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Systematic Review

Update of photobiomodulation in oral mucositis: a systematic review

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Abstract – Introduction: Oral mucositis (OM) is a common side effect of radiotherapy (RT) or radio-chemotherapy (RT/CT) for head and neck cancers. It causes lesions leading to impairment of the quality of life, dysphagia, pain, and in up to 20% of cases, a dosimetry concession, decreasing local tumor control, thereby impacting the survival rate. Positive results of photobiomodulation (PBM) to treat it have been reported in the literature. PBM has multiple parameters (type of laser, emission mode, number of sessions to be performed, wavelength, power, energy, fluence, exposure time, number of points) making it difficult to implement in clinical practice. **Materials and methods**: A literature search strategy was applied in Medline by selecting articles published between 2010 and 2020 to answer the following research question: "In patients treated with RT or RT/CT, what is the place of PBM in the management of OM?", in accordance with PICO (patient, intervention, comparison and outcomes) criteria. The inclusion criteria were all original articles (clinical cases and clinical studies) which answered the research question. Meta-analyses, systematic reviews of the literature and journals, animal or in vitro studies, studies published in a language other than French or English, and full-text articles not accessible via inter-university credits were excluded. **Results**: Seventeen articles were included, representing 1576 patients. The PBM was intraoral in 16 papers and combined intra- and extra-oral emission in 1 paper. InGaAlP diode laser and HeNe laser significantly reduced OM compared with placebo in 62.5% and 75% of the studies, respectively. Pain reduction was poorly or not documented and when it was, it did not correlate with the reduction of analgesics. Temporary or permanent interruption of radiotherapy was also poorly documented. **Discussion**: The MASCC/ISOO (2019) report is an important step forward to establish a reproducible protocol for PBM, which as our results show, is heterogeneous in use. Our results showed that the studies started PBM on the first day of RT, using a wavelength of 660 nm for diode laser and 632.8 nm for HeNe laser. However, there is no scientific evidence vis-à-vis the values for power, energy, fluence, exposure time, or number of points. Although PBM appears to be effective in reducing OM scores, its effectiveness on improving patient quality of life, pain, painkiller consumption, compliance with treatment and the occurrence of complications remains to be defined. The relationship between PBM and survival rate was not an objective of this work. We found that of the 17 articles, 15 stated that they did not illuminate the tumor site during PBM sessions. **Conclusion**: The main objective of this work was to determine the place of PBM in the treatment of OM. Overall, the results on OM scores were favorable in almost ¾ of the studies. Despite its efficacy, the questions of the adjustment of the parameters of PBM, the harmonization on OM scale and its safety on carcinologic recurrence remain to be studied. In view of the lack of comparability of studies and the lack of reported data, studies that harmonize endpoints and follow-up criteria are needed to establish a standard protocol.

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Introduction

The annual worldwide incidence of head and neck squamous cell carcinoma (HNSCC) is over 550,000 cases and is associated with 300,000 deaths per year (WHO). In France, HNSCC is the 4th leading cause of cancer (14,000 cases/year) and the 5th leading cause of cancer mortality. Treatment is based on a triad of surgery, radiotherapy (RT) and chemotherapy (CT). RT is indicated for curative or palliative treatment, exclusively, as an adjuvant to surgery or in combination with concomitant chemotherapy (RT/CT). Intensity-modulated RT is a major development. It provides better targeting of tumor volume and therefore better protection of neighboring structures. Despite this, oral mucositis (OM) remains one of the most frequent adverse effects during RT or RT/CT for HNSCC, appearing almost systematically with more than 50% grade higher than 3 [1,2]. It can lead to impairment of the quality of life, dysphagia, pain and in up to 20% of cases, a dosimetry concession, decreasing local tumor control [1,3–6].

PBM was defined in 2014 by the North American Association for Laser Therapy and World Association for Laser Therapy conference as "the therapeutic use of light absorbed by endogenous chromophores, triggering non-thermal, non-cytotoxic biological responses through photochemical or photophysical events, resulting in physiological changes" [7].

In 2019, the MASCC/ISOO (Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology) recommended incorporating a place for PBM in the prevention of OM and associated pain in patients treated for HNSCC with RT and RT/CT by proposing 3 protocols based on non-surgical cancer treatment [8]. In addition to PBM, recommendations were published by the MASCC/ISOO 2019 for the management of OM using basic oral care, anti-inflammatory agents, natural and miscellaneous agents, antimicrobials, mucosal coating agents, anesthetics and analgesics agents, cryotherapy, growth factors and cytokines.

PBM has multiple parameters (type of laser, emission mode, number of sessions to be performed, wavelength, power, energy, fluence, exposure time, number of points) making it difficult to implement in clinical practice. PBM stimulates and promotes positive tissue processes such as wound healing, regeneration, and immune responses. It also mediates inflammation, pain and aberrant immune responses.

The main objective of this work was to determine the effectiveness of PBM on OM. The secondary objectives were to collect the laser parameters and the evaluation criteria for OM treatment.

Materials and methods

Study search method

A literature search strategy was applied in Medline (PubMed database), between September 2020 and November 2020, selecting articles published between 2010 and 2020 in order to answer the following search question, in accordance with PICO (patient, intervention, comparison and outcomes) criteria: "In patients treated with RT or RT/CT, what is the place of PBM in the management of OM?"

The keywords were identified and selected from the MeSH database and combined with Boolean operators to construct the following search equation to be as exhaustive as possible: ((″Head and Neck Neoplasms″[Mesh] OR ″Squamous Cell Carcinoma of Head and Neck″[Mesh]) AND (((((″Stomatitis″[Mesh]) OR ″Radiotherapy″[Mesh]) OR ″Radiotherapy, Intensity-Modulated″[Mesh]) OR ″Chemotherapy, Adjuvant″[Mesh]) OR ″Mucositis″[Mesh]) AND ((″Lasers″[Mesh]) OR ″Laser Therapy″[Mesh]) OR (″Lasers, Gas″[Mesh] OR ″Low-Level Light Therapy″[Mesh])).

