NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of low-level laser therapy for preventing or treating oral mucositis caused by radiotherapy or chemotherapy

Oral mucositis is inflammation of the lining of the mouth that can cause pain, dryness, ulcers and difficulty with swallowing. It is a common and serious side effect of chemotherapy and radiotherapy. This procedure uses low-energy lasers, inside or outside the mouth, to treat the affected tissue. The aim is to reduce inflammation and stimulate the healing process.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2017.

Procedure name

- Low-level laser therapy for prevention or treatment of oral mucositis secondary to radiotherapy or chemotherapy

Specialist societies

- Royal College of Physicians
- British Association of Head & Neck Oncologists (BAHNO)
- British Association of Otorhinolaryngologists, Head and Neck Surgeons (ENT UK)
- Royal College of Radiologists (RCR)
- Royal College of Surgeons
- British Society for Haematology (BSH).

Description of the procedure

Indications and current treatment

Oral mucositis (OM) is a common side effect of chemotherapy or radiotherapy used for treating head and neck cancer or before bone marrow transplantation. Symptoms usually start 5 to 10 days after chemotherapy or 14 days after radiotherapy and include dryness, halitosis, pain, inflammation and oral mucosa ulceration. Chemotherapy-associated OM can resolve within a few days after completion of chemotherapy, but radiotherapy-associated OM can last for weeks. OM can affect nutritional status (which may need enteral or parental nutrition) and quality of life, and can increase hospital stay. It can also require interruptions or dose reductions in chemotherapy or radiotherapy treatment.

Comprehensive oral hygiene, good hydration, a bland soft diet and avoiding alcohol and tobacco may increase the person’s comfort. Ice, water-based moisturisers, painkillers and non-steroidal anti-inflammatory drugs can help reduce symptoms. Drugs such as palifermin are sometimes used to prevent or treat OM. Antibiotics may be needed to treat infectious complications.

What the procedure involves

Low-level laser therapy aims to treat or prevent OM by promoting healing, reducing inflammation and increasing cell metabolism. A hand-held probe is used to deliver light in the red or near-infrared spectrum to the oral mucosa. It can be delivered intra-orally or extra-orally, or as a combination of both approaches. During intraoral treatment the probe, which is about the size of a dental curing light, is introduced into the mouth. For extraoral treatment the probe is positioned close to the cheek. The procedure typically takes 20 to 30 minutes, delivered 2 to 5 times a week for the duration of the oncology treatment. The procedure may be started before treatment with chemotherapy or radiotherapy begins, with the intention of preventing OM.

Outcome measures

<u>Oral mucositis scales</u>

World Health Organization (WHO) oral mucositis scale/common toxicity criteria

Assesses anatomical, symptomatic and functional dimensions of OM.

Grade	**Description**
Grade 0 (none)	None
Grade 1 (mild)	Oral soreness, erythema
Grade 2 (moderate)	Erythema, ulcers, solid diet tolerated
Grade 3 (severe)	Oral ulcers, liquid diet only
Grade 4 (life-threatening)	Oral feeding is impossible, requires parental nutrition

Radiation Therapy Oncology Group (RTOG) scale

Based on the clinical ability to judge the anatomical changes associated with OM size and characteristics of the ulceration.

Grade	**Description**
Grade 0 (none)	No change over baseline
Grade 1 (mild)	Irritation, may experience slight pain, not requiring analgesia
Grade 2 (moderate)	Patchy mucositis that may produce inflammatory serosanguinous discharge; may experience moderate pain requiring analgesia
Grade 3 (severe)	Confluent, fibrinous mucositis, may include severe pain requiring narcotic
Grade 4 (life-threatening)	Ulceration, haemorrhage, or necrosis

National Cancer Institute Common Terminology Criteria (NCI CTC)

Grading of the severity of adverse events secondary to chemotherapy and radiotherapy toxicity.

Based on symptom observation and need for clinical management.

Grade	Description
Grade 0 (none)	None
Grade 1 (mild)	Painless ulcers, erythema, or mild soreness in the absence of lesions
Grade 2 (moderate)	Painful erythema, oedema, or ulcers but eating or swallowing possible
Grade 3 (severe)	Painful erythema, oedema, or ulcers requiring intravenous hydration
Grade 4 (life-threatening)	Severe ulceration or requiring parenteral or enteral nutritional support or prophylactic intubation
Grade 5 (death)	Death related to toxicity

Tardieu mucositis scale

Ranges from grades 0 to 3.

Grades 2 and 3 on the Tardieu scale are similar to grades 3 and 4 according to the other mucositis grading scales.

Late effects of normal tissues/subjective objective management analytic scale (LENT/SOMA)

Grade	Description
1	Normal moisture
2	Scant moisture
3	Absence of moisture, sticky, viscous saliva
4	Absence of moisture, coated mucosa

Radiation Therapy Oncology Group and European Organisation for Research and Treatment of Cancer (RTOG/EORTC) late radiation morbidity scoring scheme

Organ tissue	0	Grade 1	Grade 2	Grade 3	Grade 4
Mucous membrane	none	slight atrophy and dryness	moderate atrophy and telangiectasia; little mucous	marked atrophy with complete dryness; severe telangiectasia	ulceration
Salivary glands	none	slight dryness of mouth; good response on stimulation	moderate dryness of mouth; poor response on stimulation	complete dryness of mouth; no response on stimulation	fibrosis
Larynx	none	hoarseness; slight arytenoid oedema	moderate arytenoid oedema; chondritis	severe oedema; severe chondritis	necrosis

(Relevant organ tissues extracted by the analyst from a more general list of organs)

Oral-health related quality-of-life questionnaires

Functional assessment of cancer therapy bone marrow transplantation (FACT-BMT) quality-of-life questionnaire

Patient-reported questionnaire assessing 5 dimensions of quality of life in bone marrow transplant patients: physical well-being, social and family well-being, emotional well-being, functional well-being and additional concerns. Higher scores indicate worse oral-health related quality of life (range 0 to 164).

Oral Health Impact Profile-14 (OHIP-14)

Consists of 14 questions to assess the impact of oral conditions on 7 dimensions of oral-health related quality of life: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap. Higher scores indicate worse oral-health related quality of life (range 0 to 56).

Efficacy summary

Incidence and severity of oral mucositis

A systematic review (SR) of 18 randomised control trials (RCTs) reported the effect of prophylactic low-level laser therapy (LLLT) compared to no treatment or placebo in reducing oral mucositis (OM) in a total of 1,144 adults and children having radiotherapy (RT), chemotherapy (ChT) or haematopoietic stem cell transplantation (HSCT) to treat cancer (mainly head and neck cancer and haematological disorders). The SR included a meta-analysis (MA) of 10 RCTs (n=689) reporting that the risk of severe OM was statistically significantly lower in patients having prophylactic LLLT compared with placebo or no treatment (risk ratio [RR] 0.37, 95% confidence interval [CI] 0.20 to 0.67, I^2=80%, p=0.001). The absolute risk reduction of severe mucositis with LLLT was RR -0.35, 95% CI -0.48 to -0.21, p<0.0001, resulting in a number needed to treat of 3 patients to prevent 1 episode of severe OM. The same study reported an MA of 8 RCTs (n=603) in which patients having prophylactic LLLT had a statistically significantly lower mean of severe OM (grade 3 or 4) compared with no treatment or sham (standardised mean difference [SMD] -1.49, 95% CI -22.02 to 20.95, I^2=86%, p<0.0001)[1].

A SR of 11 RCTs reported the effects of prophylactic and therapeutic LLLT in reducing OM in 415 patients who had ChT or RT for head and neck cancer. An MA of 6 RCTs (n=240) in the SR reported a statistically significantly lower incidence of OM above grade 2 in patients having prophylactic LLLT (any energy dose) compared with standard medical care (SMC) or sham (RR 2.03, 95% CI 1.11 to 3.69, p=0.02; I^2=75%). Another MA of the same SR reported a statistically significantly higher likelihood of OM prevention in patients treated by LLLT, regardless of timing of therapy, compared to controls(RR 2.72, 95% CI 1.98 to 3.74, p<0.00001). An MA of 7 RCTs (n=259) in the SR reported a statistically significantly reduction in the severity of OM in patients having prophylactic and therapeutic LLLT compared with sham or no treatment (SMD 1.33, 95% CI, 0.68 to 1.98, p<0.00001; I^2=81%). An MA of 2 RCTs (n=56) in the SR reported a statistically significantly lower risk of OM in patients who had prophylactic LLLT before cancer treatment compared with sham (RR 1.82, 95% CI 1.08 to 3.05, p=0.02; I^2=0%). One RCT (n=38) in the same MA reported a statistically significantly lower risk of OM in patients who had prophylactic LLLT before and during cancer treatment compared with sham (RR 2.43, 95% CI 1.32 to 4.46, p=0.004). Another MA of 2 RCTs (n=86) reported a statistically significantly lower risk of OM in patients who had prophylactic LLLT during cancer treatment compared with sham (RR 3.86, 95% CI 2.27 to 6.56, p<0.00001; I^2=0%)[2].

In an RCT of 123 children who developed ChT-induced OM (grade 2 or more), median OM severity was not statistically significantly different on day 4 after completing the LLLT treatment cycle (p=0.65) or on day 7 of follow-up (p=0.07) compared with sham[3].

In an RCT of 48 patients having first-time ChT for head and neck cancer, OM severity was statistically significantly lower in patients having prophylactic LLLT for the entire duration of ChT compared with sham at week-2 follow-up (LLLT 0.25, CI 0.13 to 0.6; sham 2.28, CI 1.9 to 2.5; p=0.001), week-8 (LLLT 0.5, CI 0.13 to 1.1; sham 2.20, CI 2.0 to 2.40, p=0.001) and at the final follow-up in week 14 (LLLT 0.3, CI 0.05 to 0.8; sham 1.5, CI 1.3 to 1.8; p=0.001)[5].

In an RCT of 46 patients having RT for head and neck cancer, OM severity grade 3 or 4 was statistically significantly less frequent in patients in the prophylactic LLLT group (18% [4/22]) compared with sham (58% [14/24], p=0.016)[6].

In a case series of 26 patients who previously developed ChT-induced OM, 81% of patients (21/26) were considered successfully treated by therapeutic LLLT; 15% (4/26) no longer presented with OM and 65% (17/26) had grade 1 OM assessed by the European Organisation for Research and Treatment of Cancer (EORTC) scale. An RCT of 36 patients with haematological malignancies scheduled for ChT or RT, reported in the same publication, found that OM grade 3 (EORTC scale) was statistically significantly less frequent in patients having therapeutic LLLT (17% [3/18]) compared with sham (89% [16/18], p<0.001). The same RCT of 36 patients reported a statistically significantly longer time to development of OM grade 3 (EORTC scale) in patients having therapeutic LLLT (7 days) compared with sham (3 days, p<0.0001)[7].

In an RCT of 35 patients with haematological cancer treated by haematopoietic stem cell transplantation, the risk of severe OM (WHO scale above grade 2) was statistically significantly lower in patients having prophylactic LLLT (18% [3/17]) compared with sham (61% [11/18]; RR 0.299, CI 0.097 to 0.8597; p=0.015)[8].

Laser energy dose and wavelength

The SR of 18 RCTs reported that OM symptom reduction was larger but not statistically significantly different in studies using laser energy greater than 4 joule/cm^2 compared to lower levels of energy (p=0.06)[1].

