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REVIEW ARTICLE

A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis

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Abstract
Purpose The purpose of this study is to review the effects of low-level laser therapy (LLLT) in the prevention and treatment of cancer therapy-induced oral mucositis (OM).
Methods A systematic review and meta-analysis of randomised placebo-controlled trials of LLLT performed during chemotherapy or radiation therapy in head and neck cancer patients.
Results We found 11 randomised placebo-controlled trials with a total of 415 patients; methodological quality was acceptable at 4.10 (SD±0.74) on the 5-point Jadad scale. The relative risk (RR) for developing OM was significantly (p= 0.02) reduced after LLLT compared with placebo LLLT (RR= 2.03 (95% CI, 1.11 to 3.69)). This preventive effect of LLLT improved to RR=2.72 (95% CI, 1.98 to 3.74) when only trials with adequate doses above 1 J were included. For treatment of OM ulcers, the number of days with OM grade 2 or worse was significantly reduced after LLLT to 4.38 (95% CI, 3.35 to 5.40) days less than placebo LLLT. Oral mucositis severity was also reduced after LLLT with a standardised mean difference of 1.33 (95% CI, 0.68 to 1.98) over placebo LLLT. All studies registered possible side-effects, but they were not significantly different from placebo LLLT.
Conclusions There is consistent evidence from small high-quality studies that red and infrared LLLT can partly prevent development of cancer therapy-induced OM. LLLT also significantly reduced pain, severity and duration of symptoms in patients with cancer therapy-induced OM.

Keywords Low-level laser therapy · Oral mucositis · Cancer · Chemotherapy · Radiation therapy

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Introduction

Oral mucositis (OM) is a serious and acute side-effect for patients undergoing cancer therapy. The frequency of its appearance varies with therapy and cancer type up to 100% in oral cancer patients receiving adjuvant chemotherapy or radiotherapy [1, 2].

OM has great impact on a patient´s well-being. It may necessitate modifications of treatment planning, suspension

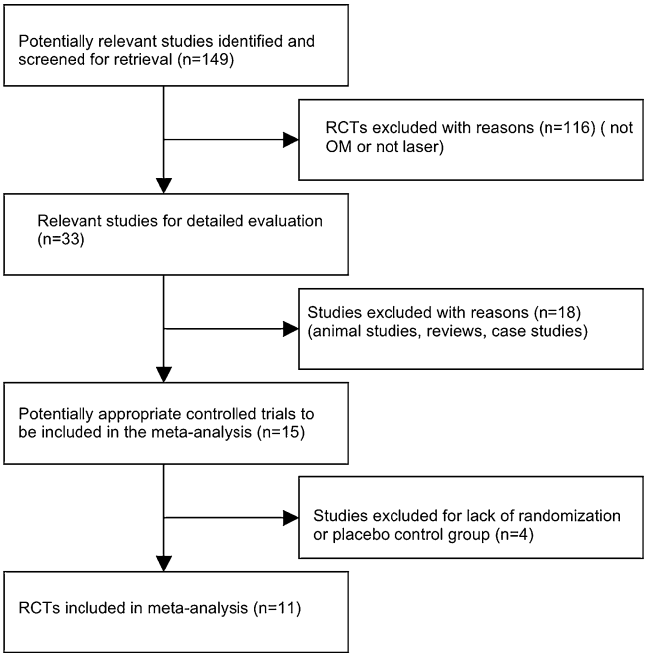

Fig. 1 Quorum flow chart showing the stages of the reviewing process and the number of studies filtered out at each stage

of therapy, need for opioid analgesics, and/or require enteral or parenteral nutrition with an impact on patient's survival [2, 3]. The additional cost of OM treatment for cancer patients can be considerable [4].