Inclusion and exclusion criteria

The inclusion criteria were all original articles (clinical cases and clinical studies), which answered the research question. Meta-analyses, systematic reviews of the literature and journals, animal or in vitro studies, studies published in a language other than French or English, and full-text articles not accessible via inter-university credits were excluded.

Data collection and analysis

After excluding duplicates, the titles and abstracts of the articles retrieved from the database were independently assessed by 2 reviewers (GL and FC) according to the inclusion and exclusion criteria. If the titles and abstracts were found to be relevant, the full text continued to the selection phase. In case of disagreement, a re-reading was performed in order to reach an agreement between the 2 reviewers. Potentially eligible articles were then subject to full-text evaluation.

Data extraction

Data were extracted and synthesized independently by the 3 reviewers using the same extraction table. The assessors had trained to use this table beforehand. The following data were collected:

- Epidemiological data: methodology, number of cases, location, histological type, tumor treatments and delivered radiation doses.
- PBM protocol: start of laser, type of laser, intra or extra oral emission mode, number of sessions, number of points, wavelength, power, energy, fluence and exposure time.
- Clinical data: frequency of assessment, mucositis scale, OM scores, pain scale, pain scores, prescriptions, interruption of radiotherapy, nasogastric tube placement, gastrostomy placement and follow-up period.

Results

The PubMed database was searched and 149 results were returned. After analysis according to the inclusion and exclusion criteria, 38 articles were retained and full-text

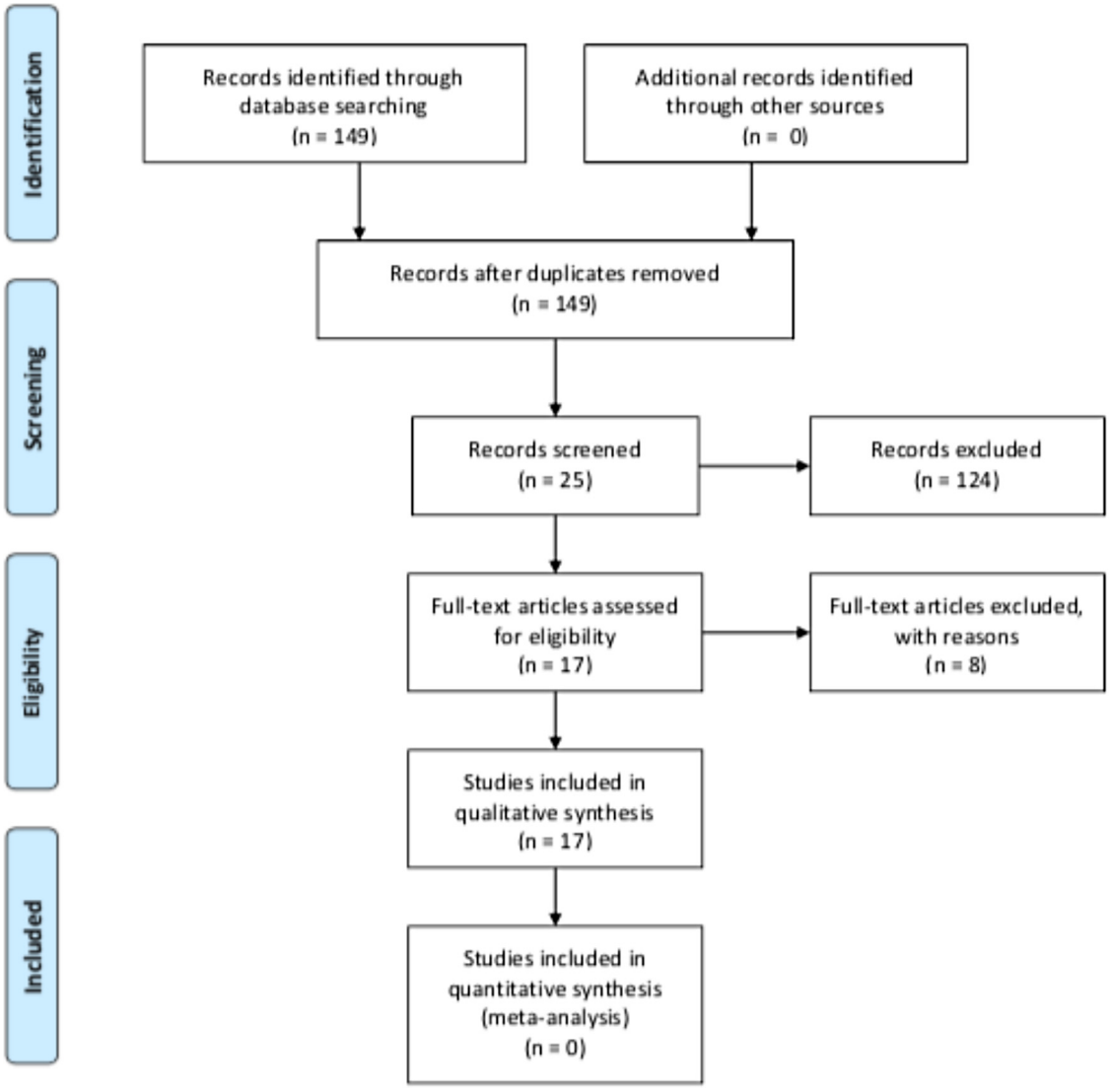


Fig. 1. Flow diagram of the screened publications.

reading allowed the inclusion of 17 articles representing 1576 patients, over a publication period from 2010 to November 2020 (Fig. 1). We found 15 clinical trials, of which 13 were randomized and 2 non-randomized, as well as 2 retrospective studies. The PBM group (LG) was compared with a control group (CG) in 13 articles, with a laser group in 2 articles and with aluminum hydroxide in 1 article. One retrospective study was non-comparative.

Table I summarizes all of the data from the articles studied.

Epidemiological data

Tumor location in the head and neck was reported in 16 articles:

- 492 patients were treated for carcinoma of the oral cavity,
- 270 patients were treated for carcinoma of the pharynx without precision,
- 325 patients were treated for carcinoma of the oropharynx,
- 22 patients were treated for carcinoma of the nasopharynx,
- 20 patients were treated for carcinoma of the hypopharynx,
- 118 patients were treated for carcinoma of the larynx.