The SR of 11 RCTs included an MA (5 RCTs, n=180) that reported a statistically significantly lower incidence of OM above grade 2 (assessed using the oral mucositis index [OMI] and WHO OM scales) in patients having prophylactic LLLT with energy levels above 1 joule compared with SMC or sham (RR 2.56, 95% CI 1.73 to 3.79, p<0.00001; I^2=32%). In 1 RCT (n=60) in the SR the incidence of OM above grade 2 was not statistically significantly different in patients having prophylactic LLLT with energy levels below 1 joule compared with SMC or sham (RR 0.50, 95% CI 0.23 to 1.08, p=0.08). An MA of 6 RCTs (n=240) in the SR reported the effect of prophylactic LLLT according to laser wavelength (red or infrared) compared with sham. The incidence of OM was statistically significantly lower in patients who had prophylactic LLLT using wavelength in the red spectrum (630 to 670 nanometres) compared with sham only (SMD 1.22, 95% CI 0.38 to 2.06, p=0.004; I^2=82%; 4 RCTs, n=157). Similarly, the incidence of OM was statistically significantly lower in patients having prophylactic LLLT using wavelength in the infrared spectrum (780 to 830 nanometres) compared to cancer treatment only (SMD 1.53, 95% CI 0.19 to 2.87, p=0.02; I^2=87%; 3 RCTs, n=102). Overall, regardless of laser wavelength, the incidence of OM was statistically lower in patients who had prophylactic LLLT compared with sham (SMD 1.33, 95% CI 0.68 to 1.98, p<0.00001; I^2=81%)[2].

In an RCT of 70 patients with oral or oropharyngeal cancers treated by RT or ChT, or by both, mean severity of OM assessed by the WHO scale was statistically significantly lower in patients who had prophylactic and therapeutic LLLT using power of 15 milliwatt and energy density of 3.8 joule/cm^2 (group 1) compared with patients who had LLLT power 5 milliwatt, energy density 1.3 joule/cm^2 (group 2) at week-2 follow-up (p=0.019), week-3 (p=0.005) and week-4 (p=0.003). Mean severity of OM assessed by the NCI scale was statistically significantly lower in patients in group 1 than group 2 on week 2 (p=0.009) and week 4 (p=0.013)[4].

Duration of OM

The SR of 18 studies included an MA (3 RCTs, n=361) reporting that patients having prophylactic LLLT had statistically significantly shorter duration of severe OM (grade 3 or 4) compared with sham or no treatment (WMD -5.32, 95% CI -9.45 to -1.19, I^2=94%, p=0.01)[1].

The SR of 11 RCTs included an MA (5 RCTs, n=157) reporting a statistically significant reduction in the duration of OM in patients having prophylactic or therapeutic LLLT compared with sham (mean difference [MD] 4.38, 95% CI 3.35 to 5.40, p<0.00001; I^2=22%)[2].

In the RCT of 46 patients, duration of severe OM (grade 3 or 4) was statistically significantly shorter in patients in the prophylactic LLLT group (10.5 days) compared with sham (16.1 days, p=0.048)[6].

Oral mucosa pain reduction

The SR of 18 RCTs included an MA (7 RCTs, n=591) reporting no statistically significant difference in incidence of oral pain between patients having prophylactic LLLT and patients having sham or no treatment (RR 0.89, 95% CI 0.76 to 1.04, I^2=96%, p=0.15). The same SR reported an MA of 2 RCTs (n=331) in which the incidence of severe pain (VAS score greater than 7) was statistically significantly lower in patients who had prophylactic LLLT compared with sham or no treatment (RR 0.26, 95% CI 0.18 to 0.37, I^2=0%, p<0.0001). An MA of 5 RCTs (n=222) reported statistically significantly lower overall mean pain scores in patients having prophylactic LLLT compared with sham or no treatment (WMD -2.46, 95% CI -4.41 to-0.77, I^2=97%, p=0.004). Another MA of 5 RCTs (n=530) reported statistically significantly lower opioid requirements in patients having prophylactic LLLT compared with sham or no treatment (RR 0.47, 95% CI 0.37 to 0.60, I^2=0%, p<0.0001)[1].

The SR of 11 RCTs on head and neck cancer patients included an MA (2 RCTs, n=55) reporting a statistically significantly lower level of pain in patients having therapeutic LLLT using a dose greater than 2 joules, compared with SMC only (SMD 2.17, 95% CI 1.48 to 2.86, p<0.00001; I^2=0%). One RCT (n=47) in the SR reported that this difference was not statistically significant in patients having prophylactic LLLT using energy dose smaller than 2 joules, compared with the SMC group (SMD 0.38, 95% CI −0.19 to 0.96, p=0.19). An MA of 3 RCTs (n=102) in the SR reported a statistically significant reduction in pain scores in patients having prophylactic or therapeutic LLLT (any energy level) compared with SMC only (SMD 1.22, 95% CI 0.68 to 1.56, p<0.00001; I^2=93%)[2].

In the RCT of 123 children who developed ChT-induced OM, median pain scores were statistically significantly lower in the therapeutic LLLT group on day 4 after completing the LLLT treatment cycle (p=0.002) and on day 7 of follow-up (p=0.0005) compared with sham[3].

In the RCT of 48 patients having first-time ChT for head and neck cancer, pain scores were statistically significantly lower for all patients having prophylactic LLLT compared with sham at week-2 follow-up (LLLT 0.7, CI 0.16 to 1.6; sham 6.8, CI 5.7 to 8.0; p=0.001), week-8 (LLLT 0.8, CI 0.13 to 1.8; sham 6.24, CI 5.17 to 7.3; p=0.001) and at the final follow-up in week 14 (LLLT 0.2, CI 0.16 to 0.73; sham 4.6, CI 3.2 to 5.9; p=0.001)[5].

In the RCT of 46 patients, severe pain (VAS score above 7) was statistically significantly less frequent in patients in the prophylactic LLLT group (8% [2/22]) compared with sham (50% [12/24], p=0.023). In the same RCT, duration of severe pain (VAS more than 7) was statistically significantly shorter in patients in the prophylactic LLLT group (10.0 days) compared with sham (16.5 days, p=0.028). Opioid requirements were also lower in patients having prophylactic LLLT before ChT (8% [2/22]) compared with sham [36% (9/24]), but the difference was not statistically significant[6].

In the RCT of 35 patients, severe pain (VAS more than 7) on the day of worse pain was statistically significantly less frequent in patients having prophylactic LLLT (20% [2/10]) compared with the sham group (73% [11/15], p=0.025). In the same RCT, the number of patients free of severe pain at appearance of the OM was not statistically significantly different between patients having prophylactic LLLT and those having sham[8].

Cancer treatment interruption

The SR of 18 studies included an MA of 5 RCTs (n=560) reporting a statistically significantly lower incidence of unplanned RT interruption due to OM in head and neck cancer patients having prophylactic LLLT, compared with sham or no treatment (RR 0.23, 95% CI 0.12 to 0.44, I^2=0%, p<0.0001)[1].

Dry mouth

In the RCT of 48 patients having first-time ChT for head and neck cancer, xerostomia was statistically significantly lower for the whole duration of ChT in patients having LLLT compared with sham at week-2 follow-up (LLLT 1.16, CI 0.7 to 1.5; sham 3.5, CI 3.05 to 3.95; p=0.001), week-8 (LLLT 1.8, CI 1.4 to 2.26; sham 3.25, CI 2.5 to 3.9; p=0.001) and at the final follow-up in week 14 (LLLT 1.5, CI 0.9 to 2.07; sham 2.75, CI 2.15 to 3.34; p=0.001)[5].

Total parenteral nutrition (TPN) requirements

In the RCT of 46 patients having cancer treatment, there was no statistically significant difference in TPN requirements between patients in the prophylactic LLLT group (17%) compared with sham (36%, p=0.677), or in the duration of TPN requirements (12.5 days in the prophylactic LLLT group, 14.3 days in the sham group, p=0.461)[6].

Weight loss

In the RCT of 46 patients, weight loss was statistically significantly less in patients in the prophylactic LLLT group (2.58 kg) compared with sham (5.57 kg, p=0.004)[6].

Safety summary

No major safety events related to the use of LLLT to treat OM were found in the literature. The SR of 11 RCTs, which reported the effects of LLLT in reducing OM in 415 patients treated by ChT or RT for head and neck cancer, stated that all the included 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 by patients.

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers listed no anecdotal adverse events. They considered that the following were theoretical adverse events: eye injury and increased risk of disease persistence and recurrence.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to low-level laser therapy for prevention or treatment of oral mucositis secondary to radiotherapy or chemotherapy. The following databases were searched, covering the period from their start to July 2017: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with oral mucositis.
Intervention/test	Low-level laser therapy for prevention or treatment of oral mucositis secondary to radiotherapy or chemotherapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 1,682 patients from 2 systematic reviews and meta-analysis[1,2], 6 randomised control trials[3-8] and 1 case series[7].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on low-level laser therapy for prevention or treatment of oral mucositis secondary to radiotherapy or chemotherapy

Study 1 Oberoi S (2014)

Details

Study type	**Systematic review and meta-analysis**
Country	US
Recruitment period	Databases searched up to 2014
Study population and number	**18 RCTs, 1,144 patients** receiving prophylactic LLLT compared to sham or no treatment
Age and sex	Adult and paediatric population
Patient selection criteria	Inclusion criteria: - Randomised or quasi-randomised studies - Studies reporting on patients with cancer or being treated by haematopoietic stem cell transplantation Exclusion criteria: - Allocation not randomly assigned - Absence of placebo or no treatment group - Randomisation was done to chemotherapy cycles or left and right buccal mucosa within a patient (rather that randomising patients) - Duplicate publications
Technique	RCTs compared patients treated by LLLT to no treatment or sham.
Follow-up	**5 days to 7 weeks**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

Study design issues: The Cochrane collaboration tool for assessment of bias in publications was used. Two authors were responsible for sifting the literature and extracting the data. Agreement between reviewers was high (kappa 0.89, 95% CI 0.78 to 1.0). A third author resolved discrepancies.

The primary outcome was the overall incidence or OM measured by the WHO, RTOG, NCI CTC and Tardieu OM classification scales. Grades 2 and 3 on the Tardieu scale are similar to grades 3 and 4 according to the other mucositis grading scales, higher score meaning more OM. Secondary outcomes were incidence of severe OM at the time-point when maximum OM was expected, overall mean OM grade or score over the observation period and duration of severe OM.

Study population issues: Half of the trials were published in Brazil, 8 in head and neck patients receiving chemo or radiotherapy and the remaining in other patients receiving chemotherapy. One study was solely paediatric (Cruz 2007) and 4 studies (Hodgson 2012b, Silva 2011, Khouri 2009 and Schubert 2007) reported on a paediatric and adult population. Intraoral laser therapy was used in all trials except (Hodgson 2012a and Hodgson 2012b).

The InGaAIP laser was used in 6 trials and the HeNE laser in 5 trials.

Thirteen studies had random sequence generation, 4 had allocation concealment, 13 had blinding on participants and personnel, 15 had blinding of outcome assessor, 15 had incomplete outcome data and 13 had selective outcome report.

Other issues: The researchers produced a funnel plot that reported potential for publication bias with absence of studies in the right lower quadrant. When attempting to account for this using a “trim and fill” technique, the effect of LLLT of severe mucositis was still statistically significant (RR 0.51, 95% CI 0.29 to 0.90, p=0.0197).

The papers by Bensadoun 1999, Arun-Maiya 2006, Schubert 2007, Cruz 2007, Antunes 2007 and Chor 2009 were also reported by paper 2 in table 2.

