Low-level laser therapy for oral mucositis in children with cancer

Melody Grace Redman [1,2] Katherine Harris,[3] Bob S Phillips [4]

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[1]Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK
[2]Yorkshire Regional Genetics Service, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[3]Department of Medical Education, University of Liverpool, Liverpool, UK
[4]Centre for Reviews and Dissemination, University of York, York, UK

Correspondence to
Dr Melody Grace Redman, Yorkshire Regional Genetics Service, Leeds Teaching Hospitals NHS Trust, Leeds, UK; meloredman@gmail.com

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ABSTRACT

Objective To assess the efficacy of oral low-level laser therapy (LLLT) – also known as photobiomodulation – in the reduction of oral mucositis experienced by children and young people with cancer undergoing chemotherapy.

Design A systematic review to evaluate the efficacy of oral LLLT for oral mucositis in children with cancer and the safety of oral LLLT in any age with cancer (International Prospective Register of Systematic Reviews/PROSPERO registration: CRD42018099772). Multiple databases and grey literature were screened. Randomised controlled trials were considered for assessing efficacy, and all studies were considered for assessing safety. Primary outcomes included severity of oral mucositis, oral pain and adverse events. Where results were compatible, meta-analysis was performed using a random-effects model. A narrative synthesis considered other outcome measures.

Results 14 studies (n>416 children) were included in the narrative synthesis of LLLT efficacy. 5 studies (n=380 children and young people) were included in the meta-analyses. Results demonstrate that LLLT may reduce the severity of oral mucositis and the level of oral pain, but further randomised controlled trials are needed to confirm or deny this. There is vast variation in different trial protocols. Insufficient blinding between LLLT or sham therapy/control led to a strong risk of performance bias. 75 studies (encompassing 2712 patients of all ages who had undergone LLLT) demonstrated minor and infrequent adverse reactions, but most studies had significant areas of weakness in quality.

Conclusion LLLT appears to be a safe therapy, but further evidence is needed to assess its efficacy as a prevention or treatment tool for oral mucositis in children with cancer.

What is already known on this topic?

- Oral mucositis is a significant, common and distressing side effect of chemotherapy and haematopoietic stem cell transplants.
- National Institute for Health and Care Excellence guidance (2018) exists for low-level laser therapy (LLLT) for the prophylaxis and treatment of oral mucositis but is largely based on adult evidence.
- Paediatric-specific guidelines (2017) gave a 'weak recommendation' for LLLT for oral mucositis prevention, with questions around the feasibility of delivering LLLT.

What this study adds?

- LLLT may reduce the severity of oral mucositis and the level of oral pain.
- Results are heterogenous and change over time; further research is needed.
- Minor and infrequent adverse device reactions were found and were poorly recorded.

INTRODUCTION

Inflammation and ulceration of the mouth (oral mucositis) is a significant and distressing side effect of chemotherapy and haematopoietic stem cell transplants (HSCTs). Oral mucositis can cause pain, problems with nutrition and psychological distress and may affect the patient's ability to continue the current chemotherapy regime.[1 2] Up to 80% of children undergoing chemotherapy may be affected by oral mucositis.[3] In blood and bone marrow transplantation, oral mucositis is associated with worse clinical and economic outcomes.[4] One mother who took part in our patient and public involvement work described her daughter's experience with oral mucositis: 'She struggled to swallow her own saliva…[she was] not really with us 'cos she'd had so much morphine'. She required two 10-day-long stays in the hospital and asked her mum, 'Can't you just put me to sleep for 3 months…?'.

Guidance from The National Institute for Health and Care Excellence exists for the use of low-level laser therapy (LLLT)—also known as photobiomodulation—for the prophylaxis and treatment of oral mucositis, but is largely based on adult evidence, and no specific protocol for delivery is given.[5] The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology produced recommendations for LLLT in 2019.[6] This guidance recognises that different protocols are needed for different groups and indications and that further studies may be helpful.[6] In 2017, paediatric-specific guidelines gave a 'weak recommendation' for LLLT for oral mucositis prevention because 'it is unknown whether it is feasible to deliver this therapy modality in routine clinical practice…'.[7]

LLLT is only being used for children and young people (CYP) in one centre within England and Wales.[8] Therefore, we sought to undertake a systematic review.

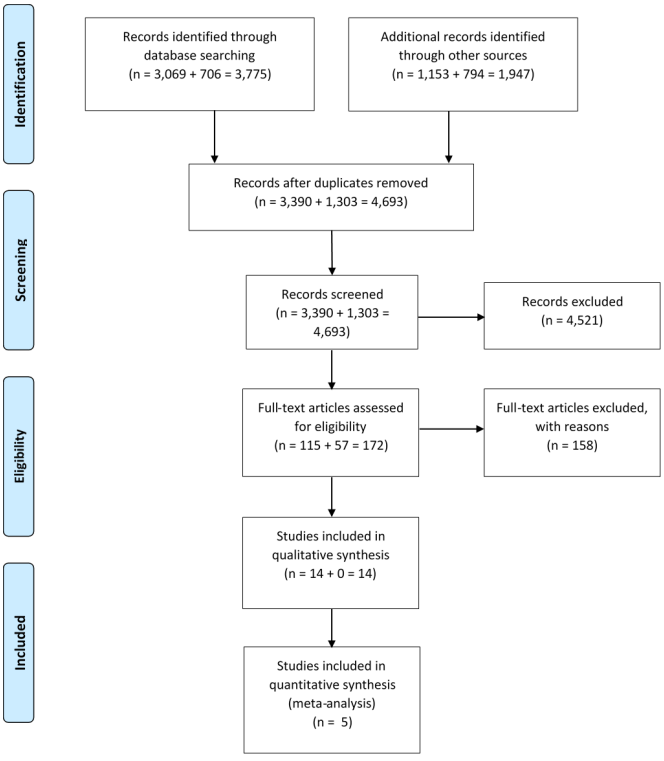

Figure 1 An adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram[13] showing the implementation of the search strategy for studies assessing efficacy identified through the first search in June 2018 and the additional studies included as a result of the update search in June 2020.

