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SPECIAL ARTICLE

Systematic review of photobiomodulation for the management of oral mucositis in cancer patients and clinical practice guidelines

Yehuda Zadik[1,2] · Praveen R. Arany[3] · Eduardo Rodrigues Fregnani[4] · Paolo Bossi[5] · Héliton Spindola Antunes[6] · René-Jean Bensadoun[7] · Luiz Alcino Gueiros[8] · Alessandra Majorana[9] · Raj G. Nair[10] · Vinisha Ranna[11] · Wim J. E. Tissing[12] · Anusha Vaddi[13] · Rachel Lubart[14] · Cesar Augusto Migliorati[15] · Rajesh V. Lalla[16] · Karis Kin Fong Cheng[17] · Sharon Elad[13] · On behalf of The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO)

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Abstract

Purpose To systematically review the literature and update the evidence-based clinical practice guidelines for the use of photobiomodulation (PBM), such as laser and other light therapies, for the prevention and/or treatment of oral mucositis (OM).

Methods A systematic review was conducted by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO) using PubMed and Web of Science. We followed the MASCC methods for systematic review and guidelines development. The rigorously evaluated evidence for each intervention, in each cancer treatment setting, was assigned a level-of-evidence (LoE). Based on the LoE, one of the following guidelines was determined: Recommendation, Suggestion, or No Guideline Possible.

Results Recommendations are made for the prevention of OM and related pain with PBM therapy in cancer patients treated with one of the following modalities: hematopoietic stem cell transplantation, head and neck (H&N) radiotherapy (without chemotherapy), and H&N radiotherapy with chemotherapy. For each of these modalities, we recommend 1–2 clinically effective protocols; the clinician should adhere to all parameters of the protocol selected. Due to inadequate evidence, currently, No Guideline Possible for treatment of established OM or for management of chemotherapy-related OM. The reported clinical settings were extremely variable, limiting data integration.

Conclusions The evidence supports the use of specific settings of PBM therapy for the prevention of OM in specific patient populations. Under these circumstances, PBM is recommended for the prevention of OM. The guidelines are subject to continuous update based on new published data.

Keywords Cancer · Chemotherapy · Laser therapy · LED · LLLT · Low-level laser therapy · Prevention · Treatment · Oral complications of cancer therapy · Oral mucositis · Pain · Photobiomodulation · Photobiostimulation · Radiotherapy · Stomatitis · Evidence-based · Guidelines

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✉ Yehuda Zadik
Yehuda.Zadik@mail.huji.ac.il

✉ Praveen R. Arany
prarany@buffalo.edu

Extended author information available on the last page of the article

Abbreviations

CT	Chemotherapy
GaAlAs	Gallium-aluminum-arsenide
H&N	Head and neck
HeNe	Helium-Neon
HSCT	Hematopoietic stem cell transplantation
InGaAlP	Indium-Gallium-Aluminum-Phosphorus
InGaAs	Indium-Gallium-Arsenide
LED	Light-emitting diode
LLLT	Low-level laser therapy
LoE	Level of evidence

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OM	Oral mucositis
MASCC /ISOO	Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology
PBM	Photobiomodulation
PTP	Photobiomodulation therapy parameters
RCT	Randomized controlled trial
RT	Radiotherapy

Introduction

Oral mucositis (OM) is a debilitating complication of high-dose chemotherapy (CT), radiation therapy (RT) to the head and neck (H&N), and hematopoietic stem cell transplantation (HSCT). OM may be associated with intense pain, increased consumption of opioids (narcotics), increased need for parenteral nutrition, and increased risk of bacteremia [1, 2]. In HSCT patients, OM is associated with a greater risk of 100-day post-HSCT mortality [3].

The term photobiostimulation was coined by Endre Mester following his observation of the effects of low-dose laser treatments on stimulation of wound healing [4]. Later, it was also noted that as well as stimulation, light therapy may also modify certain deleterious processes, such as inflammation or pain, and the term photobiomodulation (PBM) was established [5]. Some studies use the term low-level laser therapy or low-level light therapy (LLLT) to refer to PBM. Currently, PBM includes a broad range of nonionizing light sources such as lasers, light-emitting diodes (LEDs), and broadband visible light in the visible and near-infrared spectrum at very low, non-thermal doses. PBM activates endogenous chromophores eliciting photophysical and photochemical events involving several biological pathways that provide favorable clinical therapeutic results [6]. PBM stimulates and promotes positive tissue processes such as wound healing, regeneration, and immune responses and mediates negative tissue processes such as inflammation, pain, and aberrant immune responses [6, 7]. As such, PBM was suggested for the management of OM [8, 9].

The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) published comprehensive evidence-based clinical practice guidelines for mucositis, including a section about laser and light therapy [10, 11]. The previous guidelines for laser and light therapy for the management of OM in cancer patients was based on evidence indexed before 31 December 2010. The MASCC/ISOO recommended the use of LLLT at a wavelength of 650 nm, power of 40 mW, and each square centimeter treated enough to achieve a tissue energy dose of 2 J/cm^2 (2 s/site) for the prevention of OM in adults receiving HSCT conditioned with high-dose CT, with or without total body irradiation. Additionally, MASCC/ISOO suggested the use of LLLT (wavelength 632.8 nm) for the prevention of OM in patients undergoing RT, without concomitant CT, for H&N cancer [11]. No specific details were provided for this later guidelines, and a reservation that it was based on flawed randomized controlled trial (RCT) was published. No guidelines were possible in other patient populations or for other light sources due to insufficient evidence [11]. The authors called for additional well-designed research to evaluate the efficacy of laser and other light therapies in other cancer treatment settings. As part of a comprehensive update of the MASCC/ISOO clinical practice guidelines for the management of mucositis, the aim of this study was to systematically review the peer-reviewed literature since 2011 and update the clinical practice guidelines for the use of PBM (i.e., laser and other light) therapy for OM management. This aim highlights the specific objective of identifying current interventions for mucositis and ranking them based on evidence quality in order to compile guidelines for clinicians to be used in decision-making for the management of OM.

Methods

The detailed methods are described in Ranna et al. [12]. Briefly, a literature search for relevant papers indexed in the literature from January 1, 2011 to June 30, 2016 was conducted using PubMed and Web of Science, with papers selected for review based on defined inclusion and exclusion criteria [12]. The following keywords were unique for the literature search of this section: CO2, Diode, GaAlAs, HeNe, infra-red, InGaAlP, InGaAs, laser, LED, light therapy, light-emitting diode, low-level laser therapy, low-level light therapy, photobiomodulation, phototherapy, and visible light. The keywords that are shared by all sections are listed in the Ranna et al. paper [12]. We also screened the references of the systematic reviews and meta-analyses to identify additional, original studies that were not retrieved in our prior search.

Papers were reviewed by two independent reviewers and data was extracted using standard electronic forms. If there were any doubts within the reviewing team, the corresponding author of the respective study was contacted. Data identified in the current literature search were merged with the papers identified in the 2013 guidelines to cover the entire literature up to June 2016. References identified as related to PBM, laser, and light therapy during the literature triage in other sections were transferred and included in the dataset of this section. Studies reporting overlapping patient populations, or presenting sub-analysis of the same patient population were considered as a single study. Studies were scored for their level of evidence (LoE) based on Somerfield criteria, and flaws were listed according to Hadorn criteria [13, 14]. A well-designed study was defined as a study with no major flaws per the Hadorn criteria. Studies with the most robust study-design (RCTs, controlled clinical trials, and cohort studies) were used for the analysis of the collective LoE for each clinical category. Clinical categories were defined based on (i) the aim of the intervention (prevention or treatment of OM); (ii) the treatment modality [RT, CT, chemoradiotherapy (RT-CT)], or high-dose conditioning therapy for HSCT), and (iii) the route of administration of the intervention (intra-oral, extra-oral, or combined). Guidelines were classified into three types: Recommendation, Suggestion, and No Guideline Possible.

Additionally, all randomized controlled trials (RCTs) were reviewed for reports about topical or systemic adverse effects following PBM therapy. This was considered as complementary data to evaluate the safety of PBM therapy in patients undergoing anti-cancer therapy.