Author	Underlying condition	Setting	n	Wave-length (mm)	Power (mW)	Dose (J)	Irradiation time per spot (sec)	Type of laser	Laser schedule	OM assessment	Scale
Antunes 2013	Head and neck cancer	Chemo-radio	94	660	100	1	10	InGaAlP	5 sessions/week during radiation	Daily	WHO and OMAS
Arbabi-Kalati 2013	Oncologic disorders	Chemo	48	630	30	NA	NA	Mustang	Prior to chemotherapy	2 times/week	WHO
Gautam 2012 (a)	Head and neck cancer	Chemo-radio	239	632.8	24	3	125	He-Ne	5 sessions/week x45days	Weekly	RTOG/EORTC
Gautam 2012 (b)	Oral carcinoma	Chemo-radio	121	632.8	24	3.5	145	He-Ne	5 sessions/week during radiation	Weekly	RTOG/EORTC
Gouvea de Lima 2012	Head and neck cancer	Chemo-radio	75	660	10	0.1	10	GaAlAs	5 sessions/week during radiation	Every 2 weeks	NCI CTCv2
Hodgson 2012 (a)	Haematological, oncologic disorders	HSCT (allo, auto)	40	670	50	4	80	Infrared LED	Daily from day 0 to 14	3 times/week	WHO, NCI CTCAE and OMAS
Hodgson 2012 (b)	Multiple myeloma	HSCT (auto)	40	670	50	4	80	Infrared LED	Daily from day 0 to 14	3 times/week	WHO, NCI CTCAE and OMAS
Oton-Leite 2012	Head and neck cancer	Radio or Chemo-radio	60	685	35	0.8	25	InGaAlP	5 sessions/week during radiation	Mid and at the end of treatment (week 3 and week 6)	WHO
Pires-Santos 2012	Breast cancer	Chemo	12	NA	NA	NA	NA	NA	Day 0 to day 7 q 48 hours	NA	NA
Silva 2011	Haematological, oncologic disorders	HSCT (allo, auto)	42	660	40	0.16	4	InGaAlP	Daily from day -4 to day 4	Daily	WHO
Chor 2010	NA	HSCT (auto)	34	660	50	NA	NA	AsGaAl	Daily from -7 to day 0	Daily	Tardieu
Khouri 2009	Haematological disorders	HSCT (allo)	22	660 and 780	25	0.25	10	InGaAlP and GaAlAs	Daily until day 15 or day of engraftment	NA	WHO and OMAS
Antunes 2007	Haematological disorders	HSCT (allo, auto)	38	660	46.7	0.8	16.7	InGaAlP	Daily from day -7 until neutrophil recovery	Daily	WHO and OMAS
Cruz 2007	Haematological and solid malignancies	Chemo or HSCT (auto)	62	780	60	NA	NA	NA	Daily from start of chemo x5 days	Day 8 and day 15	NCI CTC
Schubert 2007	Hematologic and solid malignancies	HSCT (allo, auto)	47	650	40	0.08	2	GaAlAs	Daily from day -1 of conditioning to day 2	2 times/week	OMI
Arun Maiya 2006	Oral carcinoma	Radio	50	632.8	10	108	180	Ne-He	5 sessions/week during radiation	once at the end of treatment (week 6)	WHO
Lopes 2006	Head and neck cancer	Chemo-radio	60	685	35	2	58	InGaAlP	NA	Pre-treatment, 4 weeks and at the end of therapy	NCI CTC
Bensadoun 1999	Head and neck cancer	Radio	30	632.8	60	2	33	Ne-He	5 sessions/week during radiation	Weekly	WHO
Cowen 1997	Haematological Malignancies	HSCT (auto)	30	632.8	60	0.6	10	Ne-He	Daily from day -5 to day -1	Daily	Tardieu

Key efficacy and safety findings

Efficacy	Safety
n=18 studies, 1,144 patients	None reported

Incidence of OM

The absolute risk reduction of severe mucositis with LLLT was RR -0.35, 95% CI -0.48 to -0.21, p<0.0001 resulting in a number needed to treat of 3 patients to prevent 1 episode of severe OM.

Studies using intraoral laser reported a larger reduction in the risk of OM (RR 0.29, 95% CI 0.19 to 0.42) compared to studies using extraoral laser therapy (RR 1.19, 95% CI 0.80 to 1.78), p<0.0001.

Outcome	Number of studies	Number of patients	Effect	95% CI[a]	I^2	p
Overall incidence of severe (grade 3 or 4) mucositis*	10	689	RR 0.37	0.20 to 0.67	80%	0.001
Incidence of severe (grade 3 or 4) mucositis at anticipated time of maximal mucositis	6	546	RR 0.34	0.20 to 0.59	62%	0.0001
Overall mean grade of mucositis	8	603	SMD -1.49	-22.02 to -20.95	86%	<0.0001
Duration of severe (grade 3 or 4) mucositis	3	361	WMD -5.32	-9.45 to -1.19	94%	0.01
Incidence of any pain	7	591	RR 0.89	0.76 to 1.04	96%	0.15
Incidence of severe pain (VAS>7)	2	331	RR 0.26	0.18 to 0.37	0%	<0.0001
Overall mean pain scores	5	222	WMD -2.46	-4.41 to -0.77	97%	0.004
Number of patients requiring opioid analgesia	5	530	RR 0.47	0.37 to 0.60	0%	<0.0001
Unplanned radiotherapy interruption due to mucositis in head and neck cancer patients	5	560	RR 0.23	0.12 to 0.44	0%	<0.0001

There was no correlation between age or underlying condition and the effect of LLLT.

Symptoms reduction was larger in studies using energy >4 J/cm^2 compared to ≤4 J/cm^2, p=0.06.

Studies with an unclear or inadequate allocation concealment showed larger treatment effect (p=0.03).

*excluding the only study using the Tardieu scale did not affect the estimate of LLLT treatment (RR 0.34, 95% CI 0.20 to 0.67, p=0.001)

[a]All analysis used a random-effects model. RR<1, SMD or WMD<0 with 95% CI that do not include 1 or 0 respectively, suggest LLLT is better than placebo or no therapy.

** Maximum anticipated mucositis was week 6±1 in head and neck cancer radiotherapy/chemo-radiotherapy trials and day 10±4 in chemotherapy and HSCT trials (from date of chemotherapy initiation and stem cell infusion respectively).

Abbreviations used: CI, confidence interval; HeNe, helium neon; HSCT, haematopoietic stem cell transplantation, InGaAIP, gallium aluminium arsenide/arsenate; LLLT, low level laser therapy; NCI CTC, National Cancer Institute common terminology criteria; OM, oral mucositis; RCT, randomised control trial; RR, Risk ratio; RTGO, Radiation Therapy Oncology Group; SMD, standardised mean difference; VAS, visual analogue scale; WHO, World Health Organisation; WMD, weighted mean difference.

Study 2 Bjordal JM (2011)

Details

Study type	**Systematic review and meta-analysis**
Country	Norway
Recruitment period	Included studies were published between 1997 and 2009
Study population and number	**11 RCTs, 415 patients** receiving prophylactic or treatment LLLT were compared to sham
Age and sex	Not reported
Patient selection criteria	Inclusion criteria - Randomised studies, randomised parallel group design or crossover design - Diagnosis of OM in cancer patients after chemo or radiotherapy - LLLT with wavelengths of 632 to 1,064 nm, treating the mucosa of the oral cavity - Outcome assessors should be blind - Controls receiving laser placebo
Technique	Synthesis of randomised placebo-controlled trials studying the use of LLLT before and done during chemotherapy or radiation therapy in head and neck cancer patients.
Follow-up	**Not reported.**
Conflict of interest/source of funding	The authors of the synthesis reported no conflict of interest. The manufacturers sponsored the studies by Kuhn 2009 and Bensadour 1999.

Analysis

Follow-up issues: Studies aiming at preventing OM started LLLT 7 days before cancer treatment.

Study design issues: Methodological quality of the papers was 4.10 (SD±0.74) on the 5-point Jadad scale. A random effects model was used if heterogeneity was present in heterogeneity tests, a fixed effect model was used otherwise.
Outcome measures:

- The relative risk of LLLT over placebo for preventing occurrence of OM above 0 to 2 (OMI or WHO)
- The effect of LLLT on the severity of OM measured by the OMI or WHO 3.
- The effect of LLLT on the duration of OM (calculated as MD)
- The effect of LLLT on pain intensity was calculated as SMD versus placebo and labelled after Cohen as “poor” (0.2 to 0.5), “good” (0.5 to 0.8), or “very good” >0.8
- 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)

Study population issues:

Author	Setting	n	Wave-length (mm)	Laser output (mW)	Dose (J)	Spot size (cm^2)	Irradiation time per spot (sec)
Cowen 1997	Chemo/radio	30	633	30	3.5	0.5	105
Bensadoun 1999	Radiation	30	633	60	2	0.5	33
Arun-Maiya 2006	Radiation	50	633	10	4	1.0	600
Schubert 2007	Transplant	70	650/780	40/60	2	0.04	33-55
Cruz 2007	Chemo/child	60	633	50	0.18	0.04	3
Kuhn 2007	Chemo	34	830	100	6	0.06	54
Antunes 2007	Transplant	38	660	47	4	0.2	17
Genot-Klastersky 2008	Chemo	36	650	100	5	0.45	33
Kuhn 2009	Chemo/child	21	830	100	6	0.06	56
Abramov 2009	Chemo	22	685	35	3	0.5	54
Chor 2009	Chemo	24	660	50	2	?	40

Other issues: None

Key efficacy and safety findings

Efficacy	Safety
n=11 RCTs, 415 patients Risk ratio for occurrence of cancer therapy induced OM above grades 0 to 2 after LLLT (prevention of OM) ***Subgroup dose > 1J*** Risk ratio 2.56 95% CI 1.73 to 3.79, p<0.00001; I^2=32%, p=0.21 [5 RCTs, n=180, favours LLLT] ***Subgroup dose < 1J*** Risk ratio 0.50, 95% CI 0.23 to 1.08, p=0.08 [1 RCT, n=60, not significant] ***Overall risk ratio (all doses)*** Risk ratio 2.03 95% CI 1.11 to 3.69, p=0.02; I^2=75%, p=0.001 [6 RCTs, n=240, favours LLLT] Relative risk of OM occurrence by timing of treatment LLLT (prevention of OM) ***LLLT started before cancer treatment*** RR 1.82 95% CI 1.08 to 3.05, p=0.02; I^2=0%, p=0.33 [2 RCTs, n=56, favours LLLT] ***LLLT before and during cancer treatment*** RR 2.43, 95% CI 1.32 to 4.46, p=0.004 [1 RCT, n=38, favours LLLT] ***LLLT during cancer treatment only*** RR 3.86, 95% CI 2.27 to 6.56, p<0.00001, I^2=0%, p=0.53 [2 RCTs, n=86, favours LLLT] ***Relative risk for prevention of OM (overall)*** RR 2.72, 95% CI 1.98 to 3.74, p<0.00001; I^2=32%, p=0.21 [5 RCTs, n=180, favours LLLT] Subgroup analysis of LLLT wavelength effects on the relative risk of OM after LLLT (prevention of OM) ***Wavelengths red (630 to 670 nm)***[1] SMD 1.22, 95% CI 0.38 to 2.06, p=0.004; I^2=82%, p=0.0008 [4 RCTs, n=157, favours LLLT] ***Wavelengths infrared (780 to 830 nm)***[1] SMD 1.53, 95% CI 0.19 to 2.87, p=0.02; I^2=87%, p=0.0005 [3 RCTs, n=102, favours LLLT] Between group SMD were not statistically significantly different (p=0.99) ***Overall LLLT effect*** SMD1.33, 95% CI 0.68 to 1.98, p<0.00001; I^2=81%, p<0.0001 [7 RCTs, n=259, favours LLLT] Dose analyses of anticipated optimal dose ranges by wavelength effect on pain ***Dose ≥ 2J*** [*] SMD 2.17, 95% CI, 1.48 to 2.86, p<0.00001; I^2=0%, p=0.89 [2 RCTs, n=55, favours LLLT] ***Dose ≤ 2J **** SMD 0.38, 95% CI, −0.19 to 0.96, p=0.19 [1 RCT, n=47, not significant] ***Overall effect on pain*** SMD 1.22, 95% CI 0.68 to 1.56, p<0.00001; I^2=93%, p<0.0001 [3 RCTs, n=102, favours LLLT] Overall effect on duration of OM MD 4.38, 95% CI 3.35 to 5.40, p<0.00001; I^2=22%, p=0.28 [5 RCTs, n=157, favours LLLT] Overall effect on OM severity SMD 1.33, 95% CI, 0.68 to 1.98, p<0.0001; I^2=81%, p<0.0001. [7 RCTs, n=259, favours LLLT] [1]Test for between group differences I^2=0%, p=0.99 *Test for between group differences I^2=93%, p<0.00001	All studies investigated adverse events but none found there were side effects beyond those reported for placebo LLLT. Five trials reported explicitly that LLLT was well tolerated among patients.
Abbreviations used: CI, confidence interval; J, Joules; LLLT, low level laser therapy; MD, mean difference; nm, nanometres; OM, oral mucositis; OMI, oral mucositis index; RCT, randomised control trial; RR, relative risk; SD, standard deviation; SMD, standardised mean difference; WALT, World Association for Laser Therapy; WHO, World Health Organisation.	