In more than half of the tumors (n = 879, 55.7%), tumor histology was not provided. When it was provided, it was mainly squamous cell carcinoma (n = 703, 44.5%) and in 1 case, verrucous carcinoma (n = 1, 0.06%). Patients were treated with RT or RT/CT in 88% of the articles (n = 15), with RT alone in 12% (n = 2), sometimes combined with surgery. RT could be 2D, 3D conformal or intensity modulated delivering therapeutic doses ranging from 40 to 76 Gy.

PBM protocol

The type of laser was reported in all articles:

- 12 studies (70.5%) used different diode lasers:
- 10 studies used an InGaAlP laser [1,3,9–16],
- 1 study coupled 2 wavelengths with InGaAlP and GaA1As technologies [17],
- 1 study did not specify the type of diode technology [18].

Table I. All the data collected from the articles studied.

EPIDEMIOLOGICAL DATA							
Authors	Methodology	Grade	N	Localization	Histological type	Treatment traitement	Irradiation dose in Gy
Antunes *et al.* 2017	Randomised trial VS placebo double blind phase III	B	94 (Laser 47, control 47)	Nasopharynx (L7/C2) Oropharynx (L33/C41) Hypopharynx (L7/C4)	NR	RT (2D or 3D). RT/CT Cisplatin	70
Brandao *et al.* 2018	Retrospective study	C4	152	Oral cavity (148) Oropharynx (4)	SCC	Surgery+RT (52) RTCT (94) Induction CT+Surgery+RT (6)	60 to 70
Carvalho *et al.* 2011	Randomised trial double arms double blind	B	70 (B1=35) (B2=35)	1/ Oral cavity 24 Oropharynx 11 2/ Oral cavity 25 Oropharynx 10	NR	RT RT/CT Cisplatin	60 to 72
Dantas *et al.* 2020	Randomised trial VS placebo	B	54 (Laser 30, control 24)	Oropharynx (L17/C12) Larynx (L8/C11) Oral cavity(L4/C1) Thyroid(L1/C0) Parotid gland (L0/C2)	NR	Conformal RT 3D RT/CT	56 to 76
de Lima *et al.* 2010	Non randomised trial double arms	C4	25 (Laser 12, aluminium hydroxide 13)	Oral cavity(L1/HA3) Nasopharynx (L1/HA0) Oropharynx (L5/HA4) Larynx (L2/HA0) Hypopharynx (L2/HA1)	77% SCC+ others NR	RT	40 to 70
de Lima *et al.* 2012	Randomised trial VS placebo double blind phase III	B	75 (Laser 37, control 38)	Oropharynx (L17/C16) Larynx (L7/C9) Nasopharynx(L6/C4) Oral cavity(L3/C4) Hypopharynx(L3/C4)	SCC	RT/CT (Cisplatin)	60 to 70
Gautam *et al.* 2013	Randomised trial VS placebo triple blind	B	220 (Laser 110, control 110)	Oral cavity(L56/C53) Oropharynx (L54/C57)	NR	RT/CT (Cisplatin)	66
Gautam *et al.* 2012	Randomised trial VS placebo double blind	B	121 (Laser 60, control 61)	Oral cavity	SCC	RT/CT Cisplatin	66
Gautam *et al.* 2015	Randomised trial VS placebo double blind	B	46 (Laser 22, control 24)	Oral cavity(L5/C9) Oropharynx (L11/C11)	NR	RT 3D	66
Genot-Klastersky *et al.* 2019	Retrospective study double arms	C4	361 (Laser 222, control 139)	Oral cavity and lips (L38/C18) Pharynx (L133/C55) Larynx (L43/C57) Nasal cavity(L3/C5) Salivary gland (L5/C4)	NR	RT IMRT RT/CT (Cisplatin)	50 to 70
Legouté *et al.* 2019	Randomised trial VS placebo triple blind, multicentre phase III	B	83 (Laser 42, control 41)	Oral cavity(L9/C8) Pharynx (L33/C33)	SCC	RT 3D conformationnelle ou IMRT CT (Cisplatin, 5FU ou Cetuximab)	NR
		B			SCC	RT RT/CT	70

Table I. (continued).