Many interventions have been used in OM management, but only a handful of interventions have sufficient scientific support from positive results in controlled clinical trials to be recommended in treatment guidelines [5, 6]. Recommended nonpharmacological treatments are oral care with mouthrinse [7] and cryotherapy [8]. The latter may also be used for the prevention of OM occurrence. Pharmacological agents have largely been used for palliative care and pain relief, and some are recommended by consensus in spite of lacking scientific evidence from randomised controlled trials. These pharmacological agents include patient-controlled analgesia with morphine in transplant patients with hematological malignancies and topical anaesthetics like lidocaine alone, or in combination with diphenhydramine [9]. More recently, pharmacological focus has been directed towards the prevention of ulceration and the drug palifermin, a human keratinocyte growth factor [10] that stimulates the proliferation, migration, and differentiation of epithelial cells and is recommended in patients undergoing stem cell transplantations. In addition, amifostine is thought to inhibit harmful reactive oxygen species release [11], but the scientific evidence for this drug is sparse. More recently, pharmacological focus has been directed towards the prevention of ulceration (palifermin and amifostine) but no single intervention yet serves as a panacea for all phases of OM.

Low-level laser therapy (LLLT) is a local application of a monochromatic, narrow-band, coherent light source. LLLT is recommended as a treatment option for OM in the MASCC guidelines but with limitations due to heterogeneous laser parameters and a lack of dosage consensus in the LLLT literature. The action of LLLT is disputed, but a cytoprotective effect before and during oxidative stress has been observed after pre-treatment with LLLT [12–14]. There is some support

Table 1 Trial characteristics

First author (year)	Patient numbers (cancer therapy)	Wavelength (nm)	Laser output (mW)	Spot size (cm2)	Dose (J)	Irradiation time (s)	Outcomes and effect (+/−)
Cowen 1997	30 (chemo/radio)	633	30	0.5	3.5	105	Days+/OMI+
Bensadoun 1999	30 (radiation)	633	60	0.5	2	33	Pain+/OMI+
Arun Maiya 2006	50 (radiation)	633	10	1.0	4	600	Pain+/OMI+
Schubert 2007	70 (transplant)	650/780	40/60	0.04	2	33–50	655 nm only pain+/OMI+
Cruz 2007	60 (chemo/child)	633	50	0.04	0.18	3	n.s.
Kuhn 2007	34 (chemo)	830	100	0.06	6	54	Days+/OMI+
Antunes 2007	38 (transplant)	660	47	0.2	4	17	Pain+/WHO+
Genot-Klastersky 2008	36 (chemo)	650	100	0.45	5	33	Days+/OMI+
Kuhn 2009	21 (chemo/child)	830	100	0.06	6	56	Days+/OMI+
Abramoff 2009	22 (chemo)	685	35	0.5	3	54	Days+/OMI+
Chor 2009	24 (chemo)	660	50	?	2	40	Days+/others−

First column identifies trial by first author's last name and the publication year. Other columns represent: sample size (type of cancer therapy), laser wavelength in nm, laser output in mW, spot size in cm^2, dose in Joules, irradiation time per point, outcomes reported including mucositis severity scales (WHO or OMI), pain and duration of OM in days and dichotomized overall results given by: (+) significantly in favour of LLLT or (−) non-significant between LLLT and placebo

Table 2 Trial methodological quality scored with an "x" if the methodological criterion is fulfilled

	Randomised	Random described	Patient blind	Observer blind	Withdrawals handled	Total score
Abramoff 2008	x		x		x	3
Antunes 2007	x		x	X	x	4
Bensadoun 1999	x	X	x	x	x	5
Chor 2009	x		x	x		3
Cowen 1997	x	X	x	x	x	5
Cruz 2007	x		x	x	x	4
Genot Klast 2008	x		x	x	x	4
Kuhn 2007	x		x	x	x	4
Kuhn 2009	x	X	x	x	x	5
Arun Maiya 2006	x	X		x	x	4
Schubert 2007	x		x	x	x	4

The first column identifies each trial by first author's last name and last two digits of the publication year. The total methodological score (Jadad scale max. score=5) for each trial is given in the last column

for this protective LLLT effect in humans too [15], and a possible therapeutic window has also been identified for an anti-inflammatory effect of red and infrared LLLT [16].

Evidence-based treatment guidelines have been forwarded from the World Association for Laser Therapy (WALT) (http://www.walt.nu/dosage-recommendations.html), and optimal doses of LLLT have been identified for osteoarthritis [17], tendinopathies [18], and neck pain [19]. With the increasing body of randomised controlled trials, there seems to be a need for systematically reviewing the literature and quantify possible LLLT effects of LLLT in both prevention and treatment of cancer therapy-induced OM.