Study 3 Amadori F (2015)

Details

Study type	**RCT**
Country	Italy
Recruitment period	January 2012 to December 2013
Study population and number	**n=123 (62 LLLT, 61 sham)**, children with haematological malignancies, solid tumours or HSCT treated by LLLT or sham for OM
Age and sex	LLLT – 9.8±3.25, 44% (27/62) males Sham controls – 9.27±3.85, 48% (29/61) males
Patient selection criteria	Patients treated at a paediatric dentistry department in Brescia, Italy and presenting with OM grade 2 or greater assessed by the WHO common toxicity criteria (0=no functional limitation to 4=oral feeding is impossible). Exclusion criteria: - Patients with reduced mouth opening (less than 1 cm^2) - Patients with oral dysplastic lesions - Patients who had head and neck radiotherapy in the previous 4 weeks
Technique	Patients in the LLLT group were treated with a handle diode laser (DioBeam 830, CMS dental, Denmark). The laser was applied intraorally (buccal mucosa, lips, tongue, floor of mouth and soft palate) with 830 nm wavelength, power 150 mW, spot size 1 cm^2, 30 s per cm^2, energy density 4.5 J/cm^2. LLLT was started on day 1 of OM diagnosis and continued for 3 consecutive days (4 in total). The laser was dispensed during hospitalisation, discharged patients continued LLLT as outpatients. No patient with OM >2 was discharged.
Follow-up	**7 days**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Assessment of OM happened on day 1 (T0, day of diagnosis), day 4 (T1, after finishing LLLT therapy cycle) and on day 7 (T2, follow-up).

Study design issues: Patients were randomised by a computer. Dentists who applied LLLT did not participate in OM scoring. Pain was assessed using a VAS with drawn faces (1=no pain to 10=most severe pain). A sample of 100 patients was deemed necessary to estimate a 70% of success in patients treated by LLLT at day 7 and 40% in the sham control group, power 80%, α=0.05, β=0.2.

Study population issues:

OM appeared at a mean of 5.9 days after the beginning of chemotherapy (range 4 to 8 days).

Disease	**LLLT**	**Sham controls**
Leukaemia and lymphoma	38	34
Solid tumours	6	7
HSCT	18	20

Other issues: Allocation concealment not reported. Procedure in the sham treatment group was not described.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>

n=123 (62 LLLT, 61 sham)

<u>Median OM grading</u>

	LLLT group	Sham controls	p
T0	3	3	0.8
T1	2	2	0.65
T2	0	1	0.07

<u>Median pain scores</u>

	LLLT group	Sham controls	p
T0	4	4	0.9
T1	1	2	0.002
T2	0	1	0.0005

During the study period, children treated with laser therapy required less additional analgesia (paracetamol, tramadol or morphine) compared to sham controls, p<0.05.

</td><td>None reported.</td></tr>
<tr><td colspan="2">Abbreviations used: CI, confidence interval; HeNe, helium neon; HSCT, haematopoietic stem cell transplantation, InGaAIP, gallium aluminium arsenide/arsenate; LLLT, low level laser therapy; NCI CTC, National Cancer Institute common terminology criteria; OM, oral mucositis; RCT, randomised control trial; RR, Risk ratio; RTGO, Radiation Therapy Oncology Group; VAS, visual analogue scale; WHO, World Health Organisation.</td></tr>
</table>

Study 4 Carvalho PA (2011)

Details

Study type	**RCT**
Country	Brazil
Recruitment period	2008 to 2009
Study population and number	**n= 70 (35 group 1, 35 group 2)** prevention and treatment of OM in patients with malignant neoplasms of the oral cavity or oropharynx
Age and sex	**Group 1** – Mean 55.2±4.5 years (22 to 94), 71% males **Group 2** – Mean 58.1±10.1 Years (35 to 79), 60% males
Patient selection criteria	Inclusion criteria: - Malignant neoplasm of the oral cavity or oropharynx - Submitted to conventional 3D-RTC or IMRT with doses of facial fields equal or higher than 4000 cGy either exclusively or in association with chemotherapy (cisplatin 100 mg/m^2 every 21 days or 50 mg/m^2 per week) Exclusion criteria: - Patient previously submitted to RT
Technique	LLLT was delivered using a InGaAIP diode laser (Twin laser – MMOptics, Brazil). The device and light colour were identical in both groups, time of illumination per anatomic site was 10 seconds. Treatment was provided 5 consecutive days per week starting on the first day of RT (always before RT). Tumour areas were avoided. **Group 1** – continuous 660 nm wavelength, power 15 mW, energy density 3.8J/cm^2, spot size 4 mm^2 **Group 2** – continuous 660 nm wavelength, power 5 mW, energy density 1.3 J/cm^2, spot size 4 mm^2 All patients in the study received preventative LLLT. Patients who developed OM grade 2 began curative laser therapy (in both groups) using a different device: wavelength 660 nm, power 15 mW, energy density 3.8J/cm^2, spot size 4 mm^2. Patients were analysed in the group they had been allocated to. All patients completed an oral care protocol before starting RT including oral examination, preventative dental treatments, instructions for oral care during RT, and were prescribed mouthwashes and fluoride.
Follow-up	**7 weeks**
Conflict of interest/source of funding	None.

Analysis

Follow-up issues: In group 1, 2 patients failed to attend the LLLT sessions, 1 patient changed chemotherapy scheme, 1 patient died and 4 patients were randomised but did not start RT before the end of the study.

In group 2, 23% (8/35) of patients were excluded from the study, of which 4 missed the LLLT without justification, 1 altered the treatment due to local recurrence, 1 had gastrostomy complications, 1 died and 1 was randomised but did not start RT until study was finished.

Study design issues: Double-blind block randomised control clinical trial (blocks of 6), sealed envelope concealment. Patients were stratified by chemotherapy group.

OM was assessed on a daily basis using the NCI and WHO scales. Pain was assessed up to the 30th day of RT using a VAS (0=no pain, 10=maximum pain)

Study population issues: In group 1, 69% (24/35) of patients had cancer in the oral cavity and 31% (11/35) in the oropharynx. Fourteen patients had surgery and RT, 10 had surgery followed by chemotherapy and RT, 8 had chemotherapy and RT and 3 had RT only.

In group 2, 71% (25/35) of tumours were located in the oral cavity and 29% (10/35) in the oropharynx. Twelve patients had surgery and RT, 17 had surgery followed by RT and chemotherapy, 5 had RT and chemotherapy and 1 was treated by RT only.

Other issues: RT was interrupted in 6 patients in group 2 and 1 in group 1 (due to OM). This interruption may have improved the symptoms of OM in these patients. No sample size power calculation was reported. Allocation concealment not reported.

Key efficacy and safety findings

Efficacy	Safety
n= 70 (35 group 1, 35 group 2)	None reported.

Daily evolution of OM

	Group 1	Group 2	p
Days to develop Grade 2 OM (mean)			
WHO scale	13.5± 5.7	9.8±2.8	0.005
NCI scale	13.5±5.7	9.8±2.6	0.005
Days to develop Grade 3 OM (mean)			
WHO scale	23.6±7.2	17.1±6.0	0.014
NCI scale	19.1±6.9	17.5±7.5	0.498

Weekly evolution of OM

Week	n	Group 1		Group 2		P (WHO)	P (NCI)
		Mean (WHO)	Mean (NCI)	Mean (WHO)	Mean (NCI)		
1	27	0.00±0.00	0.00±0.00	0.11±0.42	0.11±0.42	-	-
2	27	0.78±0.93	0.78±0.93	1.41±0.93	1.56±1.09	0.019	0.009
3	27	1.59±0.97	1.74±1.10	1.74±1.10	2.33±0.48	0.005	NS
4	27	1.52±0.85	1.63±0.97	1.63±0.97	2.33±0.88	0.003	0.013
5	27	1.85±0.28	1.93±0.87	1.93±0.87	2.22±0.89	NS	NS
6	27	2.15±0.72	2.15±0.77	2.15±0.77	2.26±0.98	NS	NS
7	17	2.35±0.61	2.44±0.62	2.44±0.62	2.12±0.86	NS	NS

Group 2 presented a significantly higher mean WHO OM grade than Group 1 in weeks 2 (p=0.019), 3 (p=0.005) and 4 (p=0.003).

Group 2 presented a significantly higher mean NCI OM grade than Group 1 in weeks 2 (p=0.009) and 4 (p=0.013).

The percentage of patients presenting with grade 1 (WHO and NCI scales) was higher in Group 1 than in Group 2. The opposite occurred for grades 2, 3 and 4, p values not reported.

Only 1/35 patient had grade 4 WHO OM (occurring at week 5) in Group 1, compared to 17% (6/35) in Group 2.

Pain

The mean intensity of pain was always higher in patients in Group 2, p=0.004

Abbreviations used: 3D-RTC, 3 dimension conformal radiotherapy; IMRT, intensity modulated radiotherapy; InGaAIP, gallium aluminium arsenide/arsenate; LLLT, low level laser therapy; NCI, National Cancer Institute; OM, oral mucositis; NS, not significant RCT, randomised control trial; RT, radiotherapy; VAS, visual analogue scale; WHO, World Health Organisation.

Study 5 Arbabi-Kalati F (2013)

Details

Study type	**RCT**
Country	Iran
Recruitment period	2008 to 2009
Study population and number	**n=48 patients** (24 LLLT, 24 sham) having first-time chemotherapy for head and neck cancer had prophylactic LLLT or sham
Age and sex	**LLLT group** – Mean 44.5 ± 4.04, 50% (12/24) males **Sham** – 46.2 ± 4.4, 50% (12/24) males
Patient selection criteria	Inclusion criteria: - Chemotherapy treatment regimen with the same mucositis probability - Karnofsky performance status case ≥60 - Life expectancy ≥6 months - White blood cell count ≥1500 cell/ml and platelet count ≥100,000/ µL (microliters). Exclusion criteria - Previous or ongoing radiotherapy in the head or neck including nasopharynx, oropharynx and larynx - Previous head and neck cancer due to malignancy - Denture use, pregnancy and infection.
Technique	Prior to each episode of chemotherapy patients were treated by LLLT using 630 nm low power laser with 30 mW output power, energy dose of 5 J/cm^2. The irradiated areas included 10 spots in the oral cavity, 2 on the cheeks, 2 on the tongue, 2 on the floor of the mouth, 1 on the soft palate and 1 on the hard palate. All patients were instructed in oral hygiene practices and were asked to avoid alcohol, smoking, hot or cold drinks, and very spicy, acidic and tough foods during chemotherapy.
Follow-up	**14 weeks**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Patients in both groups were followed until the end of the chemotherapy phase. Subjects were assessed before the start of chemotherapy, 2 weeks after chemotherapy start and every 2 weeks until its end.