Objectives

- To assess the efficacy of oral LLLT in the reduction of oral mucositis experienced by CYP with cancer undergoing chemotherapy.
- To assess any adverse events associated with its use in patients with cancer of any age undergoing chemotherapy.

METHODS

The review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) international database (CRD42018099772) using standard approaches.[9 10]

Eligibility criteria

For assessing the efficacy of LLLT, randomised controlled trials (RCTs) considering CYP less than 18 years old with cancer were considered (online supplemental table 1). For assessing safety, all studies were considered for all ages of people with cancer (online supplemental table 2).

Search strategy

The 15 databases and sources searched are listed in online supplemental table 3. A 32-step search strategy was used for Embase, MEDLINE and Allied and Complementary Medicine Database (online supplemental table 4). Alternative search strategies were used for other sources. The search strategies ran from the earliest date available until 28 June 2020, including an update search. Searches were not restricted by age or language. Published and unpublished studies were considered. All studies included for efficacy had their reference lists reviewed. Additional unpublished material was sought from authors and experts in the field.

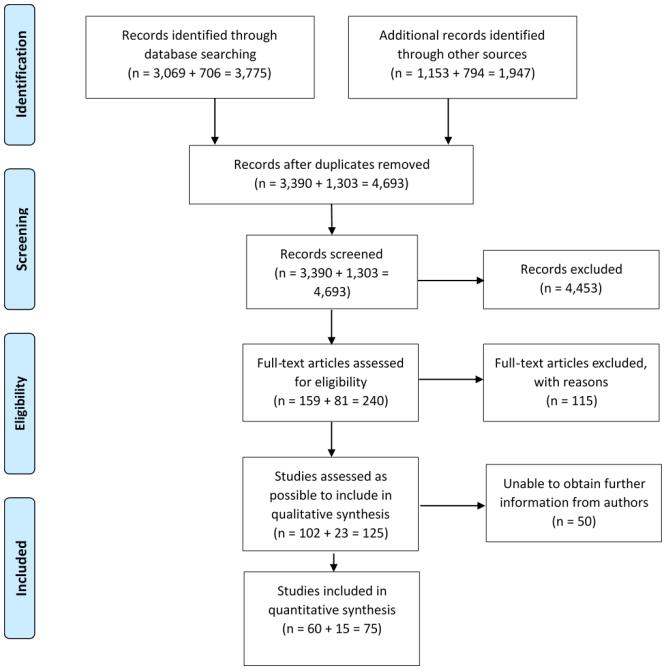

Figure 2 An adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram[13] showing the implementation of the search strategy for studies assessing safety identified through the first search in June 2018 and the additional studies included as a result of the update search in June 2020.

Data collection

Two reviewers (MGR/KH) screened all search results, obtaining full text where there was uncertainty about inclusion. Where the reviewers disagreed, a third reviewer (BSP) was consulted. Non-English studies were screened by experienced clinicians and/or academics (see the Acknowledgements section). Data extraction of the included studies was undertaken by KH or MGR and then counterchecked by the other (see online supplemental figure 1 for an example data extraction form).

Risk of bias

To assess the efficacy of LLLT, any RCTs that qualified for inclusion were analysed at a study level using the Cochrane risk of bias tool (Centre for Reviews and Dissemination. University of York, p37)[10]. When considering the adverse events associated with LLLT, studies were scrutinised using guidance provided by Loke *et al*.[11]

Statistical analysis

Random effects meta-analysis was performed using RevMan V.5.4[12] where outcome measures were comparable. The principal summary measures were ORs and standardised mean differences. Pooling was not performed where there was substantial heterogeneity ($I^2 \geq 50\%$).[9] Random effects were felt appropriate given the clinical heterogeneity of the interventions, and the Mantel–Haenszel method used as there were few events.[9]

Figures 1 and 2 adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagrams[13] demonstrate the flow of studies. Fourteen RCTs (n>416 CYP) were included in the narrative synthesis of LLLT efficacy.[14–27] Five RCTs (n=380 CYP) were included for meta-analysis.[15 16 19 21 22] Ahmed *et al*[15] declared that nearly half of their patients were below aged 17 (personal communications, MG Redman, 2020), and the other patients were young adults; we included these in

the meta-analyses. Seventy-five studies were included for safety analysis (online supplemental table 5). Relevant ongoing trials can be found in online supplemental table 6.

Quality of studies

When evaluating efficacy trials, there is a significant risk of performance bias as the outcome assessors were generally not blinded. Several RCTs provided insufficient data to assess selection bias (online supplemental figures 2 and 3).