Papers were also reviewed for the PBM therapy parameters, (PTPs) (Box 1) to enable clinical treatment recommendations. A comprehensive assessment of these parameters namely, intensity (or power, mW); power density (or irradiance, mW/cm^2); energy (J); energy density or fluence, J/cm2); site size (treated area, cm^2); time per site (seconds); number of oral sites treated, treatment probe distance or contact with tissue, mode of operation (continuous versus pulsed); and duration of the treatments relative to the timing of the anti-cancer therapies was performed. We examined these parameters in all manuscripts selected for this review and if they were not reported, we calculated the power density (irradiance, mW/cm^2). If the PTPs were reported, their validity was confirmed using standard dose equations (irradiance = power/site size; or irradiance = fluence × 1000/time per site). Studies with inconsistent reports of PTPs were excluded from the analysis.

Box 1 Photobiomodulation therapy parameters (PTPs) required for reproducible reports

(1) Device setting–user-determined:
  i. Critical
    1. Irradiance/power density (mW/cm2)
    2. Fluence/energy density (J/cm2)
    3. Time per site (sec)
  ii. Required if the "critical" parameters listed in "(1)i" are not all reported
    1. Spot size (cm^2)
    2. Distance from the tissue (cm^2)
    3. Power/intensity (mW)
    4. Energy (J)
  iii. Advised
    1. Mode of operation–(continuous/pulsed)
    2. Duty cycle (%)
    3. Frequency (Hz)
(2) Device setting–machine-determined:
  i. Wavelength (nm)
  ii. Beam divergence
(3) Delivery mode parameters:
  i. Stationary/motion
  ii. Distance from the tissue
  iii. Number of sites
(4) Treatment parameters
  i. Number of sessions
  ii. Timing compared to the anti-cancer therapy
  iii. Anatomical location

Results

A total of 701 abstracts were retrieved (323 from PubMed and 378 from Web of Science). Six papers were identified on manual literature search. After triage of the abstracts, 49 full text articles were chosen for further review. Following the review of the full papers, an additional 17 papers were excluded as they did not meet the exclusion and inclusion criteria. Following the merging, the data after 2011 with data before 2011, 24 additional papers were added. When overlapping reports were checked and the review PTPs and focus on studies with the most robust study design considered, 23 papers were excluded. Therefore, a total of 33 papers were included in this systematic review (Fig. 1).

The complete list of reviewed papers is presented in the online materials. While numerous studies were

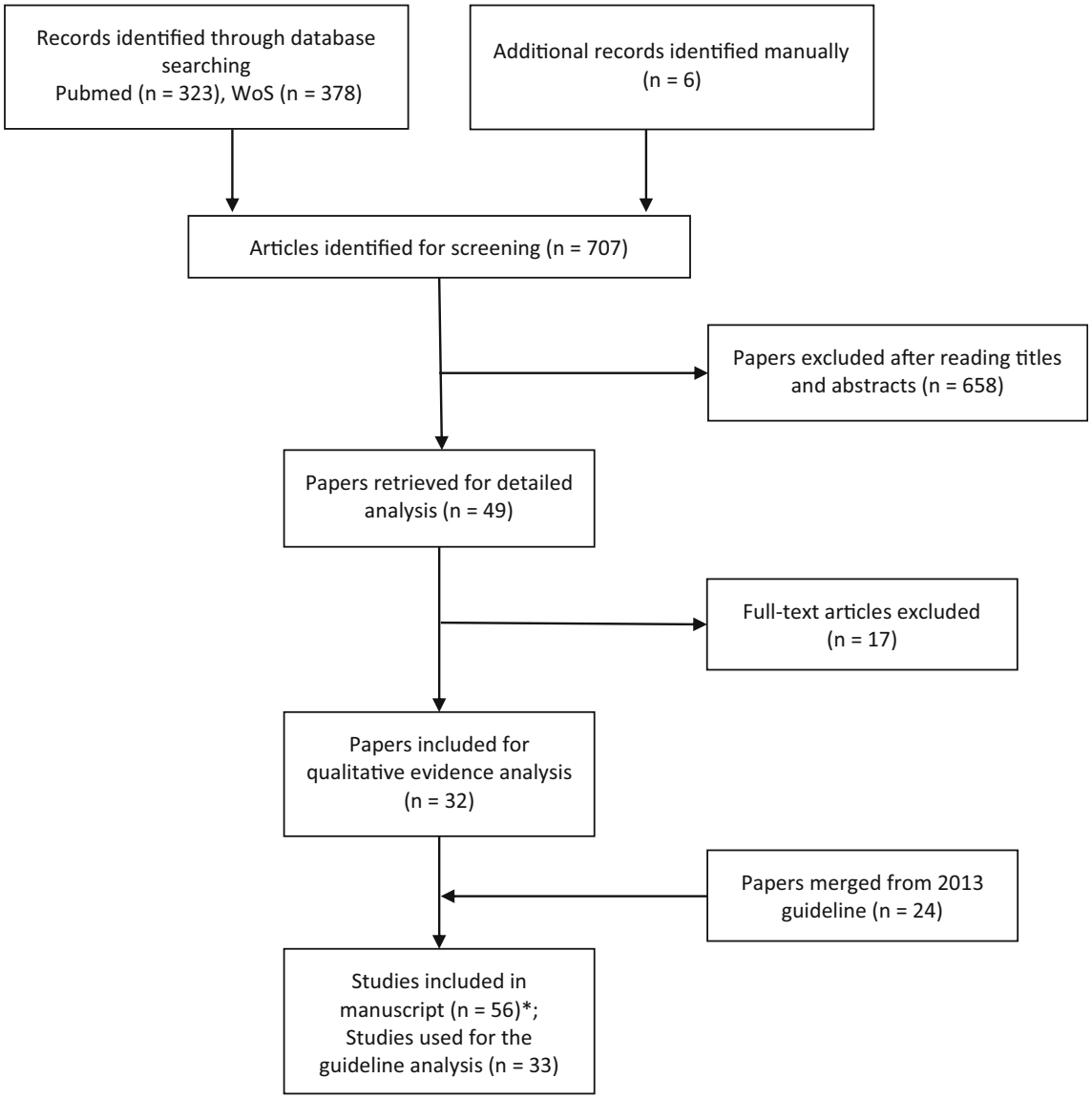

Fig. 1 Flow diagram of the information flow through the different phases of the systematic review. *The complete list of these 56 papers is presented in the online materials [65–85]. WoS, Web of Science

reviewed, guidelines were reserved for the most reproducible studies with robust design and positive results; protocols are listed in Table 1. The remaining studies included in this analysis are in Table 2 (intra-oral applications), Table 3 (extra-oral applications), and Table 4 (combined intra- and extra-oral applications).

The following sections present the data for specific clinical conditions where PBM therapy has been used, i.e., aim of intervention, anti-cancer therapy, and patient population. Details of device type and PTPs are presented in the respective tables. Adherence to the treatment parameters is essential to achieve the reported benefits; interchanging parameters and extrapolations among protocols are not recommended.

Prevention of oral mucositis in hematopoietic stem cell transplantation

Guideline The panel recommends the use of intra-oral PBM therapy using low-level laser therapy for the prevention of OM in adult patients receiving HSCT conditioned with high-dose CT, with or without total body irradiation using one of the selected protocols in Table 1 (LoE I); following the specific PTPs of the selected protocol is recommended for optimal therapy.

Intra-oral PBM was reported to be beneficial for the prevention of OM and related pain in HSCT patients in numerous RCTs (Table 2) [8, 15, 22–27, 44]. The overall trend noted

Table 1 Recommended intra-oral photobiomodulation therapy protocols for the prevention of oral mucositis

Cancer treatment modality	Protocol	Wavelength (nm)	Power density (irradiance; mW/cm^2)	Time per spot (sec)	Energy density (fluence; J/cm^2)	Spot size (cm^2)	Number of sites	Distance from the tissue	Frequency	Duration	Based on reference
HSCT	#1	632.8	31.25	40	1.0	0.8	18	<1 cm	Daily	From day after cessation of conditioning for 5 days	Barasch et al., 1995 [8]
	#2	650	1000*	2	2.0	0.04	54–70	In contact	Daily	From 1st day of conditioning till day +2 post-HSCT (for 7–13 days)	Schubert et al., 2007 [15]
RT	#1	632.8	24	125	3.0	1	12	< 1 cm	5 days/wk.	Entire RT course	Gautam et al., 2015 [16]
RT-CT	#1	660	417*	10	4.2	0.24	72	In contact	5 days/wk.	Entire RT course	Antunes et al., 2013 [17]
	#2	660	625*	10	6.2	0.04	69	In contact	3 days/wk. (alternate days)	Entire RT course	Oton-Leite et al., 2015 [18]

*Potential thermal effect. The clinician is advised to pay attention to the combination of specific parameters

CT, chemotherapy; *HSCT*, hematopoietic stem cell transplantation; *IO*, intra-oral; *NR*, not reported; *PBM*, photobiomodulation; *RT*, radiotherapy; *wk.*, week

from the available evidence is that intra-oral PBM therapy at wavelengths of 630 to 660 nm (red) is beneficial for preventing OM and related pain in HSCT patients. Significant variations were noted in PTPs (Table 2). An RCT using visible light supports this guideline as the peak of the emission spectrum used in this study was in the range of 625–660 nm (Table 2: entire spectrum used—top row; peak of the emission spectrum—bottom row) [27].

