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.

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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 effects 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 (QLQ-C30) and Quality-of-Life Questionnaire for Head and Neck

Table 1 Characteristics of included studies

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 Median age: 59.5 (30–85) years	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 (*LG* = US $9.07; *PG* = US $44.26), gastrostomy (*LG* = US $50.50; *PG* = US $129.86), and hospitalization (*PG* = US $77.03) Higher costs in the PBM group for laser therapy only (US $1880.57) 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 Median age: 61 (45–76) years	Prospective not controlled study Therapeutic PBM	Oral mucositis **RT interruption**	RT interruption	The surface laser applied transcutaneously 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) Mean age: 55.97 ± 3.5 years	Cross-sectional study Preventive PBM	**Adherence/feasibility/tolerability**	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 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%) Mean age: 58.9 ± 10.19 years	Retrospective, cohort 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 3) Nutritional status: diet	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

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 (17.93 ± 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 ($p < 0.001$)

Table 1 (continued)

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) 1) Need for supplemental analgesics using WHO analgesic ladder 2) 2) Dysphagia using need for TPN 3) 3) Weekly weight loss 4) 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**	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)* [27]	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

Table 1 (continued)

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 (±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* v4, National Cancer Institute Common Toxicity Criteria for Adverse Events Version Four; *RD*, radiodermatitits; *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

Table 2 Laser parameters

Paper	Type brand	Wavelength (nm)	Mode (CW/pulse)	Format (fiber, array)	Contact or distance	Power output (mW)	Irradiance (mW/cm^2)	Spots/area	Time/site	Time/session	Repetitions	Fluence/site (J/cm^2)	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 cm^2	10 s	720 s	5 days/week	4	72 J	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 on 6 sites	First 8 days (5 min) supine position, following 25 days (30 min)	Thirty-three sessions	1.8	NS	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 cm^2/point: 9 points	33 s per spot (Nice and Marseilles) 80 s per spot (Reims)	5 min/session (Nice and Marseilles) 12 min/session (Reims)	5 days/week (Monday to Friday) for 7 consecutive weeks	2	18 J	3 J/cm^2
Bensadoun R. J. (2021) [14]	Caremin 650	650	CW	Array	Contact	NS	28 for oral 21 for dermal pads	NS	NS	Prophylactic: 107 s (oral pads) 143 s (derma pads) Curative: 214 s (oral pads) 286 s (derma pads)	At least 3 sessions/week (5 sessions/week recommended) immediately before or after RT	NS	NS	3 J/cm^2 (prophylactic) 6 J/cm^2 (curative)

Table 2 (continued)

Paper	Type brand	Wavelength (nm)	Mode (CW/pulse)	Format (fiber, array)	Contact or distance	Power output (mW)	Irradiance (mW/cm^2)	Spots/area	Time/site	Time/session	Repetitions	Fluence/site (J/cm^2)	Fluence/session	Total fluence
Bourbonne V. (2019) [15]	Laser Heltschl FL 3500 ME-TL 10 000 SK (Schlüßlberg, Austria)	660 658	CW	Array	External: noncontact (1 cm) Intraoral: NS	External: 350 Intraoral: 100	NS	External: 2 points Intraoral: 1 point	External: 240 s Intraoral: NS	External: 480 s Intraoral: NS	3 times/week for 7 weeks	6	12 J/cm^2 6 J/cm^2	252 J 126 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	690	0.1256 cm^2	10 s	280 s	3 times/week	2	20 J/cm^2	56 J
de Pauli Paglioni M. (2021) [17]	Diode laser (Twin Flex, MMOptics Equipment, São Paulo, Brazil)	660	CW	Fiber	Contact	40	1000	0.04 cm^2	Preventive: 10 s Treatment: 60 s	NS	Daily for 5 consecutive days/week from day 1 until the end of RT	Preventive: 10 Treatment: 60	600 J/cm^2 for 10 sites	NS
Guedes C. D. C. F. V. (2018) [28]	InGaArP 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	25 100	625 3.333	4 mm^2 3 mm^2	10 s/point 28 points	280 s	7 weeks	6.3 J/cm^2 33 J/cm^2	7 J/session 28 J/session	NS

Table 2 (continued)