EPIDEMIOLOGICAL DATA										
Marin-Conde *et al.* 2019	Randomised trial VS placebo double blind		26 (Laser 11, control 15)	Oral cavity(L7/C9) Oropharynx (L4/C6)						
Martins *et al.* 2019	Randomised trial VS placebo double blind	B	50 (Laser 25, control 25)	Head and neck	NR	RT ou RT/CT	>50			
Oton-Leite *et al.* 2012	Randomised trial VS placebo	B	60 (Laser 30, control 30)	Oral Cavity Pharynx Larynx CUP	59 SCC + 1 CV	RT RT/CT (5-FU et Cisplatin)	50 to 70			
Oton-Leite *et al.* 2015	Randomised trial VS placebo double blind	B	25 (Laser 12, control 13)	Oral cavity(L5/C4) Pharynx (L7/C9)	SCC	RT 2D/ CT (Cisplatin)	70			
Soares *et al.* 2018	Randomised trial double arms simgle blind	B	42 (B1=20/B2=22)	Oral cavity (B1=18/ B2=19) Oropharynx (B1=3/B2=1) Hypopharynx ((B1=0/B2=1)	SCC	RT (2D ou 3D), RT/ CT, RT+surgery, RT/ CT+surgery	<64=10/ >64=32			
Zanin *et al.* 2010	Non randomised trial VS placebo	C4	72 (Laser 36, control 36)	Oral cavity (L19/ C16) Nasopharynx (L0/C2) Oropharynx (L3/C5)	NR	RT/CT	NR			
PBM PROTOCOL										
Authors	Start of PBM	Type of laser	Wavelength nm	Emission mode Intra/ Extra	Number of session	Power (mW)	Energy (J)	Fluence (J/cm2)	Number of points	Exposure time (s)
Antunes *et al.* 2017	Day 1 RT	Diode InGaAlP	660	Intra	5d/7	100	1	4	9/region	10s/pt = 12 min
Brandao *et al.* 2018	Day 1 RT	Diode Twin Flex	660	Intra	5d/7	40	0,4	10	26	10s/pt
Carvalho *et al.* 2011	Day 1 RT	Diode InGaAlP	1/ 660 2/ 660	Intra	5d/7	1/ 5 2/ 5	NR	1/ 3,8 2/ 1,3	NR	10s/pt
Dantas *et al.* 2020	Day 1 RT	Diode InGaAlP	660	Intra	3d/7	86.7	2/pt= 56	NR	28	3s/pt = 84s
de Lima *et al.* 2010	Day 1 RT	Diode	830	intra	5d/7	15	2,4/pt	12	12	NR
de Lima *et al.* 2012	Day 1 RT	Diode InGaAlP	660	Intra	5d/7	10	0,1	2,5	9 sites/pt NR	10s/pt
Gautam *et al.* 2013	Day 1 RT	HeNe	632.8	Intra	5d/7	NR	3/pt = 36 to 40	NR	6 sites	125s/pt
Gautam *et al.* 2012	Day 1 RT	HeNe	632.8	Intra	5d/7	24	NR	3.5	6 sites	145s
Gautam *et al.* 2015	Day 1 RT	HeNe	632.8	Intra	5d/7	24	36 to 40	3	12 sites	125s/pt
Genot-Klastersky *et al.* 2019	OM>2	Biophoton travelers oncolase = athermal laser	630	Intra	3d/7	100	NR	2 to 3	NR	33s/site = 6 minuts
Legouté *et al.* 2019	OM>2	HeNe	658	Intra	5d/7 if OM>2	100	4	4	NR	40s/pt
Marin-Conde *et al.* 2019	NR	Diode BIOLASE	940	Intra	NR	500	180	83,3	72	6 s/pt = 360s
Martins *et al.* 2019	Day 1 RT	Diode InGaAlP	660	Intra	5d/7	25	0,25/pt	6,2	61	10s/pt
Oton-Leite *et al.* 2013	7 jdays before RT	Diode InGaAlP	685	Intra	5d/7	35	0,8/pt	2	55	25s/pt
Oton-Leite *et al.* 2015	Day 1 RT	Diode InGaAlP	660	Intra	3d/7	25	0,24/pt	6,2	69	10s/pt
Soares *et al.* 2018	NR	Dual diode laser GaA1As and InGAAlP	B1: 660 et 808 B2: 660	Intra Extra (Si lésion non atteignable)	2d/7	100	9	300	NR	NR
Zanin *et al.* 2010	Day 1 RT	Diode InGaAlP	660	Intra	2d/7	30	2/pt=42	2	21	NR
EPIDEMIOLOGICAL DATA										
	OM evaluation	OM scale	Results on OM	Pain scale	Results on pain	Prescription	RT interruption	Naso gastric tube	Gastro-stomy	Follow up
Antunes *et al.* 2017	Daily	WHO OMAS	CG>LG grade ¾ (p=0,01)	VAS mod	NR	CG>LG for opioids (p=0,001)		NR	CG>LG (p=0,01)	41,3

Table I. (continued).

EPIDEMIOLOGICAL DATA										
							Permanent stops : CG>LG Dose reduction CG>LG Temporary stops GL>GC			
Brandao *et al*. 2018	Daily	CTAE	Gr3=23%, Gr4=1%	NR	NA	NR	NR	NR	NR	40,8
Carvalho *et al*. 2011	Daily	WHO NCI	G1 get OM later of grade 2 and 3 (p=0,005 et p=0,014) OM : G1<G2 at week 2,3,4 (sign)	VAS	G1>G2 (p=0,004)	NR	NR	NR	NR	NR
Dantas *et al*. 2020	Weekly	WHO	NS	VAS	NS	NR	NS	NS	NR	NR
de Lima *et al*. 2010	Bi Weekly	OTS EORTC	NS	VAS mod	HA>LG at week 13 (p=0,036)	NR	NS	NR	NR	NR
de Lima *et al*. 2012										
	2, 4, 6 weeks of RT	NCI-CTC	NS	VAS	NS	NS	CG>LG			
(n=6 CG, n=0 LG, p=0,02)	5 sessions later (p=0,01)	NR	24							
Gautam *et al*. 2012	Weekly	OMWQ-HN RTOG/EORTG	CG>LG for OM>2 at the end of RT/CT (p<0,001)	NR	NS	CG>LG for opioids (p<0,001)	NS	CG>LG (p=0,039)	NR	NR
Gautam *et al*. 201	Weekly	RTOG EORTC	CG>LG for OM>2 (p=0,001)	VAS	OMWQ-HN (p<0,001)	CG>LG for opioids (p=0,001)	NS	CG>LG (p=0,01)	NR	1
Gautam *et al*. 2015	Weekly	RTOG EORTC	CG>LG for OM>3 (p=0,016 CG>LG for MO duration (p=0,048)	VAS	CG>LG for VAS>7 (p=0,023) CG>LG for duration of VAS>7 (p=0,048)	NR	NR	NS	NR	NR
Genot-Klastersky *et al*. 2019	NR	WHO	NR	NR	NR	NR	NR	NR	NR	60
Legouté *et al*. 2019	Weekly	WHO	NS	NS	NS	NR	NS	NS	NR	60
Marin-Conde *et al*. 2019	NR	RTOG EORTC	CG>LG (p<0,01)	NR	NA	NS	NR	NR	NR	1
Martins *et al*. 2019	Weekly	WHO NCI	NA	NR	NA	NA	NA	NA	NA	NA
Oton-Leite *et al*. 2012	1, 3, 7 week of RT	WHO NCI-CTC	CG>LG with both scales (p<0,001)	VAS	CG>LG (p<0,001)	NR	2 stops in CG	NR	NR	NR
Oton-Leite *et al*. 2015	Weekly	WHO NCI	CG>LG with both scales (p<0,05)	NR	NA	NR	NR	NR	NR	NR
Soares *et al*. 2018	Bi Weekly	WHO	B1<B2 (p=0,016)	VAS	NS	B1<B2 for pain killers (p=0,043)	NS	NR	NR	NR
Zanin *et al*. 2010	Weekly	NCI + brown scale	CG>LG with both scales (p<0,001)	VAS	CG>LG (p=0,02)	NR	NR	NR	NR	2

Table II. Wavelength, power, energy, fluence, exposure time parameters. In bold, the energies that were reported per point. In diode laser, as two wavelengths were used in one test, the number of values is higher than the number of tests.