Extra-oral PBM for the management of OM was reported to have a beneficial effect in the prevention of OM in HSCT patients (Table 3). While there was evidence of clinical efficacy in two studies, one RCT and a cohort study, the LoE does not enable a guideline for extra-oral PBM [42, 43].

Prevention of oral mucositis in cancer patients treated with chemotherapy

Guideline No guideline possible.

Based on the current literature, no guideline is possible for intra-oral PBM for the prevention of OM in cancer patients treated with CT due to the absence of RCTs and significant variability of the PTPs in the studies with low LoE (Table 2) [28–31].

Prevention of oral mucositis in head and neck cancer patients treated with radiotherapy

Guideline The panel recommends the use of intra-oral PBM therapy using low-level laser therapy for prevention of OM in adult patients receiving RT to the H&N (without CT) (LoE II) (Table 1); the specific PTPs of the selected protocol should be followed for optimal therapy. Safety considerations unique to patients with oral cancer should be considered.

The efficacy of intra-oral PBM at wavelength of 632.8 nm for prevention of OM and related pain in cancer patients treated with RT to the H&N (without CT) was reported in several studies (Table 2) [16, 34, 35].

A single study combined both extra- and intra-oral laser application for the prevention of OM in patients treated with RT to the H&N and reported positive clinical results (Table 4). [35] Due to limited evidence and low LoE, no guideline is possible for this protocol.

Prevention of oral mucositis in head and neck cancer patients treated with radiotherapy and chemotherapy

Guideline The panel recommends the use of intra-oral PBM therapy using low-level laser therapy for the prevention of OM in adult patients receiving RT and CT for H&N cancer (LoE I) (Table 1); the specific PTPs of

Table 2 Studies addressing intra-oral photobiomodulation for the management of oral mucositis

Cancer treatment modality	Aim	RCTs										Non-RCTs–study design (effectiveness)	Overall level of evidence	Guideline category
		Author, Year	Cancer type	PBM source	Wave-length (nm)	Power (mW)	Energy density (Fluence; J/cm2)	Time (sec)	Power density (irradiance; mW/cm2)	Sites	Effectiveness			
HSCT	P	**Barasch et al. 1995** [8] *	**Hematol**	**He-Ne laser**	**632.8**	**25**	**1**	**40**	***31.25***	**18**	Y (1,3)	Jaguar et al. 2007 [19] – 4 (Y) Bezinelli et al. 2014 [20] – 3 (Y) De Paula Eduardo et al. 2015 [21] – 3 (Y) Bezinelli et al. – 4 (Y)	I	R
		Cowen et al. 1997 [22]	Hematol	He-Ne laser	632.8	60	1.5	10	*150*	75	Y (1,2)			
		Antunes et al. 2007 [14] *	Hematol	Diode laser	660	46.7	4	16.7	*238*	165	Y (1,2)			
		Schubert et al. 2007 [15] *	**Hematol**	**Diode laser**	**650** 780	**40** 70	**2**	***2***	***1000*** *2000*	**54–70**	Y (1,3) N			
		Khouri et al. 2009 [23]	Hematol	Diode laser	660/780	25	6.3	10	*630*	5	Y (1)			
		Silva et al. 2011 [24]	Hematol	Diode laser	660	40	4	4	*1000*	80	Y (1)			
		Silva et al. 2015 [25]	Hematol	Diode laser	660	40	4	4	*1000*	80	Y (1,2)			
		Ferreira et al. 2016 [26]	Hematol	Diode laser	650	100	70	20	*3571*	27	Y (1,3)			
		Elad et al., 2011 [27] *	Hematol	Visible light	400–900 625–660	125	1.4–1.8	90	160–200 16–20	3	Y (1,3)			
	T	None										–	–	–
CT	P	None	–									Freitas et al. 2014 [28] - 4 (Y) Ottaviani et al. 2013 [29] - 4 (Y) Cunha et al. 2012 [30] - 3 (Y) Gobbo et al. 2016 [31] - 4 (Y)	III	NGP
	T	None										–	–	–
CT/HSCT	P	None	–									Chermetz et al. 2014 [32] - 4 (Y) ^	IV	NGP
	T	Amadori et al. 2016 [33]	Hematol & solid ca. ^	Diode laser	830	150	4.5	30	*150*	7	Y (2,3)	None	III	NGP
RT	P	Bensadoun et al. 1999 [34]	H&N	He-Ne laser	632.8	60	2	33	*60*	9	Y (1,2,3)	Arora et al. 2008 [35] – 3 (Y)	II	R
		Gautam et al. 2015 [16] *	**H&N**	**He-Ne laser**	**632.8**	**24**	***3***	**125**	**24**	**12**	Y (1,2,3,4)			
	T	None										–	–	–
RT-CT	P		H&N		660	10	2.5	10	*250*	9	N	None	I	R

Table 2 (continued)

Cancer treatment modality	Aim	RCTs										Non-RCTs–study design (effectiveness)	Overall level of evidence	Guideline category
		Author, Year	Cancer type	PBM source	Wave-length (nm)	Power (mW)	Energy density (Fluence; J/cm2)	Time (sec)	Power density (irradiance; mW/cm2)	Sites	Effectiveness			
		Gouvêa de Lima et al. 2012 [36]		Diode laser										
		Gautam et al. 2013 [37] *	H&N	He-Ne laser	632.8	24–35	3–4.4	125	24–35	9	Y (1,2,3)			
		Antunes et al., 2013 [17]	**H&N**	**Diode laser**	**660**	**100**	**4.2**	**10**	***417***	**72**	Y (1,3)			
		Oton-Leite et al. 2015 [18]	**H&N**	**Diode laser**	**660**	**25**	**6.2**	**10**	***625***	**69**	Y (1)			
	T	None										–	–	–
RT/RT-CT	P	Carvalho et al, 2011 [38]	H&N	Diode laser	660	15	3.8	10	*380*	8	Y (1,2,3)**	Lima et al. 2010 [39] - 4 (Y) Gobbo et al., 2014 [40] - 4 (Y)	IV	NGP
CT/RT/RT + CT/HSCT	T	None	–									Sandoval et al. 2003 [41] - 4 (Y)	IV	NGP

Flawless studies, based on Hadorn Criteria [12], are in **bold**

Calculated data by the authors based on data from the original report, are in *italics*.

*Data confirmed with the corresponding author of the original report

**Compared to another PBM settings (no placebo control group); ^pediatric

Cancer treatment modality key: *CT*, chemotherapy; *HSCT*, hematopoietic stem cell transplantation; *RT*, radiotherapy

Aim key: *P*, prevention; *T*, treatment

Effectiveness key: 1, Mucositis severity; 2, Mucositis duration; 3, Pain severity; 4, Pain duration

Guideline category key: *NGP*, no guideline possible; *S*, suggestion; *R*, recommendation

Study design key: 3, Non-randomized controlled trial; 4, Cohort;

ca, cancer; *H&N*, head and neck malignancies; *Hematol*, hematologic malignancies; *N*, no; *PBM*, photobiomodulation; *RCT*, randomized controlled study; *Y*, yes

Table 3 Studies addressing extra-oral photobiomodulation for the management of oral mucositis

Cancer treatment modality	Aim	Author, year	Cancer type	PBM source	Wave-length (nm)	Power (mW)	Fluence (J/cm2)	Time (sec)	Irradiance (mW/cm2)	Sites	Effectiveness	Non-RCTs	Overall level of evidence	Guideline category
HSCT	P	**Hodgson et al. 2012** [42]	**Hematol ^**	**LED**	**670**	–	**4**	**80**	**50**	**3**	**Y (3)**	Whelan et al., 2002 [43]–4 (Y)	II	NGP

Flawless studies, based on Hadorn Criteria [12], are in Bold

^pediatric

Cancer treatment modality key: *HSCT*, hematopoietic stem cell transplantation

Aim key: *P*, prevention

Effectiveness key: 3, Pain severity;

Guideline category key: *NGP*, no guideline possible;

Hematol, hematologic malignancies; *LED*, light-emitting diode; *PBM*, photobiomodulation; *RCT*, randomized controlled study; *Y*, yes

the selected protocol should be followed for optimal therapy. Safety considerations unique to patients with oral cancer should be considered.