Paper	Type brand	Wavelength (nm)	Mode (CW/pulse)	Format (fiber, array)	Contact or distance	Power output (mW)	Irradiance (mW/cm^2)	Spots/area	Time/site	Time/session	Repetitions	Fluence/site (J/cm^2)	Fluence/session	Total fluence
Elgohary H. M. (2018) [18]	Laser equipment (Electro Medical Supplies, Greenham Ltd., Wantage, Oxfordshire, UK)	950	Pulsed 80%	Fiber	NS	15	NS	NS	NS	360 s	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, Schluesslberg, Austria)	660 ± 3	CW (external and intraoral)	Array with 7 emitters	5 cm distance	External: 350 Intraoral: 70	10	External 35 cm^2 Intraoral: 1 cm^2	External: 1200 s (gradse 1–2) 2400 s (grades 3–4) Intraoral: 60 s/cm^2 (grades 1–2) 120 s/cm^2 (grades 3–4)	NS	1–2 times/day, average 6 sessions	Extraoral: 12 (grades 1–2) 24 (grades 3–4) Intraoral: 4 (grades 1–2) 8 (grades 3–4)	Intraoral: 420 J (grades 1–2) 840 J (grades 3–4) Extraoral: 4 J (grades 1–2) 8 J (grades 3–4	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 (< 1cm)	24	24	1 cm^2	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/cm^2
Gautam A. P. (2012) [21] (Oral Oncology)	He-Ne laser (Technomed Electronics, Advanced Laser Therapy 1000, Chennai, India)	632.8	CW	Fiber	Non-contact (< 1 cm)	24	24	0.6 mm Spot size 1 cm^2 6 sites	145 s	870 s	Daily for 6.5 weeks	NS	NS	3.5 J/cm^2

Table 2 (continued)

Paper	Type brand	Wavelength (nm)	Mode (CW/pulse)	Format (fiber, array)	Contact or distance	Power output (mW)	Irradiance (mW/cm^2)	Spots/area	Time/site	Time/session	Repetitions	Fluence/site (J/cm^2)	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 cm^2	125 s 6 sites	750 s/session	5 times/week	3 J/cm^2	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 cm^2	125 s 12 sites	NS	5 times/week	3 J/point	36 J/session	NS
Genot-Klastersky M. T. (2020) [24]	Biophoton Travelers Oncolase TW scanning laser	630	CW	Fiber	5–10 mm distance	100	100	1 cm^2	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 cm^2 9 sites	26 s/site on 9 sites	234 s	2 times/day for 4 consecutive days	NS	NS	NS
González-Arriagada 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 mm^2	10 s/point	90 s	5 consecutive days (Monday to Friday) during all RT sessions	0.1 J	0.9 J	2.5 J/cm^2

Table 2 (continued)

Paper	Type brand	Wavelength (nm)	Mode (CW/pulse)	Format (fiber, array)	Contact or distance	Power output (mW)	Irradiance (mW/cm^2)	Spots/area	Time/site	Time/session	Repetitions	Fluence/site (J/cm^2)	Fluence/session	Total fluence
Legouté F. (2019) [28]	He-Ne laser HETSCHL®	658	Pulsed (50 Hz)	Fiber	0.5 mm	100	100	1 cm^2 per application	40 s/cm^2	NS	1 session/day, 5 sessions/week from day of OM grade 2 until the resolution of OM	4 J	NS	4 J/cm^2
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 cm^2	160 s 12 sites	NS	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 cm^2 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 mm^2 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]	InGaAlP 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; *InGaArP*, 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 subdued 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 ± 1.3 versus 6 ± 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. Legoutè 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 ± 13 days) than in the placebo (17.9 ± 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 ± 1.3 weeks) than the placebo (6 ± 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 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 treatments to a cohort of subjects they defined as at "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 necessary for more patients in the placebo arm [27, 33]. Interestingly, Morais et al. monitored the interruption of RT for any reason. 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 maintenance 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 observations 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 improvements 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 possibilities of enhancing tumor cells [44]. Several reports have indicated PBM as a supportive care technique is not harmful 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/recurrence 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 tumoral 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 recurrence. 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 feasible. 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].

Legoutè 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/cm^2), photonic fluence (pJ/cm^2), 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/cm^2. 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/cm^2 is recommended as a reference standard measure equivalent to 4.5 pJ/cm^2

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/cm^2) 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 search. Margherita Gobbo, Praveen R. Arany, Elisabetta Merigo, René-Jean Bensadoun, Alan Roger Santos-Silva, and Luiz Alcino Gueiros 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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