Study design issues: Double blind RCT, procedure was carried out with the laser ‘off’ during the same period in the sham group. The clinicians assessing patients were blinded to allocation group. The study used block randomisation groups (4 blocks).

OM was graded using the WHO criteria. Pain was evaluated based on a VAS (0= no pain, 10= severe pain). Xerostomia was assessed using the LENT SOMA scale.

Study analysis used Mann-Whitney U-tests, p values were mentioned as 0.0005 for prevention of repeated measurement error (α was divided by 10).

No patients had mucositis at baseline.

Study population issues: Tumour site was lung 17% (4/25), lymphoma 8% (2/24), GI 8% (2/24) skin 1% (1/24), breast 63% (15/24) in the LLLT group; and lung 17% (4/24), GI 33% (8/24), skin 8% (2/24) and breast 42% (10/24).

There were no differences in xerostomia level at baseline between groups (p=0.13).

Other issues: No sample size power calculations were reported. Allocation concealment was not reported.

Key efficacy and safety findings

Efficacy	Safety
n=48 patients OM intensity, xerostomia and pain (see table below) Mucositis, xerostomia and pain scores were statistically significantly inferior in the LLLT group than in the sham for all the duration of chemotherapy, p=0.001.	None reported.
Abbreviations used: LENT/SOMA, late effects of normal tissues/subjective objective management analytic; LLLT, low level laser therapy; GI, gastrointestinal; OM, oral mucositis; RCT, randomised control trial; VAS, visual analogue scale.	

OM intensity, xerostomia and pain

	Week 2	**Week 8**	**Week 14**
Mucositis			
LLLT	0.25 (0.13 to 0.6)	0.5 (0.13 to 1.1)	0.3 (0.05 to 0.8)
Sham	2.28 (1.9 to 2.5)	2.20 (2 to 2.40)	1.5 (1.3 to 1.8)
p	**0.001**	**0.001**	**0.001**
Xerostomia			
LLLT	1.16 (0.7 to 1.5)	1.8 (1.4 to 2.26)	1.5 (0.9 to 2.07)
Sham	3.5 (3.05 to 3.95)	3.25 (2.5 to 3.9)	2.75 (2.15 to 3.34)
p	**0.001**	**0.001**	**0.001**
Pain			
LLLT	0.7 (0.16 to 1.6)	0.8 (0.13 to 1.8)	0.2 (0.16 to 0.73)
Sham	6.8 (5.7 to 8)	6.24 (5.17 to 7.3)	4.6 (3.2 to 5.9)
p	**0.001**	**0.001**	**0.001**

Study 6 Gautam AP (2015)

Details

Study type	**RCT**
Country	India
Recruitment period	2009 to 2012
Study population and number	**n=46 (22 LLLT, 24 sham)** head and neck cancer patients having RT had prophylactic LLLT or sham
Age and sex	**LLLT** – 71.57±7.27 years, 91% males **Sham** – 69.67±8.68 years, 79% males
Patient selection criteria	Inclusion criteria: - Recent diagnosis of primary head and neck cancer - Scheduled to be treated by radiotherapy in at last 2/3 of the oral cavity in the radiation field - Age >60 years - ECOG performance score ≤2 (ambulatory and capable of self-care but unable to carry out any work activities greater or equal to 50% of waking hours ; range, 0=fully active to 5=dead) Exclusion criteria - Locked jaw - Medical conditions affecting healing mechanisms such as diabetes - Prior radiation for head and neck cancer - Receiving any chemo-sensitizer - Not receiving high dose radiation to the oral cavity
Technique	Patients were treated with a definitive radiotherapy dose of 66 Grays (2.0 Grays/fraction) given in 33 fractions, 5 days a week for a period of 6.5 weeks using a 6 MV linear accelerator and 3D-CRT. Patient with residual disease were eligible for higher doses of radiation but no patient received doses greater than 72 Grays. Every patient was kept on a standard of oral care and oral hygiene before and during the radiation, (frequent mouth washes with sodium bicarbonate and bland soft diet). If candidiasis was developed antifungal medication was promptly started. Patients in the treatment group received LLLT (helium-neon, λ=632.8 nm, power output =24 mW, power density=0.024 W/cm^2, beam diameter0.6 mm, beam spot size=1cm^2) at 6 anatomical sites in the oral cavity bilaterally excluding cancer site each day just before the radiotherapy session. Energy density of 3.0 J/cm^2 was delivered at each irradiation point of 1 cm^2, irradiation time/point=125 s, total dosage/session=36 to 40 J, 5 sessions/week. Distance between probe and irradiated tissues was <1cm.
Follow-up	**7 weeks**
Conflict of interest/source of funding	Authors have declared financial support from the Department of Atomic Energy-Board of Research in Nuclear Sciences, Indian Government

Analysis

Follow-up issues: There were 49 patients meeting inclusion criteria, 2 patients dropped out (changed treatment) and 1 patient died.

Study design issues: Double blinded computer randomised (number table). Repeated measures were tested using ANOVA. Sample size calculations were done based on the results of a pilot study, primary endpoint severity of OM. Twenty one patients were needed for α=0.05 and β=0.2.The 2 dropouts happened in the first 2 weeks of treatment and were excluded from the analysis.

OM grading used a RTOG/EORTC scale, pain was assessed using a VAS. Use of opioids, TPN, RT breaks and weight changes were also assessed by a blinded assessor.

Study population issues: Baseline characteristic were comparable between comparators. The number of cancers in the oral cavity and oropharynx were similar in the 2 groups.

Other issues: None

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>
n=46 (22 LLLT, 24 sham)
<table>
<tr><th></th><th>LLLT</th><th>Sham</th><th>p</th></tr>
<tr><td>Severe OM (grade 3 or 4)</td><td>18% (4/22)</td><td>58% (14/24)</td><td>0.016</td></tr>
<tr><td>Duration of severe OM</td><td>10.5 days</td><td>16.1 days</td><td>0.048</td></tr>
<tr><td>Severe pain (VAS>7)</td><td>8% (2/22)</td><td>50% (12/24)</td><td>0.023</td></tr>
<tr><td>Duration of severe pain</td><td>10.0 days</td><td>16.5 days</td><td>0.028</td></tr>
<tr><td>TPN requirements</td><td>17% (4/22)</td><td>36% (9/24)</td><td>0.677</td></tr>
<tr><td>Duration of TPN requirements</td><td>12.5 days</td><td>14.3 days</td><td>0.461</td></tr>
<tr><td>Opioid requirements</td><td>8% (2/22)</td><td>36% (9/24)</td><td>Not reported</td></tr>
<tr><td>Weight loss</td><td>2.58 Kg</td><td>5.57 Kg</td><td>0.004</td></tr>
</table>
There were no statistically significant differences in OM scores, pain and weight loss between the 2 groups for the first 2 weeks of RT.
No patient required RT break in any of the comparator groups.
</td><td>None reported</td></tr>
<tr><td colspan="2">Abbreviations used: 3D-CRT, 3-dimensional conformal radiotherapy; ECOG, Eastern Cooperative Oncology group; LLLT, low level laser therapy; OM, oral mucositis; RCT, randomised control trial; RT, radiotherapy, RTOG/EORTC, Radiation Therapy Oncology Group and European Organisation for Research and Treatment of Cancer - Late radiation morbidity scoring scheme; TPN, total parental nutrition; VAS, visual analogue scale.</td></tr>
</table>

Study 7 Genot-Klastersky MT (2008)

Details

Study type	**Case series and RCT**
Country	Belgium
Recruitment period	
Study population and number	<u>Case series</u> – **n=26** adult patients with solid tumours who presented with OM after ChT had LLLT <u>RCT</u> – **n=36 (18 LLLT, 18 sham)** patients with haematological malignancies who developed ChT or RT induced OM had LLLT or sham
Age and sex	<u>Case series</u>: median 51 (32 to 73) years, 23% males <u>RCT</u>: - LLLT: median 56 (range 23 to 73) years, 56% (10/18) males - Sham: median 44 (range 21 to 64) years, 67% (12/18) males
Patient selection criteria	**Case series** <u>Inclusion criteria:</u> - Patients with solid tumours who presented with grade ≥2 OM during a previous course of chemotherapy were eligible for LLLT secondary prevention during the next course for chemotherapy - OM lesions from previous ChT treatment had regressed from 1 to 0 by the time of the study course <u>Exclusion criteria:</u> - Patients having RT, and patients expected to have poor compliance to the treatment schedule (3 sessions a week) **RCT** <u>Inclusion criteria:</u> - Patients with haematological malignancies and OM grade 1 or 2 induced by chemotherapy with or without total body irradiation before HSCT
Technique	In both studies, LLLT was done before cancer treatment with a scanning laser combining a visible 100 mW laser and an infrared laser with power from 50, 250 and 500 mW (Traveller, Biophoton, France). The irradiation was delivered as a continuum beam to the tissues by a straight optical fibre with a 1.2 mm spot size, 2 J/cm^2, 33 s duration per site (estimated 6-minute sessions). **RCT:** Patients were randomised to LLLT or sham (laser was inactivated) and therapy was started 2 hours after the diagnosis of commencing OM and was continued in alternate working days. If OM progressed to grade 3, treatment was considered a failure.
Follow-up	**Case series – median 21 days** **RCT – 7 days**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues:
<u>RCT</u>: 37 patients were included in the therapeutic trial but 1 was ineligible because of absence of OM at randomisation.

Study design issues:
<u>Case series:</u> primary objective was to assess the efficacy of LLLT as secondary prophylaxis on the development of OM grade ≥2. The authors assumed a sample of 26 patients would allow the measurement of a success rate ≥30%, 90% power and α=0.05.

RCT: primary objective was to demonstrate if time to development of OM grade 3 could be delayed by LLLT. The authors assumed that 20 patients would need to be randomised to each group to detect an 10% incidence of grade 3 OM in the LLLT group and 60% in the sham treatment group, 90% 2-sided log rank test, α=0.05.

Of the patients who developed OM grade ≥3 OM in the sham group (16/18), 8 subsequently had LLLT.

In both studies, OM grade assessment used the EORTC scale. Assessment was done before LLLT by the nurse delivering the treatment and then once a week by an independent qualified healthcare professional, blinded to treatment.

Study population issues:

Case series: most of the eligible patients (18/26) had breast cancer and had a wide range of ChT regimens. Twenty-two patients had grade 2 OM during the previous ChT course and 4 had grade 3 OM. That course of chemotherapy was the first ever course of ChT in 10 patients, and the second course in 9 patients.