	Wavelength (nm)	Power (mW)	Energy (J)	Fluence (J/cm^2)	Exposure time (s)
Diode	660 [1,3,9,11–15,17] /685 [10] /808 [17] /830 [18] /940 [16]	5 [1] /10 [11] /15 [18] /25 [13,14] /30 [15] /35 [10] /40 [3] /86,7 [12] / 100 [9,17] / 500 [16]	0,1 [11] /**0,24/ pt [14]** /**0,25/ pt [13]** /0,4 [3] /**0,8/pt [10]** / 1 [9] /**2/pt [12,15] / 2,4/ pt [18]** /9 [17] /180 [16] / NR [1]	1,3 [1] / 2 [10,15] / 2,5 [18] / 3,8 [1] / 4 [9] / 6,2 [12,14] / 10 [3] / 12 [18] / 83,3 [16] / 300 [17] / NR [12]	3s*pt [12] / 6s*pt [16] / 10s*pt [1,3,9,11,13,14] 25s*pt [10] / NR [15,17,18]
HeNe	632.8 [2,4,19] / 658 [6]	24 [2,4] / 100 [6] / NR [19]	36 à 40[2,4] / 4 [6] /NR [19]	3 [2] / 3,5 [19] / 4 [6] / NR [4]	40s*site [6] / 125s*site [2,4]/ **145**s [19]
Athermal	630 [5]	100 [5]	NR [5]	2 à 3 [5]	33s*site [5]

- 4 studies (23.5%) used a Helium-Neon (HeNe) laser [2,4,6,19],
- 1 study (6%) used an athermal laser [5].

Emission was intraoral in 16 papers and combined intra- and extra-oral in 1 paper [17].

Thirteen trials used PBM as a preventive measure for OM [1–4,9–15,18,19], of which 1 study started PBM 1 week before the start of RT [10] and 12 at the first RT session. In 2 trials [5,6], PBM was used as a curative treatment when the OM was grade 2 or higher (WHO scale). In 2 papers [16,17], the date of onset was not reported. In all trials, PBM was continued until the end of RT.

The frequency of sessions was reported in 16 articles and varied from 5 days per week (n = 11, 68.7%) [1-4,6, 9–11,13,18,19] to 3 days per week (n = 3, 18.7%) [5,12,14] or 2 days per week (n = 2, 12.5%) [15,17]. In 1 article the frequency of sessions was not indicated [16].

Laser settings were as follows:

The parameters are summarized in the Table II.

– Wavelength (nm)

This was specified in all 17 papers, ranging from 630 to 970 nm. The most commonly used wavelength was 660nm for diode lasers and 632.8 nm for HeNe lasers. One paper compared a dual-wavelength laser with 1 arm using a 660nm wavelength and 1 arm using both a 660 nm and 808 nm wavelengths.

– Power (mW)

This was specified in 16 papers, with values ranging from 5 to 500 mW.

– Energy (J)

This was specified in 14 articles, either as energy delivered per point or as total energy. The energy delivered per point varied from 0.1 to 3 J, while the total energy ranged from 36 to 56 J. Some articles did not specify whether it was the energy delivered per point, per session or in total.

– Fluence (J/cm^2)

This was reported in 15 articles, with values ranging from 2 to 300 J/cm^2.

– Exposure time (s)

This was specified in 14 papers, with values ranging from 3 to 125 seconds per point or per site (region). The number of emission points was reported in 16 articles, ranging from 6 to 78 points (average 35 points) or per region ranging from 6 to 12. One article only specified the overall exposure time (145 seconds).

Clinical data

Progression of OM was judged to be daily [1,3], biweekly [17,18], weekly [2,4,6,12–15,19], or every fortnight [10,11]. It was unspecified in 2 articles [5,16].

Assessment of OM was performed in all trials using 1 or 2 rating scales. It was always noted and is summarized in Table III.

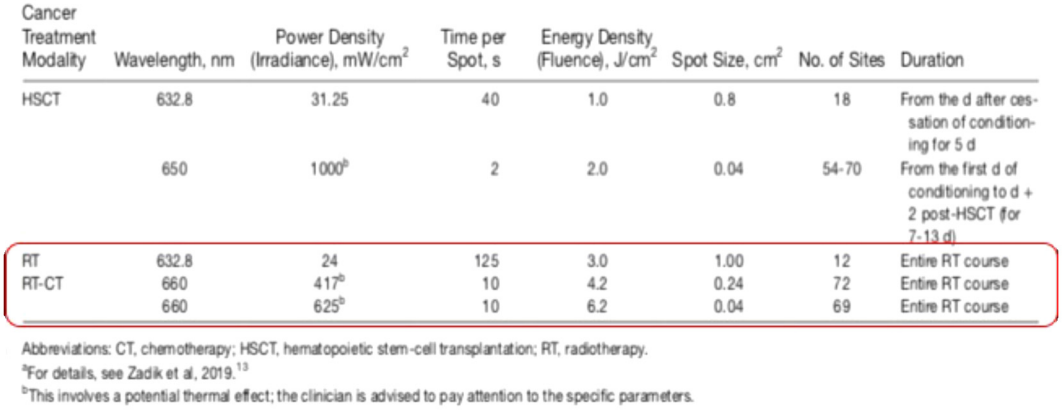
Six different scales were used, the WHO scale was used 9 times [1,5,6,9,10,12–14,17], the NCI-CTCAE 8 times [1,3,10,11,13–15,18], the RTOG/EORTC 5 times [2,4,16,18,19] and the OMAS [9], Brown Scale [15] and OMWQ-HN [4] scales respectively once each.