The efficacy of intra-oral PBM at wavelengths of 632.8 nm and 660 nm for the prevention of OM and related pain in H&N cancer patients treated by RT with CT were reported in several RCTs (Table 2) [17, 18, 36, 37]. One study reported clinical ineffectiveness at 660-nm wavelength despite the PTPs falling within the range of other positive studies [36]. The exact reason for this discrepancy remains unclear even after detailed analyses of the dose and delivery parameters.

Mixed cancer patient populations

Several studies examined the efficacy of PBM therapy for management of OM in a non-uniform group of cancer patients or mixed anti-cancer treatment modalities (Table 2) [32, 33, 39–41]. However, no guidelines are currently possible due to the significant heterogeneity in treatment parameters and patient populations.

Safety analysis

In all analyzed RCTs, no short- or long-term adverse events with PBM treatments were reported, despite significant variations in the PTPs. However, in one cohort study, 15% of patients experienced an immediate (non-painful) burning sensation after intra-oral 635-nm diode laser treatment [29].

Discussion

This paper aimed at systematically reviewing the evidence about PBM, previously termed low-level light or laser therapy, for OM, and accordingly update the MASCC/ISOO clinical practice guidelines for the management of OM [11]. Each guideline is outlined according to the cancer patient population, anti-cancer therapy, and parameters for PBM therapy. The panel identified evidence to support clinical practice guidelines for three specific clinical indications as follows:

(i) Recommendation for the prevention of OM with intra-oral PBM therapy, with specific PTPs, in HSCT patients. The current systematic review reiterates the 2013 guidelines [11] in this patient population and further extends the PTPs that may be utilized;
(ii) Recommendation for the prevention of OM with intra-oral PBM therapy, with specific PTPs, in cancer patients treated with H&N RT (without CT). This is an upgrade

Table 4 Studies addressing combined extra-oral and intra-oral photobiomodulation for the management of oral mucositis

Cancer treatment modality	Aim	RCTs	Non-RCTs – study design (effective)	Overall level of evidence	Guideline category
RT	P	None	Arora et al. 2008 [35] – 3 (Y)	IV	NGP

NGP, no guideline possible; P, prevention; RCT, randomized controlled trial; RT, radiotherapy; Y, yes; Study design key: 3, non-randomized controlled trial

of the 2013 guideline level [11] from Suggestion to Recommendation;

(iii) Recommendation for the prevention of OM with intra-oral PBM therapy, with specific PTPs, in cancer patients treated with H&N RT with CT. This is a new guideline based on recent evidence.

It should be noted that, currently, there is no evidence-based guideline for the treatment of established OM with PBM therapy and its associated pain; the guidelines are for the prevention of OM with PBM therapy. The guideline determination was influenced mostly by RCTs that met strict clinical and scientific criteria; however, clinical studies with lower LoE were assessed and contributed to the conclusions. Studies in which the PTPs were not reproducible were omitted from guideline determination.

For two cancer patient populations, HSCT and RT-CT, there were several protocols based on flawless RCTs, and each is a viable option for clinical application. The guideline states that once a certain protocol is selected, the entire PTPs of that protocol should be followed and parameters should not be interchanged or extrapolated. For example, for the prevention of OM in HSCT patients, two protocols are recommended (Table 1). If the first option is selected, the clinician may choose a specific protocol with a 632.8 nm (Helium-Neon) laser with an irradiance (power density) of 31.25 mW/cm^2, spot size of 0.8 cm^2, application for 40 s on each site, fluence (energy density) of 1 J/cm^2, on 18 sites in the oral mucosa, for five daily sessions from day after cessation of HSCT conditioning (Table 1). Given the complexity of the light-tissue interactions and incomplete understanding of the precise roles and contributions of each of these PTPs, interchanging these parameters may not result in the demonstrated clinical efficacy and can potentially impact clinical safety. With a better understanding of these variables and additional clinical trials, specific range of PTPs will likely be better defined. Accordingly, we anticipate that the guidelines will be changed in the future. Nonetheless, it is prudent to emphasize these recommended protocols represent the current literature, and do not exclude other PTPs that have not been studied systematically to date. Moreover, future studies may prove efficacy in settings that were previously thought to be inefficient.

The current standard PBM dose reporting models are based on irradiance per site (mW/cm^2), time of treatment (sec) and fluence (J/cm^2), and possibly the cumulative energy per session (total energy delivered per session) [6]. Irradiance per site likely reflects the threshold dose needed to biologically activate relevant therapeutic responses while the total energy possibly reflects the overall tissue dose needed to generate a sufficient clinical outcome. Theoretically, the cumulative energy is derived from the number of sites treated in each session, and/or the number of sessions conducted. Our attempts to correlate these PTPs with the clinical outcome did not identify a trend. Therefore, we encourage investigators to report well-designed studies about OM with negative results too.

Conducting a RCT is a complex and major undertaking. To examine the effect of low-dose biophotonics adds significant additional complexity due to the scale and kinetics of light-biological tissue interactions. Over the years, as revealed in this systematic review, clinical study design in laser and light therapy and the level of reporting of PTPs have improved dramatically. In this guideline update, numerous RCTs were assessed and more details were provided on the physical parameters. A list of PTPs that should be included when reporting PBM therapy is presented in Box 1. The importance of the detailed reporting of PTPs was discussed in the literature extensively [45–49].

The precise PBM dose delivered to the tissue is critical due to the biphasic dose response, termed the Arndt Scultz curve, where PBM therapy can activate or inhibit biological responses. [46] There are a few nuances that may influence the actual PBM dose delivered and should be considered when operating a PBM device or conducting a clinical trial: (1) the fiber optic is not necessarily identical to the probe tip, affecting reported probe surface and spot size; (2) the tip output may decrease with time, therefore routine calibration is recommended; (3) the precise distance of the probe from the tissue (estimated or calibrated) has a significant impact on the energy distribution; and (4) the specific time spent on each site (steady probe position or in-motion application) needs to be accurately reported, as approximation may hinder comparison between study outcomes. Generally, it is advisable to confer with a physicist specializing in optics or a radiation biologist to ensure the PBM settings are appropriate. We believe these recommendations will not only enable standardization of protocol parameters and improve quality of reporting, they will also improve consistency and reproducibility of clinical therapeutic outcomes.

Another major variable noted in the analysis of these studies was the number of treatment sites during each session. While it is relatively easy to locate and treat apparent clinical lesions, for preventive therapy for large mucosal areas, the number and location of the sites of the PBM therapy required to generate a clinical outcome are ambiguous. A point source would treat a limited tissue volume, and therefore large beam-spot, multi-probe clusters, novel delivery devices, or extra-oral approaches may be advantageous.

Extra-oral application of PBM has some clinical advantages regarding convenience of use because of the intra-oral discomfort and restricted mouth opening associated with OM. Moreover, these extra-oral devices offer operator convenience, enabling the treatment of large areas in a reasonable time [50]. It is important to emphasize that dose delivery for extra-oral approaches as well as the treatment dosimetry to the oral tissues remain challenging and require further investigation.

This systematic review shows that the settings used in RCTs for PBM therapy for OM did not result in immediate adverse events. However, one cohort study reported immediate burning sensation in 15% of patients, but no persistent symptoms were noted [29]. These observations demonstrate that PBM therapy is well-tolerated in cancer patients.