Overall, studies included in the safety analysis provided insufficient assurance of quality. Of the quality assessment questions considered, 69.3% were 'unclear' or 'not applicable', particularly on how information about adverse events due to LLLT was collected.

Efficacy of LLLT

Intraoral LLLT was used by all studies, except Hodgson *et al*,[22] who used extraoral LLLT. Studies considered prevention and/or treatment of oral mucositis. Protocols of LLLT administration varied widely (online supplemental table 7); wavelengths ranged from 632.8 to 955 nm. Energy delivery ranged from 1.5 to 8.0 J/cm^2. LLLT was mostly applied daily (apart from Abramoff *et al* and Fani *et al*[14 20]), but duration ranged from 4 to 15 days.

Grade of oral mucositis

Two scales were used to assess oral mucositis grading: WHO oral mucositis scale/common toxicity criteria or National Cancer Institute Common Terminology Criteria [[28] p3-4]. Hodgson *et al*[22] provided us with unpublished data using both grading systems, which allowed us to validate combining the grades for meta-analysis (online supplemental table 8). Patients aged >18 or undergoing HSCT with no cancer diagnosis were removed from the dataset of Hodgson *et al*[22] and Amadori *et al*.[16] Abramoff *et al*[14] included patients up to 23 years old; it was not possible to obtain the breakdown of data and thus all these are included.

For meta-analysis, three different timepoints were used, and results were grouped as low-grade (0–2) and high-grade (3-4) oral mucositis. A summary of the effect of LLLT on grade of oral mucositis in the included studies is presented in table 1. LLLT non-significantly reduced severe oral mucositis at all time points (days 3–5: OR 0.73, 95% CI 0.33 to 1.61; days 7–10: OR 0.35, 95% CI 0.12 to 1.03; days 11–17: OR 0.36, 95% CI 0.09 to 1.39; figure 3), but these results are heterogenous and change over time (figure 4).

Oral pain

Three studies had extractable data on oral pain. Median results from Gobbo *et al*[21] and Ahmed *et al*[15] were converted to estimates of means using an online tool.[29–31] Similarly to observed grade of mucositis, there may be a trend towards less pain experienced

Table 1 Effect of low-level laser therapy (LLLT) on grade of oral mucositis

RCT	Effect of LLLT on grade of oral mucositis
Abramoff *et al*[14]	For those undergoing prophylactic LLLT, at the third evaluation (between days 6 and 9 after commencing chemotherapy), 73% of the patients in the prophylactic laser group had grade 0 mucositis, compared with 27% in the placebo group (p=0.03).
Ahmed *et al*[15]	Includes some adults. No statistically significant difference on daily evaluation of grade; however, authors report a risk ratio of 2.8 for the occurrence of grade 3 and grade 4 oral mucositis in the sham group compared with the laser group. OR of 0.22 (95% CI of 0.02 to 2.08) of grade 3 or more oral mucositis in the laser group on day 15.
Amadori *et al*[16]	No statistically significant change. Day 4, oral mucositis median grade=2 for both laser and sham groups. Day 7, oral mucositis median grade laser=0, sham=1 (p=0.07). OR of grade 3 or more oral mucositis in laser group is 1.33 (95% CI 0.51 to 3.50) on day 4 and 0.18 (95% CI 0.01 to 3.88) on day 7.
Amadori and Bardellini[17]	Abstract reports both prophylactic and therapeutic phases to result in a statistically significant reduction of OM in the laser group. Prophylactic phase reported as significant difference at day 4 (p=0.02) and therapeutic phase significant by the end of laser/sham treatment.
Cowen *et al*[18]	Only 2 patients aged 17 out of group of 30 patients. Distribution of daily mucositis index statistically significantly lower in laser group compared with sham group on days 2–7 (inclusive) after bone marrow transplantation.
Cruz *et al*[19]	Oral mucositis severity and prevalence were similar in the laser group and control group (p=0.208). OR of grade 3 or above oral mucositis was lower in the laser group (OR=0.34, 95% CI 0.01 to 8.80) on day 8 and lower in the laser group (OR=0.69, 95% CI of 0.11 to 4.47) on day 15, but not statistically significant.
Fani *et al*[20]	Unable to ascertain how many patients were children and met full inclusion criteria. Based on the WHO scale, there is no significant difference between the groups (p>0.05). However, based on the NCI scale, there is a significant reduction in oral mucositis between the groups (p<0.05).
Gobbo *et al*[21]	On day 7, of those undergoing LLLT, one patient developed grade 4 oral mucositis, and 2 patients developed grade 3. Of those undergoing sham treatment, 8 patients developed grade 4 and 6 patients developed grade 3 oral mucositis (p<0.02). OR of grade 3 or above oral mucositis was lower in the laser group (OR=0.50, 95% CI 0.23 to 1.11) on day 4 but not statistically significant. It was also lower in the laser group (OR=0.17, 95% CI of 0.04 to 0.63) on day 7 and lower in the laser group (OR=0.08, 95% CI of 0.01 to 0.68) on day 11, and this was statistically significant.
Hodgson *et al*[22]	As displayed in the meta-analysis, OR of developing OM of grade 3 or above in laser group was lower at day 3–5 (OR=0.23, 95% CI 0.01 to 6.25) but then higher at days 8–10 (OR=1.25, 95% CI 0.23 to 6.71) and days15–17 (OR=3.29, 95% CI 0.12 to 89.81). None of these were statistically significant.
Khouri *et al*[23]	Unable to ascertain how many patients were children and met full inclusion criteria. Mean grade of oral mucositis in the laser group was 1.75±0.45, compared with 2.45±0.93 in the control group (p<0.01). The laser group had a lower frequency of oral mucositis (p=0.02).
Kuhn *et al*[24]	Statistically significant reduction of oral mucositis in laser group (32% patients grade >0) compared with the placebo group (94% patients grade>0) on day 7 after oral mucositis diagnosis (p=0.001)
Salvador *et al*[25]	Unable to ascertain how many patients were children and met full inclusion criteria. Significant reduction in severity of oral mucositis from day +7 to day +11 (p<0.05).
Silva *et al*[26]	Unable to ascertain how many patients were children and met full inclusion criteria. Statistically significant reduction in grade of oral mucositis between laser and control group (p<0.001).
Silva *et al*[27]	Unable to ascertain how many patients were children and met full inclusion criteria. Less severe oral mucositis in the laser group on day 4, 7 and 8 (p<0.05). No significant difference on all other days of assessment (up to day 21).