In the diode laser versus placebo studies, the results on OM were not significant in 2 trials [11,12], significant in 5 trials with a reduction in OM in the LG [9,10,14–16] and not applicable in 1 study [13]. De lima *et al.* [18] found no significant difference in OM score between the LG and the aluminum hydroxide group. Soares *et al.* [17] found that the use of 2 different wavelengths was significantly more effective in reducing OM than the use of 1 wavelength (p = 0.016). Carvalho *et al.* [1] used 2 different fluences and showed that the group treated with the higher of the 2 fluences had significantly later and less severe OM. In the retrospective study by Brandao *et al.* [3], the use of diode PBM resulted in 1% of grade 4 OM and 23% of grade 3 OM.

The use of a HeNe laser significantly reduced OM in all 3 studies by Gautam *et al.* with less grade 2 OM in the LG/CG [4,19] or less grade 3 OM in the LG /CG and of shorter duration [2]. For Legouté *et al.* [6], there was no significant difference. In the study using an athermal laser, the effect on OM was not reported [5].

Table III. Summary of scales used to assess OM.

Mucositis scale	Trial that used the scale or combination of scales
WHO (World Health Organization)	[5,6,12,17]
NCI-CTCAE (National Cancer Institute-Common Terminology Criteria for Adverse Events)	[3,11]
WHO + NCI-CTCAE	[1,10,13,14]
RTOG (Radiation Oncology Toxicity Grading) / EORTC (European Organization for Research and Treatment of Cancer)	[2,16,19]
WHO + OMAS (Oral Mucositis Assessment Scale)	[9]
NCI-CTCAE + Brown Scale	[15]
NCI-CTCAE + RTOG / EORTC	[18]
OMWQ-HN (Oral Mucositis Weekly Questionnaire-Head and Neck Cancer) + RTOG / EORTC	[4]



Cancer Treatment Modality	Wavelength, nm	Power Density (Irradiance), mW/cm^2	Time per Spot, s	Energy Density (Fluence), J/cm^2	Spot Size, cm^2	No. of Sites	Duration
HSCT	632.8	31.25	40	1.0	0.8	18	From the d after cessation of conditioning for 5 d
	650	1000[b]	2	2.0	0.04	54-70	From the first d of conditioning to d + 2 post-HSCT (for 7-13 d)
RT	632.8	24	125	3.0	1.00	12	Entire RT course
RT-CT	660	417[b]	10	4.2	0.24	72	Entire RT course
	660	625[b]	10	6.2	0.04	69	Entire RT course

Abbreviations: CT, chemotherapy; HSCT, hematopoietic stem-cell transplantation; RT, radiotherapy.
[a]For details, see Zadik et al, 2019.[13]
[b]This involves a potential thermal effect; the clinician is advised to pay attention to the specific parameters.

Fig. 2. Intraoral PBM protocols for the prevention of OM in HNSCC boxed in red [8].

Pain associated with OM was assessed in 11 articles using the visual analogue scale (VAS) 8 times [1,2,10-12,15,17,19], a modified VAS twice [9,18] and a numerical scale once [6]. Six articles did not provide information on how the pain was assessed [3-5,13,14,16].

The pain assessment score was not available in the Antunes *et al.* trial [9]. It was not significant in 5 trials, 2 using diode laser versus placebo [11,12], 1 using dual-wavelength laser [17] and 2 using HeNe laser versus placebo [6,19]. In 3 trials versus placebo, 2 with a diode laser and 1 with a HeNe laser [2,10,15], the authors observed a decrease in pain in the LG, including 1 for VAS $>$ 7 values that were less frequent and shorter in the LG/CG [2]. In the trial by de Lima *et al.* [18], the LG presented less pain (p = 0.036) than the aluminum hydroxide group at week 13. For Carvalho *et al.* [1], the higher fluence group had less pain than the lower fluence group (p = 0.004).

In 3 trials versus placebo, opioid consumption was higher in the CG/LG ($p < 0.001$). Soares *et al.* found that the group receiving dual-wavelength PBM consumed less pain medication compared with the group receiving single-wavelength PBM. In 2 trials [11,16], the authors found no significant difference in analgesic consumption between LG and CG.

In 6 articles [4,6,12,17–19] (2 double-arm and 4 versus placebo), no significant difference was found in terms of sessions performed and doses administered for RT. Antunes *et al.* [9] found more permanent discontinuation and dose reduction of RT in the CG than in the LG. However, the LG had more temporary stops than the CG. De Lima *et al.* [11] found a significant difference (p = 0.02) in terms of RT discontinuation which was more frequent in the CG. The LG received significantly (p = 0.03) more Grays. In the Oton-Leite study [10], 2 patients in the CG stopped RT and none in the LG, with no significant difference.

Two studies versus placebo [4,19] found significantly more nasogastric tube placement in CG patients than in LG patients. Four studies versus placebo [2,6,11,12] found no significant difference. However, Lima *et al.* [11] found that the use of a nasogastric tube was significantly later in the LG/CG (5 sessions later on average). The use of a gastrostomy was only reported in the Antunes *et al.* trial [9] where it was more frequent in the CG/LG (p = 0.01). Follow-up was reported in 8 trials and ranged from 1 to 60 months [3–6,9,11,15,16].

Discussion

The current understanding of OM pathophysiology comprises of five stages : (i) initiation of oral mucosal damage by CT or RT, (ii) primary damage from reactive oxygen species

generation, (iii) damage amplification due to host inflammatory response, (iv) mucosal ulceration as a result of epithelial apoptosis and necrosis, and ultimately followed by (v) healing. (MASC ISOO) [8].

PBM has been shown to enhance wound repair and tissue regeneration by influencing different phases of tissue healing. The inflammatory phase, in which immune cells migrate to the site of tissue injury, the proliferative phase, which includes stimulation of fibroblasts and macrophages as well as other repair components, and the remodeling phase, consisting of collagen deposition and rebuilding of the extracellular matrix at the wound site. [7]

In 2019, MASCC/ISOO [8] published recommendations that introduced the use of PBM in the treatment of OM. The recommended parameters are summarized in Figure 2.

The MASCC/ISOO report is an important step forward in establishing a reproducible protocol for PBM, which as our results show, is heterogeneous in use.