There is a discussion in the literature about the potential long-term risk of PBM therapy for malignant transformation, progression, or recurrence [51]. Whether PBM administered in regions anatomically associated with a tumor negatively impacts tumor treatment response or behavior is currently unknown. The suggested biological pathways induced by PBM, the conflicting in-vitro data of PBM-influenced tumor cell behaviors, and the limited clinical data about long-term safety demand caution when considering PBM for the management of OM. In the current literature, follow-up data has been presented in two studies [52, 53]. The authors claimed that PBM increased the progression free survival of H&N cancer patients treated with RT-CT [52].0 However, until substantial long-term safety data is available, the use of PBM in areas with known or possible tumors should be considered cautiously. The patient should be informed about the possible benefits and risks before treatment.

Additionally, laser safety standards must be used while delivering PBM as per the American National Standard Institute (ANSI Z136.1, 2014). Furthermore, standard precautions to prevent the spread of infectious disease should be followed.

The data reported in the literature present benefits for the prevention of OM and its associated pain in certain cancer populations. The pain relief correlated with reduced OM severity over time. We did not observe consistent RCT-derived data on response time in terms of the interval between PBM application and reported pain relief. However, in a cohort study, Sandoval et al. described immediate pain relief after application of 660-nm laser therapy in two-thirds of their cohort of mixed cancer patients with symptomatic OM [41]. Such data may be of great relevance for treating OM-associated pain.

Several studies were published after the cutoff date (i.e., June 2016) and are considered late-breaking reports. These studies refer to intra-oral PBM application using a variety of

Table 5 Studies addressing intra-oral photobiomodulation for the management of oral mucositis in pediatric patients

Cancer treatment modality	Aim	RCTs					Non-RCTs–study design	Comment
		Author, year	Cancer type	PBM source	Wavelength (nm)	Effectiveness		
RT/RT-CT	T	Medeiros-Filho 2017 [58]	H&N ^	Diode laser	808 808 + 660	Y (1)	None	Photodynamic therapy (methylene blue)
HSCT/CT	T	Vitale 2017 [59]	Hematol ^	Diode laser	970	Y (1,2,3,4)	None	
		Gobbo 2018 [60]	Hematol & solid ca. ^	Diode laser	660 + 970	Y (1,3)		
CT	T	Ribeiro da Silva 2018 [61]	Hematol & solid ca. ^	Laser	660	N	Leite Cavalcanti 2018 [62] - 3	Photodynamic therapy (methylene blue)

^pediatric

Cancer treatment modality key: *RT*, radiotherapy; *CT*, chemotherapy; *HSCT*, hematopoietic stem cell transplantation

Aim key: *T*, treatment

Effectiveness key: 1, Mucositis severity; 2, Mucositis duration; 3, Pain severity; 4, Pain duration

Study design key: 3, non-randomized controlled trial

ca, cancer; *H&N*, head and neck malignancies; *Hematol*, hematologic malignancies; *N*, no; *RCT*, randomized controlled trial; *Y*, yes

PTPs. This new evidence does not change the collective LoE and the guidelines set above [54–57].

PBM therapy may be considered a patient-friendly treatment modality, especially in pediatric patients that may not be able to comply with other modalities, such as mouthwash. A few recent studies on pediatric patient populations demonstrated the efficacy of intra-oral PBM (Table 5). [58–61] This adds to the previous studies in pediatric patients (Tables 2 and 3); however, the stratification of current evidence according to the type of OM and objective of study, as well as the LoE and power of the studies, do not allow setting a guideline for pediatric patients. Interestingly, these studies included, for the first time, evidence about the effectiveness of the application of PBM for the treatment of established OM, including using a photosensitizer (methylene blue) [58, 61].

Implementing the updated guidelines may be challenged by practical and economic considerations, e.g., cost, facility requirements, trained personnel, and local regulatory requirements. Additionally, the application of the guidelines may be challenged by device availability and if the available device is able to deliver the recommended PTPs. Studies have demonstrated the applicability of delivering a course of PBM therapy to cancer patients for the prevention of OM [50, 63]. Considering these challenges, PBM therapy should be considered by the clinician, among other methods recommended by the MASCC/ISOO Mucositis Study Group, where facility allows PBM therapy and when health economic justifies its use.

In summary, we conducted a systematic review and developed evidence-based clinical guidelines for PBM therapy for specific cancer patient populations. We noted the variation in the parameters presented by the various RCTs. More well-designed RCTs, including pediatric patient populations and patients treated with chemotherapy, are needed to clarify the promising potential of PBM in the management of OM in cancer patients.

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Compliance with ethical standards

Conflict of interest Per the MASCC Guidelines policy, employees of commercial entities were not eligible to serve on this MASCC Guidelines Panel. The following authors disclose no conflict of interest: YZ, ERF, HSA, RJB, LAG, AM, RGN, VR, WJET, AV, RL, CAM, KKFC and SE. The following authors disclose a potential conflict of interest as detailed in the ICMJE form for disclosure of potential conflicts of interest: PRA, PB and RVL.

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Immediate Past-President of North American Association for Photobiomodulation Therapy, Chair of Society for Photonics and Engineers, Mechanisms for Photobiomodulation Therapy, Technical Group member of Photobiomodulation therapy, Optical Society of America, Program Chair of Society for Advanced Wound Care, Wound Healing Society.

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References

1. Elad S, Zadik Y, Yarom N (2017) Oral complications of nonsurgical cancer therapies. Atlas Oral Maxillofac Surg Clin North Am 25: 133–147
2. Jones JA, Qazilbash MH, Shih YC, Cantor SB, Cooksley CD, Elting LS (2008) In-hospital complications of autologous hematopoietic stem cell transplantation for lymphoid malignancies: clinical and economic outcomes from the nationwide inpatient sample. Cancer 112:1096–1105
3. Sonis ST, Oster G, Fuchs H, Bellm L, Bradford WZ, Edelsberg J, Hayden V, Eilers J, Epstein JB, LeVeque FG, Miller C, Peterson DE, Schubert MM, Spijkervet FK, Horowitz M (2001) Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. J Clin Oncol 19:2201–2205
4. Mester E, Korenyi-Both A, Spiry T, Scher A, Tisza S (1973) Stimulation of wound healing by means of laser rays. (clinical and electron microscopical study). Acta Chir Acad Sci Hung 14: 347–356
5. Anders JJ, Lanzafame RJ, Arany PR (2015) Low-level light/laser therapy versus photobiomodulation therapy. Photomed Laser Surg 33:183–184
6. Arany PR (2016) Craniofacial wound healing with photobiomodulation therapy: new insights and current challenges. J Dent Res 95:977–984
7. de Freitas LF, Hamblin MR (2016) Proposed mechanisms of photobiomodulation or low-level light therapy IEEE journal of selected topics in quantum electronics: a publication of the IEEE Lasers and Electro-optics Society 22
8. Barasch A, Peterson DE, Tanzer JM, D'Ambrosio JA, Nuki K, Schubert MM, Franquin JC, Clive J, Tutschka P (1995) Helium-neon laser effects on conditioning-induced oral mucositis in bone marrow transplantation patients. Cancer 76:2550–2556
9. Bjordal JM, Bensadoun RJ, Tuner J, Frigo L, Gjerde K, Lopes-Martins RA (2011) A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis. Support Care Cancer 19:1069–1077
10. Lalla RV, Bowen J, Barasch A, Elting L, Epstein J, Keefe DM, McGuire DB, Migliorati C, Nicolatou-Galitis O, Peterson DE, Raber-Durlacher JE, Sonis ST, Elad S, Mucositis Guidelines

Leadership Group of the Multinational Association of Supportive Care in CCancer and, International Society of Oral Oncology (MASCC/ISOO). (2014) MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 120:1453–1461