Other issues:

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>
Case series, n=26
Median time between OM resolution after the previous course of chemotherapy and the first day of preventative LLLT was 6.5 (range 1 to 28) days.
Median duration of LLLT was 21 (range 10 to 90) days.
<u>Efficacy of LLLT</u> – 81% patients (21/26), 95% CI 61 to 93%; from which 15% (4/26) did not present with OM, and 65% (17/26) s had grade 1 OM.
Five patients had ≥grade 2 OM and mean duration of OM development was 10 (range 8 to 14) days.
RCT, n=36 (18 LLLT, 18 sham)
OM grade 3 happened in 16 patients in the sham group and 3 in the LLLT group
<table>
<tr><th></th><th>LLLT</th><th>Sham</th><th>p</th></tr>
<tr><td colspan="4">OM grade</td></tr>
<tr><td>Grade 3</td><td>17% (3/18)</td><td>89% (16/18)</td><td><0.001</td></tr>
<tr><td>Grade 2</td><td>33% (6/18)</td><td>1/18</td><td>-</td></tr>
<tr><td>Grade 1</td><td>50% (9/18)</td><td>1/18</td><td>-</td></tr>
<tr><td>Time to OM grade 3</td><td>7 days</td><td>3 days</td><td><0.0001</td></tr>
</table>
From the 16 patients in the sham group developing grade ≥3 OM, 8 received LLLT. Regression of grade 3 to grade 1 OM occurred in 3 days in the group treated by LLLT and 4 days in the 8 patients that were not treated by LLLT, p value not reported.
</td><td>None reported.</td></tr>
<tr><td colspan="2">Abbreviations used: ChT, chemotherapy; CI, confidence interval. EORTC, European Organisation for Research and Treatment of Cancer; HSCT, haematopoietic stem cell transplantation; LLLT, low level laser therapy; OM, oral mucositis; RCT, randomised control trial; RT, radiotherapy; SCT, stem cell transplantation; VAS, visual analogue scale; WHO, World Health Organisation.</td></tr>
</table>

Study 8 Ferreira B (2016)

Details

Study type	**RCT**
Country	Brazil
Recruitment period	2013 to 2014
Study population and number	**n=35 (17 LLLT, 18 sham)** patients with haematological cancer treated by HSCT had prophylactic LLLT or sham
Age and sex	**LLLT** – mean 42.44±15.59 years, 59% males **Sham** – mean 45.66±9.59 years, 44% males
Patient selection criteria	Inclusion criteria: - ≥18 years of age Exclusion criteria: - HIV positive patients - Already initiated in treatment for OM at the time of the study - Unable to cooperate with the laser treatment (psychiatric or neurologic patients) - Patients who already had OM - Patients treated by whole body irradiation
Technique	All patients had a clinical examination by a dental team. Trauma and sources of infection were excluded by panoramic radiography. During hospitalisation, patients were monitored by a dental surgeon and provided with information on oral hygiene. LLLT was delivered via a InGaAlP laser (Therapy XT-DMC, Brazil), wavelength of 650 nm, power 100 mW, energy per point of 2 J, 27 points of the oral anatomy, time 20 s by point, extremity fiber optic 0.028 cm^2, and energy density 70 J/cm^2. LLLT was applied on the first day of conditioning until day 5. The sham group received simulated laser over the same period. Patients in either group who developed grade 2 OM had LLLT using identical parameters until the lesions had healed completely. They also had the same pain management protocol (oral and subcutaneous opioids).
Follow-up	**15 days**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: There was 1 patient lost to follow-up because he could not receive LLLT due to systemic conditions.

Study design issues: Randomized (computer generated blocks of 6), parallel, superiority trial. Concealment made using opaque envelopes.

A clinician blinded to treatment allocation assessed OM using the WHO OM scale. Pain assessment used a VAS scale (0=no pain, 10=severe pain).

The dentist delivering LLLT was the only member of the team not blinded to treatment.

A sample size of 30 was considered necessary given a 57% absence of OM in the LLLT group and 5% in the sham group, power 80% and α=0.05. The sample was increased by 20% to 36 patients. The analysis was done on an intention to treat basis.

Study population issues: Underlying cancer diagnosis was leukaemia in 41%, lymphoma in 29% and myeloma in 29% of patients in the LLLT group. In the sham group, 39% had leukaemia, 28% lymphoma, 22% myeloma and 11% other forms of haematological cancer. In the LLLT group, 71% of patients was treated by autologous HSCT and 29% by allogenic HSCT. In the sham group, 56% of patients had autologous HSCT and 44% had allogenic.

Other issues: None.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>

n=35 (17 LLLT, 18 sham)

Incidence of OM (grade 2 WHO scale) was 17% (25/35), with no statistically significant difference between the groups (p=0.146).

There were no cases of severe OM in the LLLT group until day 10 post bone marrow transplantation.

The cumulative probability of severe OM in the control group was 0.9 and the time to appearance of lesions was approximately 5 days for controls compared to 11 days in the LLLT group.

Severity of OM and pain

	LLLT	Sham	RR (95% CI)	p[1]
OM, %				
No	41% (7/17)	17% (3/18)	0.705 (0.45 to 1.10)	0.146
Yes	58% (10/17)	83% (15/18)		
Severe OM, %				
No	82% (14/17)	39% (7/18)	0.299 (0.097 to 0.8597)	0.015
Yes	18% (3/17)	61% (11/18)		
Severe pain at appearance of the lesion, %				
No	100% (10/10)	67% (10/15)	-	0.061
Yes	0	33% (5/15)	-	
Severe pain on the day of worse pain, %				
No	80% (8/10)	27% (4/15)	0.27 (0.07 to 0.97)	0.025
yes	20% (2/10)	73% (11/15)		

[1]Fisher exact test

</td><td>None reported.</td></tr>
<tr><td colspan="2">Abbreviations used: CI, confidence interval; HIV, human immunodeficiency virus; HSCT, haematopoietic stem cell transplantation;; InGaAIP, gallium aluminium arsenide/arsenate; LLLT, low level laser therapy; OM, oral mucositis; RCT, randomised control trial; RR, risk ratio; RT, radiotherapy; VAS, visual analogue scale; WHO, World Health Organisation.</td></tr>
</table>

Validity and generalisability of the studies

- There were only 2 publications reporting results in a paediatric population[1,3].
- There is wide variation in the type of laser, wavelength, energy delivered and duration of irradiation used across the studies. Some papers[2,4] in table 2 report subgroup analysis according to variation in dose, duration and timing of LLLT.
- The most frequent underlying diagnoses were haematological and head and neck cancers
- The natural progression of OM can act as a confounder of the effect of LLLT.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

- **Clinical practice guidelines for the management of mucositis secondary to cancer therapy (2014) -** Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO)

  The review reported that evidence support the use of LLLT for the prevention of OM in patients receiving high-dose chemotherapy for HSCT with or without total body irradiation. It also suggest the use of LLLT in preventing OM in patients with head and neck cancer treated by RT without concomitant ChT.

  Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4164022/https:/www.ncbi.nlm.nih.gov/pmc/articles/PMC4164022/

- **Guideline for the prevention of oral and oropharyngeal mucositis in children receiving treatment for cancer or undergoing haematopoietic stem cell transplantation (2015)** - Pediatric Oncology Group of Ontario (POGO) Mucositis Prevention Guideline Development Group

  The guidance suggest that LLLT may be offered to cooperative children receiving chemotherapy or HSCT conditioning with regimens associated with a high rate of mucositis. The three specific interventions (cryotherapy, LLLT and keratinocyte growth factor) evaluated in this clinical practice guideline were associated with a weak recommendation for use. Since all systematic reviews compared the intervention against placebo or no therapy, it may be helpful to compare the relative risks to gain insight into prioritisation.

Available from
http://spcare.bmj.com/content/7/1/7

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

NICE guidelines

- Haematological cancers: Improving standards (2016). Nice guideline 47. Available from https://www.nice.org.uk/guidance/ng47

- Improving outcomes in head and neck cancers. Cancer service guideline 6, 2004. Available from https://www.nice.org.uk/guidance/csg6

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two Specialist Advisor Questionnaires for low-level laser therapy for prevention or treatment of oral mucositis secondary to radiotherapy or chemotherapy were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme sent 25 questionnaires to 1 NHS trust for distribution to patients who had the procedure (or their carers). NICE received 4 completed questionnaires.

The patient commentators raised the following issues about the safety of the procedure, which did not feature in the published evidence or the opinions of specialist advisers, and which the committee considered to be particularly relevant:

- Patient took one week to recover from procedure and reported muscular spasms on the neck pain.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received no completed submission.

Issues for consideration by IPAC

- The natural progression of OM can act as a confounder for the effect of LLLT.
- There were no safety events found in the literature.
- LLLT was often compared with standard medical care and sham interventions, so it may be difficult to infer the relative effectiveness of the procedure.

References

1. Oberoi S, Zamperlini-Netto G, Beyene J et al. (2014) Effect of prophylactic low level laser therapy on oral mucositis: a systematic review and meta-analysis. PLoS ONE [Electronic Resource] 9, e107418
2. Bjordal JM, Bensadoun RJ, Tuner J et al. (2011) A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis. Supportive Care in Cancer 19, 1069-77
3. Amadori F, Bardellini E, Conti G et al. (2016) Low-level laser therapy for treatment of chemotherapy-induced oral mucositis in childhood: a randomized double-blind controlled study. Lasers in medical science 31, 1231-1236
4. Carvalho PA, Jaguar GC, Pellizzon AC et al. (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 Oncology 47, 1176-81
5. Arbabi-Kalati F, Arbabi-Kalati F and Moridi T (2013) Evaluation of the effect of low level laser on prevention of chemotherapy-induced mucositis. Acta Medica Iranica 51, 157-62
6. Gautam AP, Fernandes DJ, Vidyasagar MS et al. (2015) Low level laser therapy against radiation induced oral mucositis in elderly head and neck cancer patients-a randomized placebo controlled trial. Journal of Photochemistry & Photobiology. B - Biology 144, 51-6
7. Genot-Klastersky MT, Klastersky J, Awada F et al. (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. Supportive Care in Cancer 16, 1381-1387
8. Ferreira B, da Motta Silveira FM and de Orange FA (2015) Low-level laser therapy prevents severe oral mucositis in patients submitted to hematopoietic stem cell transplantation: a randomized clinical trial. Supportive Care in Cancer 24, 1035-1042

Additional relevant papers

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Abramoff MM, Lopes NN, Lopes LA et al. (2008) Low-level laser therapy in the prevention and treatment of chemotherapy-induced oral mucositis in young patients. Photomedicine and Laser Surgery 26, 393-400	**RCT** n=13 FU=12m	The ease of use of LLLT, high patient acceptance, and the positive results achieved, make this therapy feasible for the prevention and treatment of OM in young patients.	Larger RCTs already included in table 2. No new safety evidence.
Antunes HS, Ferreira EM, de Matos VD et al. (2008) The Impact of low power laser in the treatment of conditioning-induced oral mucositis: a report of 11 clinical cases and their review. Medicina Oral, and Patologia Oral y Cirugia Bucal 13, E189-92	**RCT** n=38 FU=7 days	The results have indicated that the use of LLLT in HSCT patients is a powerful instrument in the treatment of overt OM and is now a standard procedure in this group of patients in the hospital where the study was conducted.	Included in paper 1 table 2.
Antunes HS, Herchenhorn D, Araujo CMM et al. (2011) Low-level laser therapy in the prevention of oral mucositis in head and neck cancer patients submitted chemoradiation-phase III trial. Supportive Care in Cancer Conference, 2011 International MASCC/ISOO Symposium: Supportiv	**Case series** n=11 FU=15 days	The results indicate that the LLLT in head and neck cancer patients submitted to chemoradiation is an effective tool in reducing the incidence G 3/4 OM, oral pain, use of narcotic and gastrostomia, and should be the new standard of care in this setting.	Studies with higher level of evidence already included. No new safety evidence.
Antunes HS, Herchenhorn D, Small IA et al. (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 Oncology 71, 11-15	**Case series** n= 94 FU=41 months (median)	This is the first study to suggest that LLLT may improve survival of head and neck cancer patients treated with chemoradiotherapy. Further studies, with a larger sample, are necessary to confirm our findings.	Studies with higher level of evidence already included. No new safety evidence.
Arora H, Pai KM, Maiya A et al. (2008) Efficacy of He-Ne Laser in the prevention and treatment of radiotherapy-induced oral mucositis in oral cancer patients. Oral Surgery Oral Medicine Oral Pathology Oral Radiology & Endodontics 105, 180-6, 186.e1	**Non-randomised comparative study** n=28 FU=7 weeks	Laser therapy applied prophylactically during radiotherapy can reduce the severity of oral mucositis, severity of pain, and functional impairment.	Studies with higher level of evidence already included. No new safety evidence.
Barasch A, Peterson DE, Tanzer et al. (1995) Helium-neon laser effects on conditioning-induced oral mucositis in bone marrow	**RCT** n=20 FU=21 days	Helium-neon laser treatment was well-tolerated and reduced the severity of conditioning-	Larger RCTs already included in table 2. No