Materials and methods

Literature search

A literature search was performed on Medline, Embase, Cinahl, PedRo, and the Cochrane Controlled Trial Register as advised by Dickersin et al. [20] for randomised controlled clinical trials. Keywords were: low-level laser therapy, low-intensity laser therapy, low-energy laser therapy, phototherapy, HeNe laser, IR laser, GaAlAs, GaAs, diode laser, NdYag, oral mucositis, and cancer. Hand searching was also performed in national physiotherapy and medical journals from Norway, Denmark, Sweden, Holland, England, Canada, and Australia. Additional information was gathered from LLLT researchers in the field.

Inclusion criteria

The randomised controlled trials were subjected to the following six inclusion criteria:

1. Diagnosis: oral mucositis in cancer patients induced after chemotherapy or radiation therapy
2. Treatment: LLLT with wavelengths of 632–1,064 nm, treating the mucosa of the oral cavity

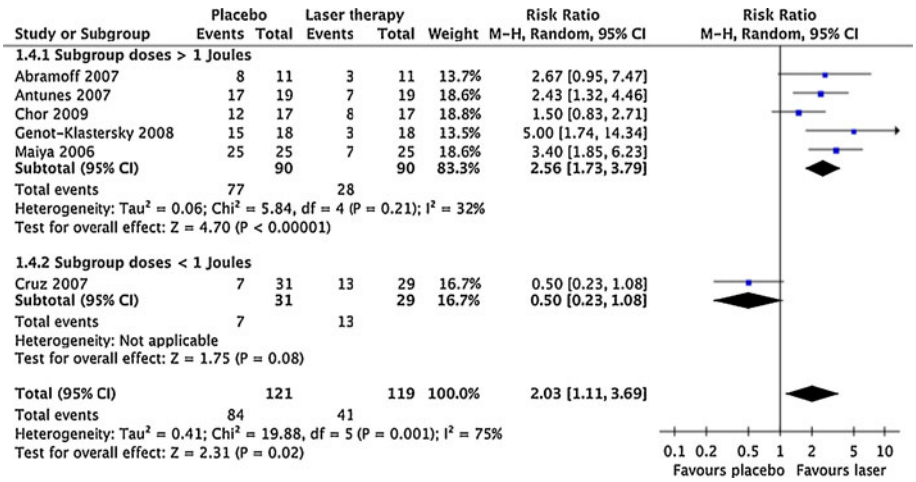

Fig. 2 Forest plot showing the meta-analysis results for prevention of OM occurrence by LLLT dose compared with placebo. Trial results plotted on the *right-hand side* indicate effects in favour of LLLT, and the combined effects are plotted as *black diamonds* for doses above 1 J, below 1 J and overall regardless of dose, respectively