NCI, National Cancer Institute; RCT, randomised controlled trial.

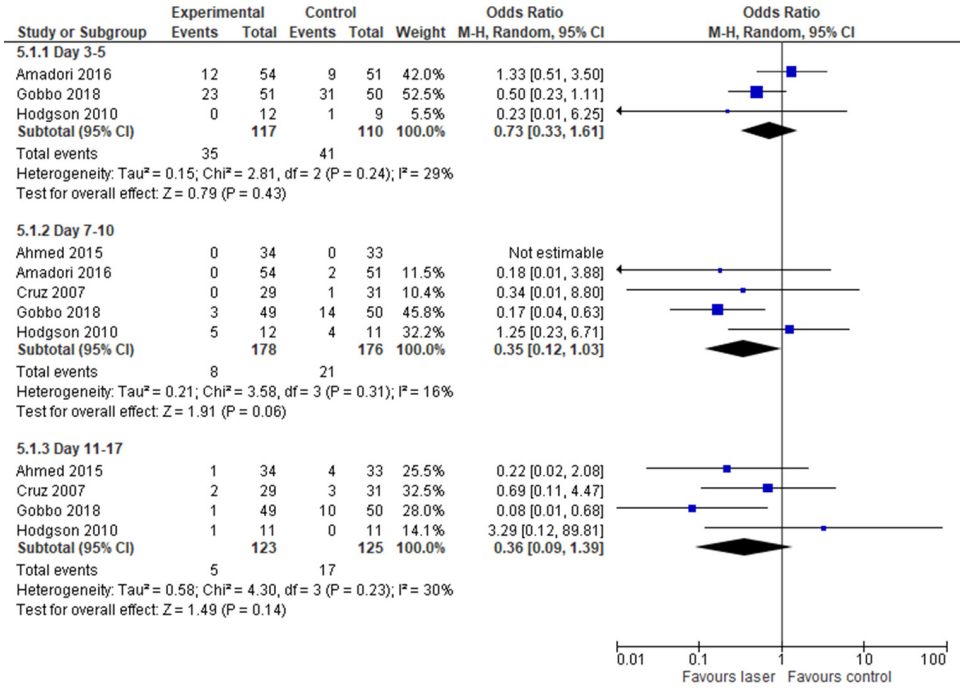

Figure 3 Forest plot of comparison: ORs comparing likelihood of patients developing grade 3+ (severe) oral mucositis in the laser group and the control group. Key: each study is labelled by its main author and year of publication and is represented by a square, the size of which reflects the relative size of the study, and the horizontal line passing through it represents the 95% CI. Random indicates the random-effects model; for CIs, the bracketed region denotes the upper and lower ends; I^2 represents heterogeneity between the randomised controlled trials; the 'p' value after 'test for overall effect' represents the probability that the overall effect is due to chance; the black diamond on each plot represents the pooled OR, with its breadth including the CIs. M-H, Mantel-Haenszel meta-analysis method.

from day 7 onwards after LLLT had been commenced (online supplemental figures 4 and 5 and online supplemental table 9).

Other outcome measures

Three RCTs[16 19 21] considered the use of analgesia, with one suggesting reduced use in the treated arm (online supplemental table 10). Three RCTs[18 19 22] considered the impact on diet, but no difference was found between the two groups (online supplemental table 11). One RCT looked at interruptions to cancer treatment; results are awaiting publication.[17] No RCTs looked at duration of hospitalisation. One study looked at quality of life,[27] but these results cannot be extracted for children alone (online supplemental table 12).

Safety of LLLT

As oral mucositis is an adverse event associated with chemotherapy/radiotherapy, LLLT, if effective, may have appeared to induce fewer or less severe adverse events than any control group. Therefore, where there was any ambiguity about wording around the monitoring or occurrence or causality of adverse

