized clinical trials and meta-analyses, it is still infrequently used in routine practice [48]. A significant limitation is the additional time required by the patients and the operators, which may hinder the feasibility of the technique in several settings. Hence, while adherence is not always easy to achieve due to treatment logistics, the operator benefits (improved cancer treatment outcomes), patient benefits (less treatment complication, improved QoL), and public health (cost-benefits) should be accounted for in evaluating clinical supportive cancer care practices.

Cost-effectiveness

Antunes et al. performed a study to assess the cost-effectiveness of PBM treatments in preventing OM in HNC patients [11]. The average total cost per PBM session was calculated as the annual sum of total variable, fixed, and semi-fixed costs divided by the annual number of laser sessions performed at the National Cancer Institute of Brazil. The authors analyzed the costs related to grades 3 and 4 OM and possible hospitalization, as the costs associated with RT, CT, and medications. They noted average cost per laser session was US $41.18, considering 14 applications for 240 working days per year, which would be reduced by 40% if the service operated at total capacity. Operator salaries and administrative costs had significantly impacted costs more than the PBM sessions themselves. Nonetheless, preventing the onset of severe grades OM was advantageous since placebo treatments were far more expensive concerning the higher number of complications: opioid use (PBM group = US $9.07; placebo = US $44.26), gastrostomy (PBM group = US $50.50; placebo = US $129.86), and hospitalization (placebo = US $77.03). Authors demonstrated that PBM treatments were more cost-effective than placebo up to a threshold of at least US $5000 per OM case prevented. In accordance to the data reported in our review, similar findings have been reported in other studies by Elting et al., Nonzee et al., and Murphy et al., although costs were more significant in those studies due to differences in the health and reimbursement systems [49–51].

PBM: clinical protocols and dose approach

As noted in several previous reviews, we also noted considerable variations in the types of devices (lasers/LEDs), mode of application, frequency of treatment, and treatment parameters [46, 52] and went over many of the pertinent issues about protocols in our prior review [1]. In the final section here, we outline the current state of knowledge about PBM dosimetry concerning the protocols used in the studies included in this review without a specific reference to specific pathology or therapeutic responses (Table 2).

Generally, studies in the literature do not consistently report PBM parameters due to a lack of clear reporting guidelines or descriptions of standardized reference protocols. Inconsistencies in reporting dosing and delivery appear to primarily contribute to partial or lack of success with PBM therapy. For this reason, the World Association of Photobiomodulation Therapy (WALT) has employed several novel dosimetry approaches such as the treatment surface irradiance (TSI in mW/cm²), photonic fluence (pJ/cm²), and nonthermal treatments [53–56] that aim at optimizing the practical implementation of PBM dosimetry. This concept was motivated by the realization that including individual wavelength energy within PBM dosing could prevent overdosing and enable precise dose combination with multiple wavelengths, accounting for the restricted availability of PBM devices globally [21]. This concept of the photonic fluence dose includes the individual photon energy (eV) in the total energy (fluence, dose) calculations and is reported as pJ/cm². As there are several preferred PBM wavelengths, and newer devices enable multiple wavelengths to be used concomitantly, it is anticipated there would be a substantial variation in the reported photonic fluence dose. Hence, the 810-nm photonic fluence at 3 J/cm² is recommended as a reference standard measure equivalent to 4.5 pJ/cm².
and is termed 1 Einstein. This term has been adapted from the greenhouse field that employs it to determine photosynthesis efficacy at discrete wavelengths. A key aspect of the new dose concept is reporting the treatment surface irradiance (TSI in mW/cm²) is emphasized as it enables the most accurate assessment of power density accounting for spot size as well as the distance of the probe from the target [54]. Another critical aspect of the dosing recommendations is the nonthermal nature of PBM and the importance of monitoring and restricting tissue surface temperature below 45 °C [55, 56].

In summary, to improve the clinical safety and consistency of PBM treatments, it is imperative to document and implement PBM device and delivery parameters rigorously. The variation in efficacy with PBM therapy remains a major obstacle in its routine implementation in supportive cancer care that can be dealt through improved communication and consensus development among experts. Moreover, given that cancer treatments involve many side effects that undermine their efficacy, accounting for the secondary outcomes such as QoL, pain, cost-effectiveness could improve clinical outcomes.

Conclusions

Cancer treatments involve many side effects, each accompanied by a series of secondary outcomes that can majorly impact QoL and undermine treatment efficacy. Complications such as pain, functional impairment, and nutritional deficiency may lead to poor prognosis and unwanted treatment interruptions. The supportive care of our patients should be pursued as a primary objective, since it may improve life quality, acceptance of treatment, and oncological outcomes. The evidence for PBM therapy is becoming more popular, as outlined by this review, and represents an innovative tool for improving clinical outcomes in our patients and clinical safety and consistency of PBM treatments. Improved understanding of PBM mechanisms and precise dose parameters are enabling the generation of more robust protocols. The variation in efficacy with PBM therapy remains a major obstacle in its routine implementation in supportive cancer care that can be dealt through improved communication and consensus development among experts. Given its established efficacy, supporting more clinical and basic science research in this novel field is imperative to maximize its safety and efficacy.

Author contribution Margherita Gobbo and Giulia Ottaviani had the idea for the article and performed the literature analysis, revision, and data analysis. Margherita Gobbo drafted the article, Giulia Ottaviani checked and reviewed the work. All the authors critically revised the work.

Declarations

Ethical approval Not applicable

Conflict of interest The authors declare no competing interests.

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