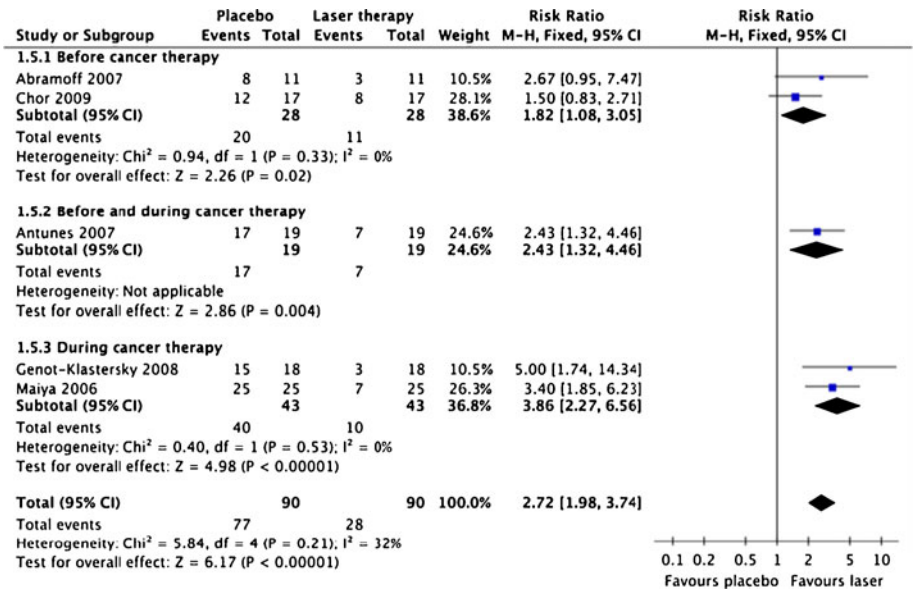

Fig. 3 Forest plot showing the meta-analysis results for prevention of OM occurrence by LLLT wavelengths compared with placebo. Trial results plotted on the *right-hand side* indicate effects in favour of LLLT, and the combined effects are plotted as *black diamonds* for red wavelengths (630–670 nm), infrared wavelengths (780–830 nm), and overall regardless of wavelength, respectively (published online only)

3. Design: randomised parallel group design or crossover design
4. Blinding: outcome assessors should be blinded
5 Control group: receiving identical placebo laser
6. Specific endpoints for prevention of oral mucositis above a certain grade, oral mucositis severity, duration in days, and pain intensity

Outcome measures

1. The relative risk (RR) over placebo for preventing occurrence of oral mucositis above a certain grade (0–2) with LLLT
2. The effect of LLLT on the severity of oral mucositis measured by the Oral Mucositis Index (OMI) or WHO scales were calculated as the SMD versus placebo.
3. The effect of LLLT on the duration of days oral mucositis was calculated as the weighted mean difference versus placebo
4. The effect of LLLT on pain intensity was calculated as the standardised mean difference (SMD) versus placebo and labelled after Cohen [21] as "poor" (0.2–0.5), "good" (0.5–0.8), or "very good" (>0.8)
5. Subgroup analyses were planned for (1) doses of <1 J and >1 J (minimum dose according to WALT guidelines for other inflammatory conditions), (2) red and infrared wavelengths with their anticipated optimal dose ranges (1–4 J for red wavelengths and 3–8 J for infrared wavelengths)

A statistical meta-analysis software package developed by Cochrane Collaboration (Revman 5.0.22) was used for the statistical calculations. If heterogeneity was present in heterogeneity tests, a random effects model was used for calculations. If heterogeneity was absent, a fixed effects model was used for calculation of the overall effects.

Analysis of bias, including methodological quality, funding source, and patient selection

Positive bias direction, caused by flaws in trial methodology, funding source

Trials were subjected to methodological assessments by the 5-point Jadad checklist [22]. For-profit funding sources

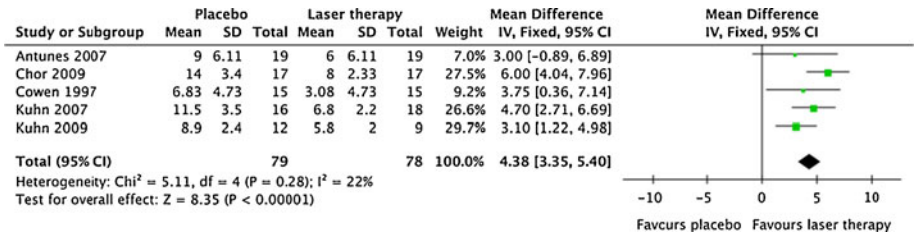

Fig. 4 Forest plot showing the meta-analysis results for duration of OM after LLLT compared with placebo as a weighted mean difference. Trial results plotted on the *right-hand side* indicate effects in favour of LLLT, and the combined effect including variance is plotted as a *black diamond* at the bottom of the forest plot

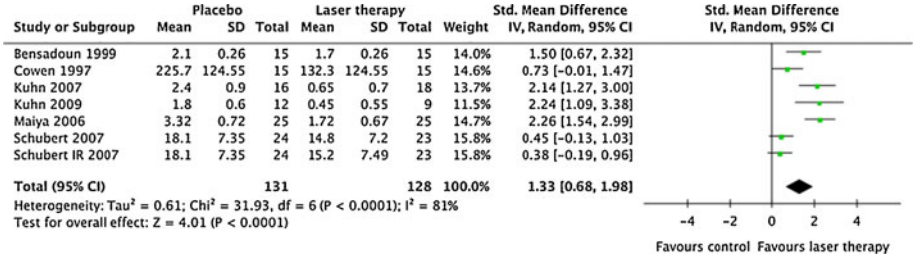

Fig. 5 Forest plot showing the meta-analysis results for LLLT effect on OM severity compared with placebo as a standardised mean difference (combines results from different OM severity scales). Trial results plotted on the *right-hand side* indicate effects in favour of LLLT, and the combined effect including variance is plotted as a *black diamond*

have been shown to affect trial conclusions in a positive direction [23], which made us include an analysis of funding sources. Methodological assessments were made independently according to the Jadad 5-point scale by two of the authors (JMB and RABLM).