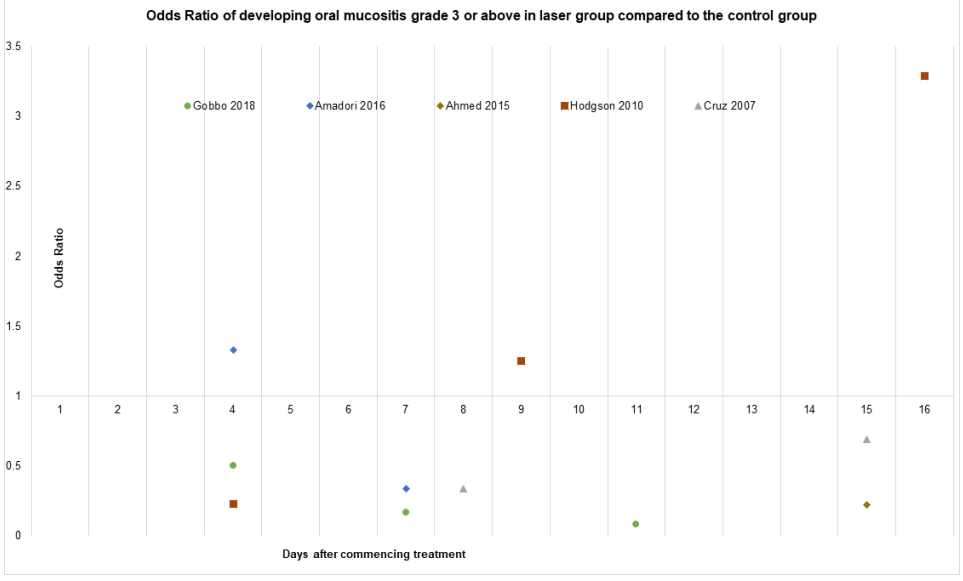

Figure 4 Graph comparing the ORs of developing oral mucositis grade 3 or more (severe to lifethreatening) in the laser group compared to the control group.

events, attempts were made to contact authors. Adverse reactions or adverse device effects which could be related to LLLT were sought.

A total of 125 identified studies would be expected to provide some information on the safety of LLLT. Despite attempts to contact authors, data were unavailable on adverse device effects or adverse reactions from 50 studies (which would have provided information on >1459 individuals who had LLLT).

Of the 75 included studies (encompassing 2712 patients who had LLLT), 24 studies were known to include children. The documentation of how adverse events were monitored was generally limited, affecting the quality assessment for the studies. There is a real challenge of monitoring and identifying adverse events due to LLLT. For example, Elad *et al* state, 'The treatment was well tolerated with no adverse events related to the study device'.[32] However, they discuss adverse events found in the treatment (LLLT) group of 10 patients (they report 2 patients with a traumatic ulcer from self-biting and 1 patient with herpes simplex virus type 1 positive ulceration) and go on to explain that the oral adverse events are typical of HSCT.[32] Definitions and monitoring methods regarding adverse events may be related to the cancer treatment and not to the LLLT. One study, where 22 children underwent LLLT, found adverse device events in 2 children and 1 issue with tolerability: 1 child was found to have some slight gingival bleeding after vomiting flowing laser treatment, and another child had a blood spot on the palate (attributed to mucositis rather than LLLT).[33] The same study also found that a 4-year-old boy refused to wear protective glasses, which are a necessary precaution for LLLT.[33] These issues were the only clear adverse device events indicated in 2420 patients.

A previous in vitro study raised concerns that LLLT exposure may lead to adverse effects on tumour behaviour, potentially affecting patient survival.[34] However, Antunes *et al* published a retrospective matched case–control study comparing those who had undergone LLLT with those who had not; this did not show any reduction in survival.[35] Genot *et al* retrospectively reviewed 361 patients and found that for the 62% who underwent LLLT, there was no statistically significant impact on overall survival, time to local recurrence or progression-free survival.[36] Fischlechner *et al* also considered overall survival and found no difference between 126 patients who had undergone LLLT and 126 matched controls.[37]

Additional analyses

It was not possible to undertake subgroup analysis due to the small number of heterogeneous studies.

DISCUSSION

Fourteen studies (n>416 CYP) were considered in the narrative synthesis around LLLT efficacy and five studies (n=380 CYP) in meta-analyses. A robust search strategy was used to identify these studies, but the results are inconclusive. Insufficient blinding between LLLT or sham therapy/control meant a strong risk of performance bias. There is some potential that LLLT may reduce the severity of oral mucositis and the level of oral pain, but further larger randomised controlled trials would reduce uncertainty. Future RCTs should include protocols considering LLLT for both prevention and treatment, and should compare LLLT to sham therapy, ensuring appropriate blinding.

Heterogeneity between RCTs was anticipated, given a vast range of LLLT protocols used (online supplemental table 7). Some simplifications were made to pool the data, such as combining NCI and WHO oral mucositis grades, and presenting efficacy over a group of days rather than identical time points.

This systematic review has highlighted some challenges of assessing the efficacy of LLLT. It is not clear what the optimal LLLT protocol is or the significance of different alternative parameters. This is in keeping with existing literature reflecting the challenges of assessing medical devices.[38]

The meta-analyses demonstrated that LLLT may reduce the correlated outcomes of severe mucositis and oral pain. However, these findings are heterogenous and imprecise. Seventy-five studies (encompassing 2712 patients of all ages who had LLLT) demonstrated minor and infrequent adverse reactions, but most studies had significant areas of weakness in quality. It is important to ensure accurate recording of adverse reactions/adverse device effects in future studies and interpret this with caution, given limitations around the quality assurance of these studies.

Antunes *et al* considered cost-effectiveness of LLLT for adults in Brazil and estimated the average cost of delivery of one 20 min session of LLLT was US$41.18, including costs of equipment, furniture, facilities, salaries for a supporting team (including two dentists and two supporting staff) and medical supplies.[39] This may vary substantially, depending on the implementation of LLLT and the existing infrastructure.