11. Migliorati C, Hewson I, Lalla RV, Antunes HS, Estilo CL, Hodgson B, Lopes NN, Schubert MM, Bowen J, Elad S, Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). (2013) Systematic review of laser and other light therapy for the management of oral mucositis in cancer patients. Support Care Cancer 21:333–341
12. Ranna V, Cheng K, Castillo D, Porcello L, Vaddi A, Lalla R, Bossi P, Elad S (2019) Development of the MASCC/ISOO Clinical Practice Guidelines for Mucositis: an overview of the methods. Support Care Cancer. https://doi.org/10.1007/s00520-019-04891-1
13. Hadorn DC, Baker D, Hodges JS, Hicks N (1996) Rating the quality of evidence for clinical practice guidelines. J Clin Epidemiol 49: 749–754
14. Somerfield MPJ, Pfister D, Bennett C, Recht A, Smith T, Weeks J, Winn R, Duraant J (2000) ASCO clinical practice guidelines: process, progress, pitfalls, and prospects classic papers and current comments, vol 4, pp 881–886
15. Schubert MM, Eduardo FP, Guthrie KA, Franquin JC, Bensadoun RJ, Migliorati CA, Lloid CM, Eduardo CP, Walter NF, Marques MM, Hamdi M (2007) A phase III randomized double-blind placebo-controlled clinical trial to determine the efficacy of low level laser therapy for the prevention of oral mucositis in patients undergoing hematopoietic cell transplantation. Support Care Cancer 15: 1145–1154
16. Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya AG, Guddattu V (2015) Low level laser therapy against radiation induced oral mucositis in elderly head and neck cancer patients-a randomized placebo controlled trial. J Photochem Photobiol B 144:51–56
17. Antunes HS, Herchenhorn D, Small IA, Araujo CM, Viegas CM, Cabral E, Rampini MP, Rodrigues PC, Silva TG, Ferreira EM, Dias FL, Ferreira CG (2013) Phase III trial of low-level laser therapy to prevent oral mucositis in head and neck cancer patients treated with concurrent chemoradiation. Radiother Oncol 109:297–302
18. Oton-Leite AF, Silva GB, Morais MO, Silva TA, Leles CR, Valadares MC, Pinezi JC, Batista AC, Mendonca EF (2015) Effect of low-level laser therapy on chemoradiotherapy-induced oral mucositis and salivary inflammatory mediators in head and neck cancer patients. Lasers Surg Med 47:296–305
19. Jaguar GC, Prado JD, Nishimoto IN, Pinheiro MC, de Castro DO Jr, da Cruz Perez DE, Alves FA (2007) Low-energy laser therapy for prevention of oral mucositis in hematopoietic stem cell transplantation. Oral Dis 13:538–543
20. Bezinelli LM, de Paula Eduardo F, da Graca Lopes RM, Biazevic MG, de Paula Eduardo C, Correa L, Hamerschlak N, Michel-Crosato E (2014) Cost-effectiveness of the introduction of specialized oral care with laser therapy in hematopoietic stem cell transplantation. Hematol Oncol 32:31–39
21. de Paula Eduardo F, Bezinelli LM, da Graca Lopes RM, Nascimento Sobrinho JJ, Hamerschlak N, Correa L (2015) Efficacy of cryotherapy associated with laser therapy for decreasing severity of melphalan-induced oral mucositis during hematological stem-cell transplantation: a prospective clinical study. Hematol Oncol 33:152–158
22. Antunes HS, de Azevedo AM, da Silva Bouzas LF, Adao CA, Pinheiro CT, Mayhe R, Pinheiro LH, Azevedo R, D'Aiuto de Matos V, Rodrigues PC, Small IA, Zangaro RA, Ferreira CG (2007) Low-power laser in the prevention of induced oral mucositis in bone marrow transplantation patients: a randomized trial. Blood 109:2250–2255
23. Khouri VY, Stracieri AB, Rodrigues MC, Moraes DA, Pieroni F, Simoes BP, Voltarelli JC (2009) Use of therapeutic laser for prevention and treatment of oral mucositis. Braz Dent J 20:215–220
24. Silva GB, Mendonca EF, Bariani C, Antunes HS, Silva MA (2011) The prevention of induced oral mucositis with low-level laser therapy in bone marrow transplantation patients: a randomized clinical trial. Photomed Laser Surg 29:27–31
25. Silva LC, Sacono NT, Freire Mdo C, Costa LR, Batista AC, Silva GB (2015) The impact of low-level laser therapy on oral mucositis and quality of life in patients undergoing hematopoietic stem cell transplantation using the oral health impact profile and the functional assessment of cancer therapy-bone marrow transplantation questionnaires. Photomed Laser Surg 33:357–363
26. Ferreira B, da Motta Silveira FM, de Orange FA (2016) Low-level laser therapy prevents severe oral mucositis in patients submitted to hematopoietic stem cell transplantation: a randomized clinical trial. Support Care Cancer 24:1035–1042
27. Elad S, Luboshitz-Shon N, Cohen T, Wainchwaig E, Shapira MY, Resnick IB, Radiano R, Lubart R, Or R (2011) A randomized controlled trial of visible-light therapy for the prevention of oral mucositis. Oral Oncol 47:125–130
28. Freitas AC, Campos L, Brandao TB, Cristofaro M, Eduardo Fde P, Luiz AC, Marques MM, Eduardo Cde P, Simoes A (2014) Chemotherapy-induced oral mucositis: effect of LED and laser phototherapy treatment protocols. Photomed Laser Surg 32:81–87
29. Ottaviani G, Gobbo M, Sturnega M, Martinelli V, Mano M, Zanconati F, Bussani R, Perinetti G, Long CS, Di Lenarda R, Giacca M, Biasotto M, Zacchigna S (2013) Effect of class IV laser therapy on chemotherapy-induced oral mucositis: a clinical and experimental study. Am J Pathol 183:1747–1757
30. Cunha CB, Eduardo FP, Zezell DM, Bezinelli LM, Shitara PP, Correa L (2012) Effect of irradiation with red and infrared laser in the treatment of oral mucositis: a pilot study with patients undergoing chemotherapy with 5-FU. Lasers Med Sci 27:1233–1240
31. Gobbo M, Ottaviani G, Rupel K, Ciriello F, Beorchia A, Di Lenarda R, Zacchigna S, Biasotto M (2016) Same strategy for pitfalls of radiotherapy in different anatomical districts. Lasers Med Sci 31: 471–479
32. Chermetz M, Gobbo M, Ronfani L, Ottaviani G, Zanazzo GA, Verzegnassi F, Treister NS, Di Lenarda R, Biasotto M, Zacchigna S (2014) Class IV laser therapy as treatment for chemotherapy-induced oral mucositis in onco-haematological paediatric patients: a prospective study. Int J Paediatr Dent 24:441–449
33. Amadori F, Bardellini E, Conti G, Pedrini N, Schumacher RF, Majorana A (2016) Low-level laser therapy for treatment of chemotherapy-induced oral mucositis in childhood: a randomized double-blind controlled study. Lasers Med Sci 31:1231–1236
34. Bensadoun RJ, Franquin JC, Ciais G, Darcourt V, Schubert MM, Viot M, Dejou J, Tardieu C, Benezery K, Nguyen TD, Laudoyer Y, Dassonville O, Poissonnet G, Vallicioni J, Thyss A, Hamdi M, Chauvel P, Demard F (1999) Low-energy He/Ne laser in the prevention of radiation-induced mucositis. A multicenter phase III randomized study in patients with head and neck cancer. Support Care Cancer 7:244–252
35. Arora H, Pai KM, Maiya A, Vidyasagar MS, Rajeev A (2008) Efficacy of He-Ne laser in the prevention and treatment of radiotherapy-induced oral mucositis in oral cancer patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 105:180–186, 186.e1
36. Gouvea de Lima A, Villar RC, de Castro G Jr, Antequera R, Gil E, Rosalmeida MC, Federico MH, Snitcovsky IM (2012) Oral mucositis prevention by low-level laser therapy in head-and-neck cancer patients undergoing concurrent chemoradiotherapy: a phase III randomized study. Int J Radiat Oncol Biol Phys 82:270–275
37. Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya AG, Nigudgi S (2013) Effect of low-level laser therapy on patient reported