Results

Literature search and exclusion procedure

The literature search revealed 149 papers for oral mucositis and laser therapy. Thirty-three were regarded as potentially relevant papers. Of these, nine studies were reviews and six studies were case studies while another three were animal studies. Three controlled studies were excluded for lack of randomization while one study lacked a placebo-control group [24]. The exclusion/inclusion procedure is described according to the [25] Quorum standard in Fig. 1.

The final sample consisted of 11 randomised placebo-controlled trials published from 1997 until 2009 with a total of 415 patients [26–36]. The OMI was used in seven trials and the WHO was used in one trial as measures of OM severity. The characteristics of the included trials and laser parameters are listed in Table 1.

Methodological quality

The assessors gave similar methodological gradings for all the included studies, and a consensus meeting was not needed. Methodological quality was high for the included studies with a mean score of 4.10 (SD±0.74). The individual method scores are given in Table 2.

Funding sources analysis

Laser manufacturers were acknowledged for support in two trial reports [29, 35]. One trial report explicitly stated that no conflicts of interest existed [27] while another trial stated that funding came from an independent non-profit source [32]. Six trials did not explicitly mention conflicts of interest in their trial reports. But none of the affiliations and addresses in these reports indicated industry involvement. Double checking the "Instructions to Authors" in the journals in which these trial reports appeared, revealed that the journals demanded declarations from the authors about

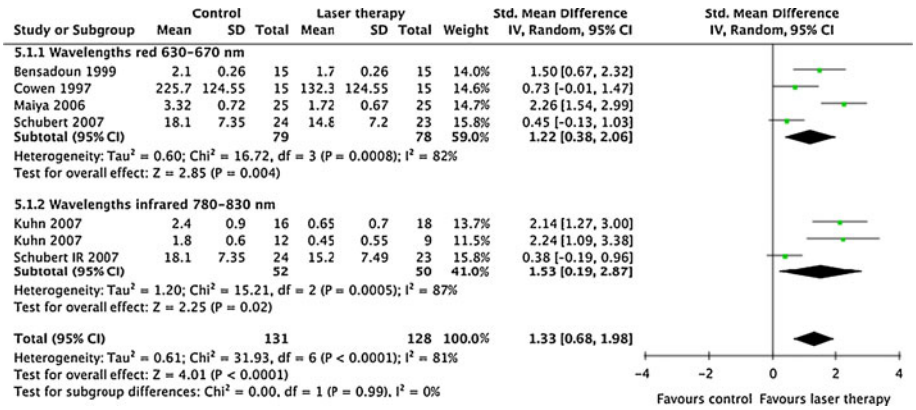

Fig. 6 Forest plot showing the subgroup meta-analysis results for infrared LLLT doses of ≤2 J or >2 J of the effect on OM severity compared with placebo as a standardised mean difference (combines results from different OM severity scales). Trial results plotted on the *right-hand side* indicate effects in favour of LLLT, and the combined effect including variance is plotted as a *black diamond* (published online only)