transplantation patients. Cancer 76, 2550-6		induced oral mucositis in BMT patients.	new safety evidence
Bensadoun RJ, Franquin JC, Ciais G et al. (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. Supportive Care in Cancer 7, 244-5	**RCT** n= 30 FU=7 weeks	LLLT therapy is capable of reducing the severity and duration of oral mucositis associated with radiation therapy. In addition, there is a tremendous potential for using LLLT in combined treatment protocols utilizing concomitant chemotherapy and radiotherapy.	Larger RCTs already included in table 2. No new safety evidence
Bezinelli LM, Eduardo FP, Neves VD et al. (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. European Journal of Cancer Care 25, 668-74	**Case series** n=69 FU=30 days	The study has shown that quality of life improves over time in patients undergoing LLLT therapy for mucositis prevention	Studies with higher level of evidence already included. No new safety evidence.
Carneiro-Neto JN, de-Menezes JD, Moura LB et al. (2017) Protocols for management of oral complications of chemotherapy and/or radiotherapy for oral cancer: Systematic review and meta-analysis current. Medicina Oral, and Patologia Oral y Cirugia Bucal 22, e15-e23	**Systematic review and meta-analysis** n=6 FU=4 to 7 weeks	The protocols suggestive for managements of oral mucositis and pain with MuGard - mucoadhesive hydrogel; PerioAid Tratamiento antiseptic mouthrinse with chlorhexidine and cetylpyridinium chloride; Episil plus benzydamine - bioadhesive oromucosal gel; 0.03% of Triclosan mouthwash Colgate Plax; and Diode Laser Therapy of low-level are safe for oncology patients applied according to adopted clinical parameters.	Includes only 1 paper reporting the effects of LLLT. No new safety events.
Chermetz M, Gobbo M, Ronfani L et al. (2014) Class IV laser therapy as treatment for chemotherapy-induced oral mucositis in onco-haematological paediatric patients: a prospective study. International Journal of Paediatric Dentistry 24, 441-9	**Case series** n=18 FU=11	Given class IV laser therapy appears to be safe, non-invasive, and potentially effective, prospective, randomized, controlled trials are necessary to further assess efficacy and to determine optimal treatment parameters.	Studies with higher level of evidence already included. No new safety evidence.
Clarkson JE , Worthington HV , Furness S et al. (2010) Interventions for treating oral mucositis for patients with cancer receiving treatment. Cochrane Database of Systematic Reviews ,	**Systematic review** n= 2 trials on LLLT FU=7 days or until healing	There is limited evidence from two small trials that low level laser treatment reduces the severity of the mucositis. Less opiate is used for PCA versus continuous infusion. Further, well designed, placebo or no treatment controlled trials assessing the effectiveness of	Includes only 2 paper reporting the effects of LLLT. No new safety events.

		interventions investigated in this review and new interventions for treating mucositis are needed.	
Corti L, Chiarion-Sileni V, Aversa S et al. (2006) Treatment of chemotherapy-induced oral mucositis with light-emitting diode. Photomedicine and Laser Surgery 24, 207-13	**Case series** n=24 FU=20 days	This pilot study shows that LED treatment is safe and capable of reducing the duration of chemotherapy-induced mucositis. This result needs to be confirmed in an adequate phase III study.	Studies with higher level of evidence already included. No new safety evidence.
Cowen D, Tardieu C, Schubert M et al. (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. International Journal of Radiation Oncology, Biology, and Physics 38, 697-703	**RCT** n=20 FU=20 days	Helium-Neon laser treatment was well tolerated, feasible in all cases, and reduced high dose chemoradiotherapy-induced oral mucositis. Optimal laser treatment schedules still needs to be defined.	Included in paper 1 table 2.
Cruz LB, Ribeiro AS, Rech A et al. (2007) Influence of low-energy laser in the prevention of oral mucositis in children with cancer receiving chemotherapy. Pediatric Blood & Cancer 48, 435-40	**RCT** n=60 FU=16 days	This study showed no evidence of benefit from the prophylactic use of low-energy laser in children and adolescents with cancer treated with chemotherapy when optimal dental and oral care was provided.	Included in paper 1 table 2.
de Castro JF, Abreu EG, Correia AV et al. (2013) Low-level laser in prevention and treatment of oral mucositis in pediatric patients with acute lymphoblastic leukemia. Photomedicine and Laser Surgery 31, 613-8	**Case series** n=40 FU=5 days	Prophylactic laser produced a better outcome than when patients did not receive any preventive intervention, and red laser (660 nm) was better than infrared (830 nm) in the prevention and treatment of OM.	Studies with higher level of evidence already included. No new safety evidence.
de Paula Eduardo F , Bezinelli LM, da Graca Lopes RM et al. (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. Hematological Oncology 33, 152-8	**Non-randomised comparative study** n=104 FU=11 days	The association of cryotherapy with laser therapy was effective in reducing OM severity in HSCT patients who underwent melphalan conditioning.	Studies with higher level of evidence already included.
Eduardo FP, Bezinelli L, Luiz AC et al. (2009) Severity of oral mucositis in patients undergoing hematopoietic cell transplantation and an oral laser phototherapy protocol: a survey of 30 patients. Photomedicine and Laser Surgery 27, 137-44	**Case series** n=30 FU=8 days	The low grades of OM observed in this survey show the beneficial effects of laser phototherapy, but randomized clinical trials are necessary to confirm these findings.	Studies with higher level of evidence already included.
Eduardo FP, Bezinelli LM, Orsi MC et al. (2011) The influence of dental care associated with	**Non-randomised comparative study** n=62	Dental care associated with laser therapy reduces the extension and severity	Studies with higher level of evidence

laser therapy on oral mucositis during allogeneic hematopoietic cell transplant: retrospective study. Einstein 9, 201-6	FU=100	of oral mucositis in patients with allogeneic hematopoietic transplant. Further studies are necessary to clarify the isolate efficacy of laser therapy in these conditions, mainly regarding the influence of reduced oral mucositis on the graft versus host disease.	already included.
Eduardo FP, Bezinelli LM, de Carvalho DL et al. (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. Pediatric Transplantation 19, 316-25	**Non-randomised comparative study** n=51 FU=7 days	Specialized oral care, including LLLT, is feasible and affordable for HSCT paediatric patients, although some adaptation in the patient's oral hygiene routine must be adopted with help from parents/companions and clinical staff.	Studies with higher level of evidence already included. No new safety events.
Elad S, Luboshitz-Shon N, Cohen T et al. (2011) A randomized controlled trial of visible-light therapy for the prevention of oral mucositis. Oral Oncology 47, 125-30	**RCT** n=20 FU=21 days	The treatment was well tolerated with no adverse events related to the study device. Patients highly accepted this treatment modality. These findings suggest that this VLT-device is safe and effective for the prevention of oral mucositis in patients undergoing HSCT.	Larger RCTs already included in table 2. No new safety evidence
Figueiredo AL, Lins L, Cattony AC et al. (2013) Laser therapy in the control of oral mucositis: a meta-analysis. Revista Da Associacao Medica Brasileira 59, 467-74	**Systematic review and meta-analysis** n=7 FU=NA	These data demonstrated significant prophylatic effect of OM grade > 3 in patients undergoing LT. Further studies, with larger sample sizes, are needed for better evaluation of the prophylactic effect of OM grade > 3 by LT.	Papers already included in paper 2, table 2. No new safety events.
Freitas AC, Campos L, Brandao TB et al. (2014) Chemotherapy-induced oral mucositis: effect of LED and laser phototherapy treatment protocols. Photomedicine and Laser Surgery 32, 81-7	**Non-randomised comparative study** n=40 FU=10 days	These findings suggest that LED therapy is more effective than LPT in the treatment of COIM, with the parameters used in the present study.	Studies with higher level of evidence already included. No new safety events.
Gautam AP, Fernandes DJ, Vidyasagar MS et al. (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. Supportive Care in Cancer 21, 1421-1428	**RCT** n=220 FU=7 weeks	LLLT was effective in improving the patient's subjective experience of OM and QOL in HNC patients receiving CRT	Papers already included in paper 1, table 2.
Gautam AP, Fernandes DJ, Vidyasagar MS et al. (2012) Low level helium neon laser therapy	**RCT** n=121 FU= 2 weeks	Low Level He-Ne Laser decreased the incidence of CRT induced severe OM	Papers already included in

for chemoradiotherapy induced oral mucositis in oral cancer patients - a randomized controlled trial. Oral Oncology 48, 893-7		and its associated pain, opioid analgesics use and TPN.	paper 1, table 2.
Gobbo M, Ottaviani G, Bussani R et al. (2013) Methotrexate-induced oral mucositis in rheumatoid arthritis disease: Therapeutic strategy in a case report. Photonics and Lasers in Medicine 2, 71-76	**Case report** n=1 FU=14	LLLT could represent an innovative technique to relieve pain related to methotrexate side effects thus avoiding dangerous discontinuation of therapy.	Studies with higher level of evidence already included. No new safety events.
Gouvêa LA , Villar RC, Castro G et al. (2012) Oral mucositis prevention by low-level laser therapy in head-and-neck cancer patients undergoing concurrent chemoradiotherapy: a phase III randomized study. International journal of radiation oncology, biology, and physics 82, 270-5	**RCT** n=75 FU=6 weeks	LLLT was not effective in reducing severe oral mucositis, although a marginal benefit could not be excluded. It reduced RT interruptions in these head-and-neck cancer patients, which might translate into improved CRT efficacy.	Papers already included in paper 1, table 2.
Hodgson BD, Margolis DM, Salzman E et al. (2012) Amelioration of oral mucositis pain by NASA near-infrared light-emitting diodes in bone marrow transplant patients. Supportive Care in Cancer 20, 1405-1415	**RCT** n=80 FU=14 days	Conclusion Phototherapy demonstrated a significant reduction in patient-reported pain as measured by the WHO criteria in this patient population included in this study. Improvement trends were noted in most other assessment measurements.	Papers already included in paper 1, table 2.
Jaguar GC, Prado JD, Nishimoto IN et al. (2007) Low-energy laser therapy for prevention of oral mucositis in hematopoietic stem cell transplantation. Oral Diseases 13, 538-43	**Non-randomise comparative study** n=49 FU=21 days	This study suggests that laser therapy can be useful in oral mucositis to HSCT patients and improve the patient's quality of life. However, controlled randomized trials should be performed to confirm the real efficacy of laser therapy.	Studies with higher level of evidence already included. No new safety events.
Khouri VY, Stracieri AB, Rodrigues MC et al. (2009) Use of therapeutic laser for prevention and treatment of oral mucositis. Brazilian Dental Journal 20, 215-20	**Non-randomised comparative study** n=22 FU=15 days	In conclusion, laser reduced the frequency and severity of OM, suggesting that therapeutic laser can be used both as a new form of prevention and treatment of OM.	Studies with higher level of evidence already included. No new safety events.
Kuhn A, Porto F A, Miraglia P et al. (2009) Low-level infrared laser therapy in chemotherapy-induced oral mucositis: a randomized placebo-controlled trial in children. Journal of Pediatric Hematology/Oncology 31, 33-7	**RCT** n=21 FU=7 days	The study has shown evidence that laser therapy in addition to oral care can decrease the duration of chemotherapy-induced OM. The results confirm the promising results observed in adult cancer patients and should encourage paediatric oncologists to use laser therapy as first-line option in children with	Papers already included in paper 2, table 2.