measures of oral mucositis and quality of life in head and neck cancer patients receiving chemoradiotherapy–a randomized controlled trial. Support Care Cancer 21:1421–1428
38. Carvalho PA, Jaguar GC, Pellizzon AC, Prado JD, Lopes RN, Alves FA (2011) Evaluation of low-level laser therapy in the prevention and treatment of radiation-induced mucositis: a double-blind randomized study in head and neck cancer patients. Oral Oncol 47:1176–1181
39. Lima AG, Antequera R, Peres MP, Snitcosky IM, Federico MH, Villar RC (2010) Efficacy of low-level laser therapy and aluminum hydroxide in patients with chemotherapy and radiotherapy-induced oral mucositis. Braz Dent J 21:186–192
40. Gobbo M, Ottaviani G, Perinetti G, Ciriello F, Beorchia A, Giacca M, Di Lenarda R, Rupel K, Tirelli G, Zacchigna S, Biasotto M (2014) Evaluation of nutritional status in head and neck radiotreated patients affected by oral mucositis: efficacy of class IV laser therapy. Support Care Cancer 22:1851–1856
41. Sandoval RL, Koga DH, Buloto LS, Suzuki R, Dib LL (2003) Management of chemo- and radiotherapy induced oral mucositis with low-energy laser: initial results of A.C. Camargo Hospital. J Appl Oral Sci 11:337–341
42. Hodgson BD, Margolis DM, Salzman DE, Eastwood D, Tarima S, Williams LD, Sande JE, Vaughan WP, Whelan HT (2012) Amelioration of oral mucositis pain by NASA near-infrared light-emitting diodes in bone marrow transplant patients. Support Care Cancer 20:1405–1415
43. Whelan HT, Connelly JF, Hodgson BD, Barbeau L, Post AC, Bullard G, Buchmann EV, Kane M, Whelan NT, Warwick A, Margolis D (2002) NASA light-emitting diodes for the prevention of oral mucositis in pediatric bone marrow transplant patients. J Clin Laser Med Surg 20:319–324
44. Cowen D, Tardieu C, Schubert M, Peterson D, Resbeut M, Faucher C, Franquin JC (1997) Low energy helium-neon laser in the prevention of oral mucositis in patients undergoing bone marrow transplant: results of a double blind randomized trial. Int J Radiat Oncol Biol Phys 38:697–703
45. Enwemeka CS (2009) Intricacies of dose in laser phototherapy for tissue repair and pain relief. Photomed Laser Surg 27:387–393
46. Huang YY, Sharma SK, Carroll J, Hamblin MR (2011) Biphasic dose response in low level light therapy - an update. Dose Response 9:602–618
47. Enwemeka CS (2008) Standard parameters in laser phototherapy. Photomed Laser Surg 26:411
48. Jenkins PA, Carroll JD (2011) How to report low-level laser therapy (LLLT)/photomedicine dose and beam parameters in clinical and laboratory studies. Photomed Laser Surg 29:785–787
49. (2006) Standards for the design and conduct of systematic reviews with low-level laser therapy for musculoskeletal pain and disorders. Photomed Laser Surg 24:759–760
50. Treister NS, London WB, Guo D, Malsch M, Verrill K, Brewer J, Margossian S, Duncan C (2016) A feasibility study evaluating extraoral photobiomodulation therapy for prevention of mucositis in pediatric hematopoietic cell transplantation. Photomed Laser Surg 34:178–184
51. Sonis ST, Hashemi S, Epstein JB, Nair RG, Raber-Durlacher JE (2016) Could the biological robustness of low level laser therapy (photobiomodulation) impact its use in the management of mucositis in head and neck cancer patients. Oral Oncol 54:7–14
52. Antunes HS, Herchenhorn D, Small IA, Araujo CMM, Viegas CMP, de Assis Ramos G, Dias FL, Ferreira CG (2017) Long-term survival of a randomized phase III trial of head and neck cancer patients receiving concurrent chemoradiation therapy with or without low-level laser therapy (LLLT) to prevent oral mucositis. Oral Oncol 71:11–15
53. Brandao TB, Morais-Faria K, Ribeiro ACP, Rivera C, Salvajoli JV, Lopes MA, Epstein JB, Arany PR, de Castro G Jr, Migliorati CA, Santos-Silva AR (2018) Locally advanced oral squamous cell carcinoma patients treated with photobiomodulation for prevention of oral mucositis: retrospective outcomes and safety analyses. Support Care Cancer 26:2417–2423
54. Rodrigues GH, Jaguar GC, Alves FA, Guollo A, Camandoni VO, Damascena AS, Lima VCC (2017) Variability of high-dose melphalan exposure on oral mucositis in patients undergoing prophylactic low-level laser therapy. Lasers Med Sci 32:1089–1095
55. Gonzalez-Arriagada WA, Ramos LMA, Andrade MAC, Lopes MA (2018) Efficacy of low-level laser therapy as an auxiliary tool for management of acute side effects of head and neck radiotherapy. J Cosmet Laser Ther 20:117–122
56. Soares RG, Farias LC, da Silva Menezes AS, de Oliveira ESCS, Tabosa ATL, Chagas PVF, Santiago L, Santos SHS, de Paula AMB, Guimaraes ALS (2018) Treatment of mucositis with combined 660- and 808-nm-wavelength low-level laser therapy reduced mucositis grade, pain, and use of analgesics: a parallel, single-blind, two-arm controlled study. Lasers Med Sci 33:1813–1819
57. Marín-Conde F, Castellanos-Cosano L, Pachón-Ibañez J, Serrera-Figallo MA, Gutiérrez-Pérez JL, Torres-Lagares D (2018) Photobiomodulation with low-level laser therapy reduces oral mucositis caused by head and neck radio-chemotherapy: prospective randomized controlled trial. Int J Oral Maxillofac Surg, in press
58. Medeiros-Filho JB, Maia Filho EM, Ferreira MC (2017) Laser and photochemotherapy for the treatment of oral mucositis in young patients: randomized clinical trial. Photodiagn Photodyn Ther 18: 39–45
59. Vitale MC, Modaffari C, Decembrino N, Zhou FX, Zecca M, Defabianis P (2017) Preliminary study in a new protocol for the treatment of oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation (HSCT) and chemotherapy (CT). Lasers Med Sci 32:1423–1428
60. Gobbo M, Verzegnassi F, Ronfani L, Zanon D, Melchionda F, Bagattoni S, Majorana A, Bardellini E, Mura R, Piras A, Petris MG, Mariuzzi ML, Barone A, Merigo E, Decembrino N, Vitale MC, Berger M, Defabianis P, Biasotto M, Ottaviani G, Zanazzo GA (2018) Multicenter randomized, double-blind controlled trial to evaluate the efficacy of laser therapy for the treatment of severe oral mucositis induced by chemotherapy in children: laMPO RCT. Pediatr Blood Cancer 65:e27098
61. Ribeiro da Silva VC, da Motta Silveira FM, Barbosa Monteiro MG, da Cruz MMD, Caldas Junior AF, Pina Godoy G (2018) Photodynamic therapy for treatment of oral mucositis: pilot study with pediatric patients undergoing chemotherapy. Photodiagn Photodyn Ther 21:115–120
62. Leite Cavalcanti A, Jose de Macedo D, Suely Barros Dantas F, Dos Santos Menezes K, Filipe Bezerra Silva D, Alves de Melo Junior W, Fabia Cabral Cavalcanti A (2018) Evaluation of oral mucositis occurrence in oncologic patients under antineoplastic therapy submitted to the low-level laser. Coadjuvant Ther J Clin Med 7
63. Bezinelli LM, Eduardo FP, Neves VD, Correa L, Lopes RM, Michel-Crosato E, Hamerschlak N, Biazevic MG (2016) Quality of life related to oral mucositis of patients undergoing haematopoietic stem cell transplantation and receiving specialised oral care with low-level laser therapy: a prospective observational study. Eur J Cancer Care (Engl) 25:668–674
64. Chor A, Torres SR, Maiolino A, Nucci M (2010) Low-power laser to prevent oral mucositis in autologous hematopoietic stem cell transplantation. Eur J Haematol 84:178–179
65. Eduardo FP, Bezinelli L, Luiz AC, Correa L, Vogel C, Eduardo CP (2009) Severity of oral mucositis in patients undergoing hematopoietic cell transplantation and an oral laser phototherapy protocol: a survey of 30 patients. Photomed Laser Surg 27:137–144
66. Eduardo Fde P, Bezinelli LM, Orsi MC, Rodrigues M, Ribeiro MS, Hamerschlak N, Correa L (2011) The influence of dental care associated with laser therapy on oral mucositis during allogeneic