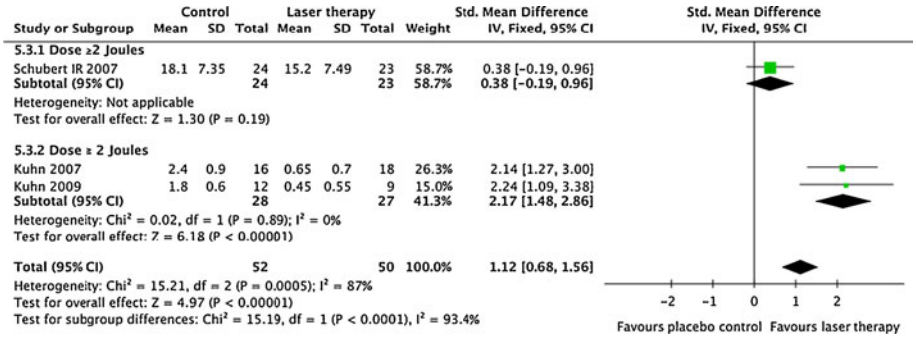

Fig. 7 Forest plot showing the meta-analysis results for LLLT effect on pain compared with placebo as a standardised mean difference (combines results from different pain scales). Trial results plotted on the *right-hand side* indicate effects in favour of LLLT, and the combined effect including variance is plotted as a *black diamond* (published online only)

possible conflicts of interest before publication. For this reason, the lack of mention has been accepted by the authors as a lack of conflicts of interest, rather than undeclared conflicts of interest. In total, bias from for-profit funding sources occurred in just two of 11 papers which the authors consider has negligible influence on the review conclusion.

Relative risk for occurrence of cancer therapy-induced OM after LLLT

Six studies started LLLT before OM ulcers occurred and presented categorical data for the risk of developing OM above a certain grade (OM grades 0, 1, 2) during cancer therapy. There was a significant preventive effect of LLLT with a relative risk at 2.03 (95% CI, 1.11 to 3.69) less for cancer therapy-induced OM to occur. The analysis revealed significant heterogeneity (I^2=54%, p=0.03) between trials, and the results are summarised in Fig. 2.

Analysis of irradiation parameters revealed that one study [32] had given a lower dose (0.18 J) than the minimum recommended WALT dose of 1 J. After sub-grouping trials with doses above 1 J, heterogeneity disappeared (I^2=16%, p=0.31). The relative risk for preventing OM to occur increased to 2.72 (95% CI, 1.98 to 3.74). The results for each study subgrouped by their timing of LLLT subgroups and the total RR are presented in Fig. 3.

Subgroup analysis of LLLT wavelength effects on the relative risk for occurrence of OM after LLLT

The subgroup analysis revealed no heterogeneity between trials with anticipated optimal doses for the red (630–670 nm) and the infrared (780–830 nm) subgroups, respectively (p>0.21 and I^2<32%), and there were no significant wavelength differences in relative risks between red and infrared at 2.72 (95% CI, 1.98 to 3.74) and infrared at 3.48 (95% CI, 1.79 to 6.75).

Effect on duration of oral mucositis

Five studies presented data for this outcome, and LLLT reduced significantly the number of days with oral mucositis grade 2 or worse with 4.38 (95% CI, 3.35 to 5.40) days. The results for each individual study and the combined results are summarised in Fig. 4.

Effect on mucositis severity

Six trials presented seven different comparisons of continuous data for mucositis severity. As the trials used different mucositis index scales, the combined results were calculated as the SMD. The combined SMD effect size was 1.33 (95% CI, 0.68 to 1.98) and heterogeneity was present (p< 0.0001 and I^2=81%). The results for each trial and the combined effect size are presented in Fig. 5.

Dose analyses of anticipated optimal dose ranges by wavelength

A subgroup analysis of anticipated optimal dose ranges for red and infrared wavelengths on OM severity, revealed that infrared wavelengths (6 J in both trials) gave an SMD at 2.17 (95% CI, 1.48 to 2.86) without signs of heterogeneity between trials (I^2=0% and p=0.89). A dose of 2 J with an infrared wavelength was ineffective SMD 0.38 (95% CI, −0.19 to 0.96) in reducing mucositis severity. The dose analyses are presented in Fig. 6.

Effect on pain relief

Four trials reported continuous data on pain intensity from different scales. The combined analysis revealed a significant effect of LLLT with an SMD at 1.22 (95% CI, 0.19 to 2.25) but also significant heterogeneity caused by one trial [27]. Removal of this study restored homogeneity (I^2=0% and p=0.58), but reduced the effect size to 0.61 (95% CI, 0.29 to 0.94) (see Fig. 7).