Further work

While this review was robust in nature and included grey literature, there is currently insufficient direct data to draw any firm conclusions about the role of LLLT in children with cancer. Ongoing and unreported trials (online supplemental table 6) should be considered for inclusion in any future systematic review. Further studies to evaluate protocols, devices, timing and efficacy in prevention and treatment of oral mucositis in children with cancer are recommended.

CONCLUSION

LLLT appears to be a safe therapy in adults and children from available study data, and it may have the potential to provide some reduction in children's experience of oral mucositis and associated pain. However, LLLT is only being used for children and young people (CYP) in one centre within England and Wales.[8] Where LLLT is used in other countries, protocols vary greatly between institutions, and clarity around the optimal delivery protocols is needed. For an institution to be able to introduce LLLT, some degree of dedicated infrastructure is needed to ensure laser safety. Further research is needed to assess if LLLT is an efficacious and cost-effective tool for the prevention or treatment of oral mucositis in children with cancer.

Twitter Melody Grace Redman @MelodyRedman and Bob S Phillips @drbobphillips

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terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs
Melody Grace Redman http://orcid.org/0000-0003-3112-3188
Bob S Phillips http://orcid.org/0000-0002-4938-9673

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32 Elad S, Luboshitz-Shon N, Cohen T, *et al*. A randomized controlled trial of visible-light therapy for the prevention of oral mucositis. *Oral Oncol* 2011;47:125–30.
33 Noirrit-Esclassan E, Valera MC, Vignes E, *et al*. Photobiomodulation with a combination of two wavelengths in the treatment of oral mucositis in children: the PEDIALASE feasibility study. *Arch Pediatr* 2019;26:268–74.
34 Kreisler M, Christoffers AB, Willershausen B, *et al*. Low-Level 809 nm GaAlAs laser irradiation increases the proliferation rate of human laryngeal carcinoma cells in vitro. *Lasers Med Sci* 2003;18:100–3.
35 Antunes HS, Herchenhorn D, Small IA, *et al*. Long-Term survival of a randomized phase III trial of head and neck cancer patients receiving concurrent chemoradiation therapy with or without low-level laser therapy (LLLT) to prevent oral mucositis. *Oral Oncol* 2017;71:11–15.
36 Genot MT, Klastersky J, Lalami Y. Evaluation of low level laser/photobiomodulation for cancer therapy-induced mucositis as a potential stimulation of tumor growth in head/neck cancer patients: a retrospective analysis. *Support Care Cancer* 2019;27:S125.
37 Fischlechner R, Kofler B, Schartinger VH, *et al*. Does low-level laser therapy affect the survival of patients with head and neck cancer? *Lasers Med Sci* 2021;36:599–604.
38 Rothery C, Claxton K, Palmer S, *et al*. Characterising uncertainty in the assessment of medical devices and determining future research needs. *Health Econ* 2017;26 Suppl 1:109–23.
39 Antunes HS, Schluckebier LF, Herchenhorn D, *et al*. Cost-Effectiveness of low-level laser therapy (LLLT) in head and neck cancer patients receiving concurrent chemoradiation. *Oral Oncol* 2016;52:85–90.

Supplementary Table 1: Population, Intervention, Comparison, Outcome & Study Design (PICOS) for assessing the efficacy of oral LLLT

Population	CYP less than 18 years old with a diagnosis of any form of cancer[1]
Intervention	Any form of oral LLLT or photobiomodulation as prevention or treatment for oral mucositis.
Comparison	No oral LLLT
Outcome	May consider outcomes such as (but not restricted to) oral mucositis, oral pain, adverse events, etc. **Primary outcomes:** Severity of oral mucositis Timing and intensity of oral pain and ChIMES[2] score Acceptability, effectiveness, and adherence to oral low-level laser therapy Symptoms, other than pain, considered important to the paediatric population Duration of action of oral low-level laser therapy Oral temperature Any adverse events. **Additional outcomes:** Interruptions to cancer treatment Oral pain on a 0 (no pain) to 10 (maximum pain) scale Quality of life Normalcy of diet (days of total parenteral nutrition) Duration of hospitalisation (days).
Study design	Must be an RCT

[1] Where studies included any CYP less than 18 years old, they were eligible for inclusion. See Supplementary Table 6 for a breakdown of the number of children in each study, including where the number is unknown.

[2] Jacobs S, Baggott C, Agarwal R, et al. Validation of the Children's International Mucositis Evaluation Scale (ChIMES) in paediatric cancer and SCT. *Br J Cancer* 2013;109:2515-22. https://doi.org/10.1038/bjc.2013.618

Supplementary Table 2: PICOS for assessing the safety of oral LLLT

Population	People of any age with a diagnosis of any form of cancer
Intervention	Any form of oral LLLT or photobiomodulation as prevention or treatment for oral mucositis.
Comparison	No oral LLLT
Outcome	May consider outcomes such as (but not restricted to) oral mucositis, oral pain, adverse events, etc. **Primary outcome:** Adverse events
Study design	Any study

Supplementary Table 3: Databases and sources searched

Databases and sources searched
EMBASE, MEDLINE®, Allied and Complementary Medicine Database (AMED), Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, International Society of Paediatric Oncology, American Society of Clinical Oncology, Multinational Association of Supportive Care in Cancer, International Cancer Research Portfolio, National Cancer Research Institute, National Cancer Institute Clinical Trials, ISRCTN registry, Web of Science, ClinicalTrials.gov, Centerwatch

Supplementary Table 4: The search strategy used for identifying studies through MEDLINE

MEDLINE search strategy
1. exp NEOPLASMS/
2. exp LEUKEMIA/
3. exp LYMPHOMA/
4. exp RADIOTHERAPY/
5. exp Antineoplastic agents/
6. Bone Marrow Transplantation/
7. neoplasm$.mp.
8. cancer$.mp.
9. (leukaemi$ or leukemi$).mp.