hematopoietic cell transplant: retrospective study Einstein (Sao Paulo, Brazil) 9: 201–206
67. Eduardo Fde P, Bezinelli LM, de Carvalho DL, Lopes RM, Fernandes JF, Brumatti M, Vince CS, de Azambuja AM, Vogel C, Hamerschlak N, Correa L (2015) Oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation: clinical outcomes in a context of specialized oral care using low-level laser therapy. Pediatr Transplant 19:316–325
68. Arbabi-Kalati F, Arbabi-Kalati F, Moridi T (2013) Evaluation of the effect of low level laser on prevention of chemotherapy-induced mucositis. Acta Med Iran 51:157–162
69. de Castro JF, Abreu EG, Correia AV, da Mota Vasconcelos Brasil C, da Cruz Perez DE, de Paula Ramos Pedrosa F (2013) Low-level laser in prevention and treatment of oral mucositis in pediatric patients with acute lymphoblastic leukemia. Photomed Laser Surg 31: 613–618
70. Wong SF, Wilder-Smith P (2002) Pilot study of laser effects on oral mucositis in patients receiving chemotherapy. Cancer J 8:247–254
71. Nes AG, Posso MB (2005) Patients with moderate chemotherapy-induced mucositis: pain therapy using low intensity lasers. Int Nurs Rev 52:68–72
72. Corti L, Chiarion-Sileni V, Aversa S, Ponzoni A, D'Arcais R, Pagnutti S, Fiore D, Sotti G (2006) Treatment of chemotherapy-induced oral mucositis with light-emitting diode. Photomed Laser Surg 24:207–213
73. Cruz LB, Ribeiro AS, Rech A, Rosa LG, Castro CG Jr, Brunetto AL (2007) Influence of low-energy laser in the prevention of oral mucositis in children with cancer receiving chemotherapy. Pediatr Blood Cancer 48:435–440
74. Abramoff MM, Lopes NN, Lopes LA, Dib LL, Guilherme A, Caran EM, Barreto AD, Lee ML, Petrilli AS (2008) Low-level laser therapy in the prevention and treatment of chemotherapy-induced oral mucositis in young patients. Photomed Laser Surg 26:393–400
75. Kuhn A, Porto FA, Miraglia P, Brunetto AL (2009) Low-level infrared laser therapy in chemotherapy-induced oral mucositis: a randomized placebo-controlled trial in children. J Pediatr Hematol Oncol 31:33–37
76. Antunes HS, Ferreira EM, de Matos VD, Pinheiro CT, Ferreira CG (2008) The impact of low power laser in the treatment of conditioning-induced oral mucositis: a report of 11 clinical cases and their review. Med Oral Patol Oral Cir Bucal 13:E189–E192
77. Arun Maiya G, Sagar MS, Fernandes D (2006) Effect of low level helium-neon (He-Ne) laser therapy in the prevention & treatment of radiation induced mucositis in head & neck cancer patients Indian. J Med Res 124:399–402
78. Zanin T, Zanin F, Carvalhosa AA, Castro PH, Pacheco MT, Zanin IC, Brugnera A Jr (2010) Use of 660-nm diode laser in the prevention and treatment of human oral mucositis induced by radiotherapy and chemotherapy. Photomed Laser Surg 28:233–237
79. Simoes A, Eduardo FP, Luiz AC, Campos L, Sa PH, Cristofaro M, Marques MM, Eduardo CP (2009) Laser phototherapy as topical prophylaxis against head and neck cancer radiotherapy-induced oral mucositis: comparison between low and high/low power lasers. Lasers Surg Med 41:264–270
80. Kelner NCJ (2007) Low energy laser in prevention of oral mucositis in patients receiving radiotherapy and/or chemotherapy in Pernambuco cancer hospital. Appl Cancer Res 27:182–187
81. Oton-Leite AF, Correa de Castro AC, Morais MO, Pinezi JC, Leles CR, Mendonca EF (2012) Effect of intraoral low-level laser therapy on quality of life of patients with head and neck cancer undergoing radiotherapy. Head Neck 34:398–404
82. Oton-Leite AF, Elias LS, Morais MO, Pinezi JC, Leles CR, Silva MA, Mendonca EF (2013) Effect of low level laser therapy in the reduction of oral complications in patients with cancer of the head and neck submitted to radiotherapy. Spec Care Dentist 33:294–300
83. Genot-Klastersky MT, Klastersky J, Awada F, Awada A, Crombez P, Martinez MD, Jaivenois MF, Delmelle M, Vogt G, Meuleman N, Paesmans M (2008) The use of low-energy laser (LEL) for the prevention of chemotherapy- and/or radiotherapy-induced oral mucositis in cancer patients: results from two prospective studies. Support Care Cancer 16:1381–1387
84. Moraes JJCQA, De Biase RCCG, Leite EP, Cabral Junior CR, Limeira Junior FA (2009) The effect of low level laser therapy in different wavelengths in the treatment of oral mucositis - Porposal for extra-oral implementation. Laser Phys 19:1–8
85. Soto M, Lalla RV, Gouveia RV, Zecchin VG, Seber A, Lopes NN (2015) Pilot study on the efficacy of combined intraoral and extraoral low-level laser therapy for prevention of oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation. Photomed Laser Surg 33:540–546

Affiliations

Yehuda Zadik[1,2] · Praveen R. Arany[3] · Eduardo Rodrigues Fregnani[4] · Paolo Bossi[5] · Héliton Spindola Antunes[6] · René-Jean Bensadoun[7] · Luiz Alcino Gueiros[8] · Alessandra Majorana[9] · Raj G. Nair[10] · Vinisha Ranna[11] · Wim J. E. Tissing[12] · Anusha Vaddi[13] · Rachel Lubart[14] · Cesar Augusto Migliorati[15] · Rajesh V. Lalla[16] · Karis Kin Fong Cheng[17] · Sharon Elad[13]

Eduardo Rodrigues Fregnani
eduardofregnani@me.com

Paolo Bossi
paolo.bossi@unibs.it

Héliton Spindola Antunes
hspindola@inca.gov.br

René-Jean Bensadoun
renejean.bensadoun@che-nice.com

Luiz Alcino Gueiros
Luiz.mgueiros@ufpe.br

Alessandra Majorana
alessandra.majorana@unibs.it

Raj G. Nair
r.nair@griffith.edu.au

Vinisha Ranna
Vinisha.Ranna@mountsinai.org

Wim J. E. Tissing
w.j.e.tissing@umcg.nl

Anusha Vaddi
anushareddy999@gmail.com

Rachel Lubart
Rachel.Lubart@biu.ac.il

Cesar Augusto Migliorati
cmigliorati@dental.ufl.edu

Rajesh V. Lalla
Lalla@uchc.edu

Karis Kin Fong Cheng
Karis_cheng@nuhs.edu.sg

Sharon Elad
SElad@URMC.Rochester.edu

[1] Department of Oral Medicine, Oral and Maxillofacial Center, Medical Corps, Israel Defense Forces, Tel-Hashomer, Israel

[2] Department of Oral Medicine, Sedation and Maxillofacial Imaging, Hebrew University-Hadassah School of Dental Medicine, P.O.Box 12272, Jerusalem 9112102, Israel

[3] Department of Oral Biology and Biomedical Engineering, School of Dental Medicine, Engineering and Applied Sciences, University at Buffalo, 3435 Main Street, B36A Foster Hall, Buffalo, NY 14214, USA

[4] Oral Medicine Service, Hospital Sírio-Libanês São Paulo, São Paulo, Brazil

[5] Department of Medical and Surgical Specialties, Radiological Sciences and Public Health - Medical Oncology, ASST-Spedali Civili, University of Brescia, Brescia, Italy

[6] Clinical Research Division, National Cancer Institute of Brazil (INCA), Rio de Janeiro, Brazil

[7] Gérant, Responsable de Service, Centre de Haute Energie, Nice, France

[8] Departamento de Clínica e Odontologia Preventiva, Universidade Federal de Pernambuco, Recife, PE, Brazil

[9] University of Bresciam, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, Dental Clinic Oral Medicine, Brescia, Italy

[10] Griffith University and Gold Coast University Hospital, Southport, Australia

[11] Department of Oral and Maxillofacial Surgery, The Mount Sinai Hospital, New York, NY, USA

[12] Division of Pediatric Oncology/Hematology/Immunology, Beatrix Childrens Hospital, University Medical Center Groningen, Groningen, The Netherlands

[13] Oral Medicine, Eastman Institute for Oral Health, University of Rochester Medical Center, Rochester, NY, USA

[14] Departments of Physics and Chemistry, Bar-Ilan University, Ramat-Gan, Israel

[15] College of Dentistry, University of Florida, Gainesville, FL, USA

[16] Section of Oral Medicine, University of Connecticut Health, Farmington, CT, USA

[17] Yong Loo Lin School of Medicine, Clinical Research Centre, National University of Singapore, Level 2, Singapore, Singapore