		chemotherapy-induced OM.	
Lang-Bicudo L, Eduardo FP , Eduardo CP et al. (2008) LED phototherapy to prevent mucositis: a case report. Photomedicine and Laser Surgery 26, 609-13	**Case report** n=1 FU=15 days	LED therapy was a safe and effective method for preventing oral mucositis in this case report. However, further randomized studies with more patients are needed to prove the efficacy of this method.	Studies with higher level of evidence already included. No new safety events.
Lima AG, Antequera R, Peres MP et al. (2010) Efficacy of low-level laser therapy and aluminum hydroxide in patients with chemotherapy and radiotherapy-induced oral mucositis. Brazilian Dental Journal 21, 186-92	**Non-randomised comparative study** n=25 FU=7 weeks	In both groups, no interruption of RT was needed. The prophylactic use of both treatments proposed in this study seems to reduce the incidence of severe OM lesions. However, the LLLT was more effective in delaying the appearance of severe OM.	Studies with higher level of evidence already included. No new safety events.
Lino MD, Carvalho FB, Oliveira LR et al. (2011) Laser phototherapy as a treatment for radiotherapy-induced oral mucositis. Brazilian Dental Journal 22, 162-5	**Case report** n=1 FU=6 weeks	Treatment results indicate that the use of LPT on oral mucositis was effective and allowed the patient to carry on the RT without interruption. However, long-term and controlled clinical trials are necessary to establish both preventive and curative protocols using LPT.	Studies with higher level of evidence already included. No new safety events.
Medeiros-Filho JB, Maia FE M, Ferreira MC (2017) Laser and photochemotherapy for the treatment of oral mucositis in young patients: Randomized clinical trial. Photodiagnosis & Photodynamic Therapy 18, 39-45	**RCT** n=15 FU=8 days	PCT+LLLT had a greater therapeutic effect in comparison to LLLT alone regarding the reduction in the degree of severity of chemotherapy-induced oral mucositis.	Larger RCTs already included in table 2. No new safety evidence
Oton-Leite AF, Correa de Castro AC, Morais MO et al. (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	**RCT** n=60 FU=7 weeks	Laser therapy reduces the impact of radiotherapy on the QOL of patients with head and neck cancer.	Papers already included in paper 1, table 2.
Oton-Leite AF, Silva GB, Morais MO et al. (2015) Effect of low-level laser therapy on chemoradiotherapy-induced oral mucositis and salivary inflammatory mediators in head and neck cancer patients. Lasers in Surgery & Medicine 47, 296-305	**Non-randomised comparative study** n=20 FU=3 weeks	These findings demonstrated that LLLT was effective in reducing the severity of chemoradiotherapy-induced OM and was associated with the reduction of inflammation and repair.	Studies with higher level of evidence already included. No new safety events.
Ottaviani G, Gobbo M, Sturnega M et al. (2013) Effect of class IV laser therapy on chemotherapy-induced oral mucositis: A clinical and experimental study.	**Non-randomised comparative study** n=20 FU=3 weeks	High-power laser therapy has been particularly effective in promoting the formation of new arterioles within the granulation tissue. The results provide	Studies with higher level of evidence already included.

American Journal of Pathology 183, 1747-1757		important insights into the mechanism of action of biostimulating laser therapy on OM in vivo and pave a way for clinical experimentation with the use of high-power laser therapy.	No new safety events.
Paula EF, Bezinelli LM, Graça LRM et al. (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. Hematological oncology 33, 152-8	**Non-randomised comparative study** n=71 FU=11 days	OM Grades III and IV were present with high frequency only in the control group. The association of cryotherapy with laser therapy was effective in reducing OM severity in HSCT patients who underwent melphalan conditioning.	Studies with higher level of evidence already included. No new safety events.
Rimulo AL, Ferreira MC, Abreu MH et al. (2011) Chemotherapy-induced oral mucositis in a patient with acute lymphoblastic leukaemia. European Archives of Paediatric Dentistry: Official Journal of the European Academy of Paediatric Dentistry 12, 124-7	**Case report** n=1 FU=10 days	LED was effective in the treatment of mucositis, as it diminished pain symptoms and accelerated the tissue repair process.	Studies with higher level of evidence already included. No new safety events.
Sandoval RL, Koga DH, Buloto LS et al. (2003) Management of chemo- and radiotherapy induced oral mucositis with low-energy laser: initial results of A.C. Camargo Hospital. Journal of Applied Oral Science 11, 337-41	**Case series** n=18 FU=20 days	Low-energy laser was well-tolerated and showed beneficial effects on the management of oral mucositis, improving the quality of life during the oncologic treatment.	Studies with higher level of evidence already included. No new safety events.
Schubert MM, Eduardo FP, Guthrie KA et al. (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. Supportive Care in Cancer 15, 1145-54	**RCT** n=70 FU=21 days	While these results are encouraging, further study is needed to truly establish the efficacy of this mucositis prevention strategy. Future research needs to determine the effects of modification of laser parameters (e.g., wavelength, fluency, repetition rate of energy delivery, etc.) on the effectiveness of LLE laser to prevent OM.	Papers already included in paper 1, table 2.
Silva GB, Mendonça EF, Bariani C et al. (2011) The prevention of induced oral mucositis with low-level laser therapy in bone marrow transplantation patients: a randomized clinical trial. Photomedicine and laser surgery 29, 27-31	**RCT** n=42 FU=11 days	The results indicate that the preventive use of LLLT in patients who have undergone HSCT is a powerful instrument in reducing OM incidence.	Papers already included in paper 1, table 2.
Silva LC, Sacono NT, Freire MC et al. (2015) The Impact of Low-Level Laser Therapy on Oral Mucositis and Quality of Life in Patients Undergoing	**RCT** n=39 FU=7 days	LLLT did not influence the oral and general health-related QoL of patients undergoing HSCT, although it was clinically	Does not report on the efficacy of LLLT. Not powered to

Hematopoietic Stem Cell Transplantation Using the Oral Health Impact Profile and the Functional Assessment of Cancer Therapy-Bone Marrow Transplantation Questionnaires. Photomedicine and Laser Surgery 33, 357-63		effective in reducing the severity of chemotherapy-induced OM.	detect changes in quality of life. No new safety events.
Simões A, Eduardo FP, Luiz AC et al. (2009) Laser phototherapy as topical prophylaxis against head and neck cancer radiotherapy-induced oral mucositis: comparison between low and high/low power lasers. Lasers in surgery and medicine 41, 264-270	**Case series** n=39 FU=	These findings are desired when dealing with oncologic patients under RT avoiding unplanned radiation treatment breaks and additional hospital costs.	Studies with higher level of evidence already included. No new safety events.
Soto M, Lalla RV, Gouveia RV et al. (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. Photomedicine and Laser Surgery 33, 540-6	**Non-randomised comparative study** n=20 FU=20 days	This study indicates that a combined protocol of intraoral and extraoral application of LLLT can reduce the severity of oral mucositis in pediatric patients undergoing HSCT. Randomized double-blind clinical trials with a larger number of subjects are needed to further test such combined protocols.	Studies with higher level of evidence already included. No new safety events.
Treister NS, London WB, Guo D et al. (2016) A Feasibility Study Evaluating Extraoral Photobiomodulation Therapy for Prevention of Mucositis in Pediatric Hematopoietic Cell Transplantation. Photomedicine and Laser Surgery 34, 178-84	**Case series** n=13 FU=15 days	Daily delivery of external PBT and completion of OM evaluations is feasible in children undergoing HCT.	Studies with higher level of evidence already included. No new safety events.
Vitale MC, Modaffari C, Decembrino N et al. (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 in Medical Science. ,	**RCT** n=16 FU=11 days	Laser therapy appears to be a safe and innovative approach in the management of oral mucositis. In this preliminary study, HPLT encourages to consider laser therapy as a part of onco-haematological protocol, providing to decrease pain and duration of OM induced by CT and HSCT. Further researches will be needed, especially randomized, controlled clinical trials with a large number of enrolled patients and a long term of follow-up to confirm the efficacy of laser therapy in prevention and control of OM in onco-haematological paediatric patients.	Larger RCTs already included in table 2. No new safety evidence
Whelan HT, Connelly JF, Hodgson BD et al. (2002) NASA	**Case series** n=32	Although more studies are needed, LED therapy	Studies with higher level of

light-emitting diodes for the prevention of oral mucositis in pediatric bone marrow transplant patients. Journal of Clinical Laser Medicine & Surgery 20, 319-24	FU=14	appears useful in the prevention of OM in paediatric BMT patients.	evidence already included. No new safety events.
Wong SF, and Wilder-Smith P (2002) Pilot study of laser effects on oral mucositis in patients receiving chemotherapy. Cancer Journal 8, 247-54	**Case series** n=15 FU=28 days	The laser therapy does not appear to promote wound healing by affecting the intraoral perfusion, as assessed by Doppler measurements. The mechanisms involved in the mediating of the observed effects remain unknown at this time. Continued research is warranted to determine the optimal laser wavelength and parameters.	Studies with higher level of evidence already included. No new safety events.
Worthington HV , Clarkson JE , Bryan G et al. (2011) Interventions for preventing oral mucositis for patients with cancer receiving treatment. Cochrane Database of Systematic Reviews ,	**Systematic review** n=1 study (LLLT) FU=7 days	The strength of the evidence was variable and implications for practice include consideration that benefits may be specific for certain cancer types and treatment. There is a need for further well designed, and conducted trials with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent.	Only one study reporting on outcomes associated with the intervention of interest.
Zanin T, Zanin F, Carvalhosa AA et al. (2010) Use of 660-nm diode laser in the prevention and treatment of human oral mucositis induced by radiotherapy and chemotherapy. Photomedicine and Laser Surgery 28, 233-7	**Non-randomised comparative study** n=72 FU=7 weeks	Laser therapy was effective in preventing and treating oral effects induced by radiotherapy and chemotherapy, thus improving the patient's quality of life.	Studies with higher level of evidence already included. No new safety events.

Literature search strategy

Databases	**Date searched**	**Version/files**
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	17/07/2017	Issue 7 of 12, July 2017
HTA database (Cochrane Library)	17/07/2017	Issue 7 of 12, July 2017
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	17/07/2017	Issue 7 of 12, July 2017
MEDLINE (Ovid)	17/07/2017	1946 to July Week 1 2017
MEDLINE In-Process (Ovid)	17/07/2017	July 14, 2017
EMBASE (Ovid)	17/07/2017	1974 to 2017 Week 29
PubMed	17/07/2017	-
BLIC	17/07/2017	-

Trial sources searched March 2017

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched March 2017

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

1 exp Stomatitis/
2 Candidiasis, Oral/
3 Mucositis/
4 Stevens-Johnson Syndrome/
5 stomatit*.tw.
6 mucosit*.tw.
7 ((Oral* or Mouth*) adj4 (cand* or inflam* or swell* or thrush* or ulcer*)).tw.
8 stevens johnson syndrome.tw.
9 or/1-8
10 laser therapy/ or low-level light therapy/

11 Phototherapy/
12 ((laser* or Light* or Photo*) adj4 (treat* or intervent* or therap*)).tw.
13 (photobiomodula* or PBM).tw.
14 (Low level therap* or LLLT).tw.
15 or/10-14
16 9 and 15
17 Animals/ not Humans/
18 16 not 17