Table 3 Summarised recommended treatment parameters

Wavelength (nm)	Laser output (mW)	Spot size (cm^2)	Dose per point (J)	Minimum irradiation time per point (s)	Minimum no. of irradiation points	Minimum sessions per week during cancer therapy	Minimum no. days to start LLLT before cancer therapy (for prevention)
Red (633–685)	10–60	0.1–1.0	3	30	6	3	7
Infrared (780–830)	50–100	0.1–0.5	6	30	6	3	7

Side effects of LLLT

All the studies investigated possible side-effects, but none found side-effects or adverse effects beyond those reported for placebo LLLT. Five trials reported explicitly that LLLT was well tolerated among patients.

Discussion

This systematic review has revealed moderate to strong evidence for the efficacy of LLLT in cancer therapy-induced OM. A possible limitation to our findings is the small sample size of the included trials. Our finding is partly contradicting a Cochrane review [6] which was recently updated [37]. Our review deviates from their conclusions because we have included more studies and subgroup analyses by dose range and wavelengths. The overall scientific quality of the trials was methodologically acceptable, but the heterogeneous treatment procedures and dosing may cause confusion. In the MASCC guidelines, the evidence behind LLLT is characterized as promising, but it is added that conflicting evidence with large operator variability and expensive equipment (gas lasers) limits more widespread clinical use [5]. The lasers used in the studies reviewed are relatively inexpensive diode lasers (from $2,500) with low optical outputs (10–100 mW), which have substituted the older more expensive gas lasers from the early LLLT trials [30, 31]. After reviewing the apparent discrepancies of the material, our subgroup analyses revealed plausible causes for the few conflicting results. A common misunderstanding in the LLLT literature is caused by reporting clinical doses for diode lasers with small spot sizes in Joules/cm^2 rather than in Joules. If the spot size is very small, then the irradiation time will be very short. This led to under-dosing in one of the included trials, where they irradiated for 3 s per point [32]. WALT recommends that doses in clinical studies should be reported in Joules instead of Joules/cm^2. LLLT wavelengths and doses were fairly homogeneous in the other studies. Red wavelengths from 633 to 685 nm, and previous studies found no significant differences between red wavelengths in this range [38]. For infrared wavelengths, 830 nm was used in all trials but one underdosed trial [32]. Doses were also fairly consistent across trials ranging from 1 to 6 J except the underdosed trial finding no significant effect from a dose 0.18 J. Treatment times per point varied considerably with the variation in laser outputs, but at least 17 s of irradiation per point was need to achieve beneficial results (median, 50 s). The number of treatment session varied from 3 to 30 in this material, but this heterogeneity must be seen in conjunction with the heterogeneity in durations of chemotherapy and radiation therapy regimens. Our interpretation is that LLLT needs to be performed at least every other day for the duration of chemotherapy and radiation therapy regimens, or as long as OM ulcers are present. The trials which aimed at the prevention of OM started LLLT at 7 days before chemotherapy/radiation therapy regimens. It should be a target for future trials to compare treatment start at different timepoints before cancer therapy to avoid unnecessary LLLT.

From the evidence, we propose a fairly simple procedure for diode lasers for prevention and treatment of cancer therapy-induced OM. LLLT should be performed with a red or infrared diode laser with outputs of 10–100 mW in a stationary manner (not scanning). The parameters are summarised in Table 3.

In manifested OM, lesions and inflammatory areas should be specifically targeted for irradiation. Our findings relate well to the emerging LLLT evidence of optimal doses in inflammatory conditions such as rheumatoid arthritis [39] and acute postoperative pain [16]. It is also interesting to note that the variety of different cancer therapies involved in the included trials did not seem to seriously interfere with the beneficial effects of LLLT. How LLLT efficacy compares with the efficacy of pharmacological agents in OM, is outside the scope for this review but this should certainly be a topic for future research. In terms of side-effects, LLLT was well tolerated and no serious incidents or withdrawals due to treatment intolerance were reported.

Conclusions

We conclude that there is moderate to strong evidence in favour of LLLT applied with doses of 1–6 J per point in the oropharyngeal area in cancer patients receiving chemotherapy or radiation therapy. There are limitations to the material in terms of small sample size in the included trials. However, the material was consistently in favour of LLLT in both in the prevention of OM occurrences and reductions of severity, pain, and duration of OM ulcers.

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Conflicts of interest None

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