10. (tumour$ or tumor$).mp.
11. malignan$.mp.
12. neutropeni$.mp.
13. carcino$.mp.
14. adenocarcinoma$.mp.
15. lymphoma$.mp.
16. (radioth$ or radiat$ or irradiat$).mp.
17. (bone adj marrow adj5 transplant$).mp.
18. chemo$.mp.
19. or/1-18
20. exp STOMATITIS/
21. Candidiasis, Oral/
22. stomatitis.mp.
23. mucositis.mp.
24. (oral adj6 mucos$).mp.
25. (mycosis or mycotic).mp.
26. mIAS.ti,ab.
27. or/20-26
28 . laser/
29. laser$.mp.
30. (diode$ or photobiomodulat $ or light $ or infrared or cold-laser or phototherapy).mp.
31. or/28-30
32. 19 and 27 and 31

Supplementary Table 5: List of included studies for considering safety of LLLT

Reference	Country
Luna Oliva I, Robles García M, López Serrano B, Pérez BP, Sáez de la Fuente I, Torres Lagares D, et al. 980nm diode laser effectiveness in induced oral mucositis treatment. Med Oral Patol Oral Cir Bucal. 2012 May 1;17(Supplement1):S260. doi:10.4317/medoral.17643760	Spain
Jeandet I, Martignoles JA, Tronchon S, Brouillat C, Filiol S, Villemagne C, et al. A cohort pilot study on the use of a preventive treatment of oral mucositis using low-level laser therapy on patients undergoing a haematopoietic stem cell transplantation Bone Marrow Transplant. 2016;51(1):S232.	France
Treister NS, London WB, Guo D, Malsch M, Verrill K, Brewer J, et al. A feasibility study evaluating extraoral photobiomodulation therapy for prevention of mucositis in pediatric hematopoietic cell transplantation. Photomed Laser Surg. 2016 Apr;34(4):178-84. doi: 10.1089/pho.2015.4021.	USA
Schubert MM, Eduardo FP, Guthrie KA, Franquin JC, Bensadoun RJ, Migliorati CA, et al. A phase III randomized double-blind placebo-controlled clinical trial to determine the efficacy of low level laser therapy for the prevention of oral mucositis in patients undergoing hematopoietic cell transplantation. Support Care Cancer. 2007 Oct;15(10):1145-54. doi: 10.1007/s00520-007-0238-7.	USA
Elad S, Luboshitz-Shon N, Cohen T, Wainchwaig E, Shapira MY, Resnick IB, et al. A randomized controlled trial of visible-light therapy for the prevention of oral mucositis. Oral Oncol. 2011 Feb;47(2):125-30. doi: 10.1016/j.oraloncology.2010.11.013.	Israel