Despite a satisfactory level of evidence, the number of published trials is low. Indeed, prevention of OM is of major interest and in recent years, lasers and PBM have taken a prominent place in medicine.

Epidemiologically, the first point to note is that OM is not specific to the treatment of oral cavity cancers. It appears in the other locations of HNSCC which represented more than 68% of the indications for patient irradiation in the trials found in this research. Only 1 article was devoted to OM for exclusively oral cancers [19]. Surprisingly, no article mentioned the presence of mucositis of the mucous membranes of the ear-nose-throat (ENT) sphere, which is admittedly more difficult to objectify, but whose associated symptomatology could pose the same problem as OM, even though the construction of our search equation made it possible to find articles dealing with it. This confirms the central problem of OM in the treatment of HNSCC by RT or RT/CT. The histological type of the cancer was indicated in only half of the cases. When it was provided, it was mostly squamous cell carcinoma [3,6,10,14,16–19], in correlation with the epidemiology of HNSCC.

Two laser models for PBM treatment of OM emerged from this research, the InGaAlP diode laser and the HeNe laser. The results on their ability to reduce OM were significant compared with CG in 62.5% and 75% of the studies respectively, although the number of studies, 8 and 4 respectively, is low for the scientific evidence to be strong.

When looking at the clinical aspects of reduced OM intensity, two questions arise:

- Does the pain decrease? Of the 6 studies in which there was a reduction in OM and pain was assessed, 4 found a significant reduction of pain [1,2,10,15], but the consumption of analgesics was not reported. In the 2 studies where the results were not significant [17,19], there was a significant reduction in the use of analgesics, including opioids.
- Does it provide better compliance with RT or RT/CT? Out of 5 studies in which the OM was decreased and the course of RT was reported [4,9,10,17,19], only 1 found a significant difference between the groups [9]. However, while the LG had fewer permanent interruptions and dose reductions, it had more provisional interruptions than the CG. Only 1 other study reported less interruption of RT, but PBM was not effective on OM [11].

For diode lasers, the most commonly used wavelength was 660 nm, the wavelength recommended by MASCC/ISOO for the prevention of OM in RT/CT [8]. PBM at this wavelength was superior to placebo in 3 [9,14,15] of the 5 trials found and not significant in 2 trials [12,18]. In 1 trial, fluence adjustment significantly improved the efficacy of PBM at a wavelength of 660 nm [1]. This fluence of 3.8 J/cm^2 is close to that recommended by MASCC/ISOO [8]. The concomitant use of a second emission at a wavelength other than 660 nm was reported once [17] and showed significantly better results compared with single wavelength emission. Three other wavelengths have been used with diode lasers, 2 of which (685, 980 nm) showed significant results [10,16] and 1 of which had results that were not significant [18].

Although the 660 nm wavelength appears to be the reference for diode lasers, there is some evidence that the results also depend on other settings. However, this research shows that of the 12 diode laser studies, the settings of the other laser parameters were diverse when reported:

- 10 different power settings ranging from 5 to 500 W,
- 11 different energies ranging from 0.1 to 180 J,
- 10 different fluences ranging from 1.3 to 300 J/cm^2,
- 6 different exposure times ranging from 3 to 25 seconds per point,
- 10 different numbers of dots or regions ranging from 12 to 71 dots, sometimes described in regions, sometimes without knowing the number of dots per region.

For HeNe lasers, the most used wavelength was 632.8 nm. The 3 studies reported significant results [2,4,19], but they were performed by the same team. Although this wavelength is recommended by MASCC/ISOO [8] for RT alone, this work does not show any particular evidence. The other wavelength found for HeNe did not report results [6]. It is difficult to discuss the other settings since 3 of the 4 studies were from the same team and the settings were quite similar in all 3 trials.

Only 1 study used an extraoral emission mode and only when the lesions were unreachable with an intraoral laser [17].

Although the intraoral mode has disadvantages linked to the pain caused by OM or post-surgical and/or radiation trismus, it is the mode that is almost exclusively found. Extra-oral emission could provide some advantages by being free of the number of regions or points and by its ease of use. These types of extra-oral PBM lasers are available on the market.

PBM has been used mainly for the prevention of OM and little for curative purposes. MASCC/ISOO recommendations are in line with this. The aim of prevention is twofold: to improve the quality of life by controlling the adverse effects of RT and to prevent therapeutic concession. PBM may be more complicated to perform, especially intra-orally, in the presence of grade $>$2 OM,

although we did not find this in this study. To be effective, the sessions should be regular, varying from 2 to 5 times a week, which is possible and acceptable for patients when PBM sessions are coupled with radiotherapy sessions.

It is not possible to determine the optimal number of weekly sessions with our data since in each subgroup (2d/7, 3d/7, 5d/7) the results were sometimes significant and sometimes not. Determining the lowest possible number of sessions can be considered as an important element for patient compliance.

Evaluation of the effectiveness of PBM is based on the assessment of OM by a scale. This study highlights the use of a large number of scales, making it difficult to compare trials to assess both its effectiveness and the optimal settings for PBM.

Indeed, although there is a WHO scale which appears to be relevant since it integrates pain, clinical and nutritional parameters, 13 teams either coupled it with another scale or used another one. The NCI-CTCAE scale is very similar to the WHO scale but the existence of several versions could also make comparisons between trials difficult. Two other scales commonly used to classify OM are the RTOG and OMAS scales but they do not use nutritional criteria. The ability of the patient to tolerate the oral intake of fluids and solids remains crucial for the morbidity of OM.

The relationship between PBM and survival rate was not an objective of this work. We found that of the 17 articles, 15 stated that they did not illuminate the tumor site during PBM sessions. Two articles addressed the issue of survival between LG and CG [5,9]. For Genot-Klatersky *et al.* [5], there was no significant difference in survival data (OS, PFS, LRFS) between CG and LG. For Antunes *et al.* [9], patients in the LG had a better therapeutic response to RT/CT, resulting in a significantly better PFS ($p < 0.03$) and a better complete response rate ($p = 0.013$). This can be explained by the fact that such patients have better tolerance to treatment and therefore less therapeutic concession. However, the sample sizes of both trials are small.

PBM effects on targeted tumor sites remain unknown and need to be elucidated by further clinical studies.

Conclusion

The main objective of this work was to determine the place of PBM in the treatment of OM. Overall, the results on OM scores were favorable in almost ¾ of the studies. However, the contribution on pain reduction, analgesic consumption and patient compliance to RT and RT/CT remains to be discussed. The secondary objective was to determine the optimal settings for PBM. We noted that:

- Two types of laser are recommended: the InGaAlP diode laser and the HeNe laser, with wavelengths of 660 nm and 632.8 nm respectively.
- PBM should be started at the same time as RT or RT/CT and continued throughout the treatment.

The limitations of the use of PBM that were found in this work are:

- The diversity of PBM parameter settings which do not currently allow for precise protocolisation.
- The diversity of the assessment of OM and pain which is necessary to allow a comparison between studies.
- The lack of data on the consumption of analgesics and on adverse events such as the cessation of radiotherapy, the use of a nasogastric tube or gastrostomy, which could support the contribution of PBM.
- The lack of long-term carcinological follow-up, *i.e.*, during the entire period of carcinological surveillance, to confirm the safety of PBM on the risk of relapse. In view of the importance of the question posed, it is essential to systematically couple a survival analysis to clinical trials evaluating the effectiveness of PBM in the treatment of OM.

In view of the lack of comparability of studies and the lack of reported data, studies that harmonize endpoints and follow-up criteria are needed to establish a standard protocol.

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References

1. Carvalho PAG, Jaguar GC, Pellizzon AC, Prado JD, Lopes RN, Alves FA. 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 2011;47:1176–1181.
2. Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya AG, Guddattu V. 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 mars 2015;144:51–56.
3. Brandão TB, Morais-Faria K, Ribeiro ACP, Rivera C, Salvajoli JV, Lopes MA, *et al.* Locally advanced oral squamous cell carcinoma patients treated with photobiomodulation for prevention of oral mucositis: retrospective outcomes and safety analyses. Support Care Cancer 2018;26:2417–2423.
4. Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya AG, Nigudgi S. 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 2013;21:1421–1428.
5. Genot-Klastersky MT, Paesmans M, Ameye L, Kayumba A, Beauvois S, Dragan T, *et al.* Retrospective evaluation of the safety of low-level laser therapy/photobiomodulation in patients with head/neck cancer. Support Care Cancer 2020;28:3015–3022.
6. Legouté F, Bensadoun RJ, Seegers V, Pointreau Y, Caron D, Lang P, *et al.* Low-level laser therapy in treatment of chemoradiotherapy-induced mucositis in head and neck cancer: results of a randomised, triple blind, multicentre phase III trial. Radiat Oncol 2019;14:83.
7. Zecha JA, Raber-Durlacher JE, Nair RG, Epstein JB, Bensadoun RJ. *et al.* Low level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 1: mechanisms of action, dosimetric, and safety considerations. Support Care Cancer 2016;24:2781–2792.

8. Elad S. The MASCC/ISOO mucositis guidelines 2019: the second set of articles and future directions. Support Care Cancer 2020; s00520-019-05153-w.
9. Antunes HS, Herchenhorn D, Small IA, Araújo CMM, Viégas CMP, de Assis Ramos G, *et al.* 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 2017;71:11–15.
10. Oton-Leite AF, Elias LSA, Morais MO, Pinezi JCD, Leles CR, Silva MAGS, *et al.* Effect of low level laser therapy in the reduction of oral complications in patients with cancer of the head and neck submitted to radiotherapy: LLLT for oral complications in cancer patients. Spec Care Dentist 2013;33:294–300.
11. Gouvêa de Lima A, Villar RC, de Castro G, Antequera R, Gil E, Rosalmeida MC, *et al.* 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 2012;82:270–275.
12. de Dantas JBL, Martins GB, Lima HR, Carrera M, de Reis SRA, Medrado ARAP. Evaluation of preventive laser photobiomodulation in patients with head and neck cancer undergoing radiochemotherapy: laser in patients with head and neck cancer. Spec Care Dentist 2020;40:364–373.
13. Martins AFL, Nogueira TE, Morais MO, Oton-Leite AF, Valadares MC, Batista AC, *et al.* Effect of photobiomodulation on the severity of oral mucositis and molecular changes in head and neck cancer patients undergoing radiotherapy: a study protocol for a cost-effectiveness randomized clinical trial. Trials 2019;20:97.
14. Oton-Leite AF, Silva GBL, Morais MO, Silva TA, Leles CR, Valadares MC, *et al.* Effect of low-level laser therapy on chemoradiotherapy-induced oral mucositis and salivary inflammatory mediators in head and neck cancer patients: EFFECT OF LOW-LEVEL LASER THERAPY IN CANCER PATIENTS. Lasers Surg Med avr 2015;47:296–305.
15. Zanin T, Zanin F, Carvalhosa AA, de Souza Castro PH, Pacheco MT, Zanin ICJ, *et al.* Use of 660-nm Diode Laser in the Prevention and Treatment of Human Oral Mucositis Induced by Radiotherapy and Chemotherapy. Photomed Laser Surg avr 2010;28:233–237.
16. Marín-Conde F, Castellanos-Cosano L, Pachón-Ibañez J, Serrera-Figallo MA, Gutiérrez-Pérez JL, Torres-Lagares D. 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 juill 2019;48:917–923.
17. Soares RG, Farias LC, da Silva Menezes AS, de Oliveira e Silva CS, Tabosa ATL, Chagas PVF, *et al.* 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 nov 2018;33:1813–1819.
18. de Lima AG, Antequera R, de Peres MPS, Snitcosky IML, Federico MHH, Villar RC. Efficacy of low-level laser therapy and aluminum hydroxide in patients with chemotherapy and radiotherapy-induced oral mucositis. Braz Dent J 2010;21:186–192.
19. Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya GA. Low Level Helium Neon Laser therapy for chemoradiotherapy induced oral mucositis in oral cancer patients – A randomized controlled trial. Oral Oncol sept 2012;48:893–897.