Genot M, Awada A, Awada F, Jaivenois MF, Crombez P, Delmelle M, et al. A randomized study testing the efficacy of low-energy laser irradiation for treatment of oral mucositis in patients with haematological malignancy treated with intensive chemotherapy with or without radiotherapy and bone marrow transplant. Support Care Cancer. 2007;15:707-8.	Belgium
Hodgson BD, Margolis DM, Salzman DE, Eastwood D, Tarima S, Williams LD, et al. Amelioration of oral mucositis pain by NASA near-infrared light-emitting diodes in bone marrow transplant patients. Support Care Cancer. 2012 Jul;20(7):1405-15. doi: 10.1007/s00520-011-1223-8.	USA
Simões A, Benites BM, Benassi C, Torres-Schroter G, de Castro JR, Campos L. Antimicrobial photodynamic therapy on treatment of infected radiation-induced oral mucositis: Report of two cases. Photodiagnosis Photodyn Ther. 2017 Dec;20:18-20. doi: 10.1016/j.pdpdt.2017.08.007.	Brazil
Freitas AC, Campos L, Brandão TB, Cristófaro M, Eduardo Fde P, Luiz AC, et al. Chemotherapy-induced oral mucositis: effect of LED and laser phototherapy treatment protocols. Photomed Laser Surg. 2014 Feb;32(2):81-7. doi: 10.1089/pho.2013.3576.	Brazil
Sharon-Buller A, Sela M. CO2-laser treatment of ulcerative lesions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004 Mar;97(3):332-4. doi: 10.1016/j.tripleo.2003.11.012	Israel
Oton-Leite AF, Corrêa de Castro AC, Morais MO, Pinezi JC, Leles CR, Mendonça EF. Effect of intraoral low-level laser therapy on quality of life of patients with head and neck cancer undergoing radiotherapy. Head Neck. 2012 Mar;34(3):398-404. doi: 10.1002/hed.21737.	Brazil
Arun Maiya G, Sagar MS, Fernandes D. Effect of low level helium-neon (He-Ne) laser therapy in the prevention & treatment of radiation induced mucositis in head & neck cancer patients. Indian J Med Res. 2006 Oct;124(4):399-402.	India
Oton-Leite AF, Silva GB, Morais MO, Silva TA, Leles CR, Valadares MC, et al. Effect of low-level laser therapy on chemoradiotherapy-induced oral mucositis and salivary inflammatory mediators in head and neck cancer patients. Lasers Surg Med. 2015 Apr;47(4):296-305. doi: 10.1002/lsm.22349.	Brazil
Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya AG, Nigudgi S. Effect of low-level laser therapy on patient reported measures of oral mucositis and quality of life in head and neck cancer patients receiving chemoradiotherapy--a randomized controlled trial. Support Care Cancer. 2013 May;21(5):1421-8. doi: 10.1007/s00520-012-1684-4.	India
Salvador DRN, Soave DF, Sacono NT, de Castro EF, Silva GBL, E Silva LP, et al. Effect of photobiomodulation therapy on reducing the chemo-induced oral mucositis severity and on salivary levels of CXCL8/interleukin 8, nitrite, and myeloperoxidase in patients undergoing hematopoietic stem cell transplantation: a randomized clinical trial. Lasers Med Sci. 2017 Nov;32(8):1801-1810. doi: 10.1007/s10103-017-2263-1.	Brazil
Amadori F, Bardellini E, Majorana A. Effectiveness of IIIt in the prevention and treatment of chemotherapy-induced oral mucositis in children. Support Care Cancer. 2018;26(2 Suppl 1):S139.	Italy
de Paula Eduardo F, Bezinelli LM, da Graça Lopes RM, Nascimento Sobrinho JJ, Hamerschlak N, Correa L. Efficacy of cryotherapy associated with laser therapy for decreasing severity of melphalan-induced oral mucositis during hematological stem-cell transplantation: a prospective clinical study. Hematol Oncol. 2015 Sep;33(3):152-8. doi: 10.1002/hon.2133.	Brazil
Arora H, Pai KM, Maiya A, Vidyasagar MS, Rajeev A. Efficacy of He-Ne Laser in the prevention and treatment of radiotherapy-induced oral mucositis in oral cancer patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008 Feb;105(2):180-6, 186.e1. doi: 10.1016/j.tripleo.2007.07.043.	India
Lima AG, Antequera R, Peres MP, Snitcosky IM, Federico MH, Villar RC. Efficacy of low-level laser therapy and aluminum hydroxide in patients with chemotherapy and radiotherapy-induced oral mucositis. Braz Dent J. 2010;21(3):186-92. doi: 10.1590/s0103-64402010000300002.	Brazil
González-Arriagada WA, Ramos LMA, Andrade MAC, Lopes MA. Efficacy of low-level laser therapy as an auxiliary tool for management of acute side effects of head and neck radiotherapy. J Cosmet Laser Ther. 2018 Apr;20(2):117-122. doi: 10.1080/14764172.2017.1376097.	Brazil
Carvalho PA, Lessa RC, Guollo A, Carraro DM, Lopes RN. Evaluation of laser therapy in the prevention of oral mucositis related to radiotherapy: Comparison among the effects of three different low-power laser protocols. Head Neck. 2015;37(Suppl 1):E187-8.	Brazil
Ahmed KM, Hussein SA, Noori AJ, Abdulateef SN, Abdulla BK. Evaluation of Low Level Laser Therapy in the management of chemotherapy-induced oral mucositis in pediatric and young cancer patients: a randomized clinical trial. Eur Sci J. 2015;11(27):209-22.	Iraq
Leite Cavalcanti A, José de Macêdo D, Suely Barros Dantas F, Dos Santos Menezes K, Filipe Bezerra Silva D, Alves de Melo Junior W, et al. Evaluation of oral mucositis occurrence in oncologic patients under antineoplastic therapy submitted to the low-level laser coadjuvant therapy. J Clin Med. 2018 Apr 24;7(5):90. doi: 10.3390/jcm7050090.	Brazil
Barasch A, Peterson DE, Tanzer JM, D'Ambrosio JA, Nuki K, Schubert MM, et al. Helium-neon laser effects on conditioning-induced oral mucositis in bone marrow transplantation patients. Cancer. 1995 Dec 15;76(12):2550-6. doi: 10.1002/1097-0142(19951215)76:12<2550::aid-cncr2820761222>3.0.co;2-x.	USA
Cruz LB, Ribeiro AS, Rech A, Rosa LG, Castro CG Jr, Brunetto AL. Influence of low-energy laser in the prevention of oral mucositis in children with cancer receiving chemotherapy. Pediatr Blood Cancer. 2007 Apr;48(4):435-40. doi: 10.1002/pbc.20943.	Brazil
Lino MD, Carvalho FB, Oliveira LR, Magalhães EB, Pinheiro AL, Ramalho LM. Laser phototherapy as a treatment for radiotherapy-induced oral mucositis. Braz Dent J. 2011;22(2):162-5. doi: 10.1590/s0103-64402011000200013.	Brazil

Simões A, Eduardo FP, Luiz AC, Campos L, Sá PH, Cristófaro M, et al. Laser phototherapy as topical prophylaxis against head and neck cancer radiotherapy-induced oral mucositis: comparison between low and high/low power lasers. Lasers Surg Med. 2009 Apr;41(4):264-70. doi: 10.1002/lsm.20758.	Brazil
Schulze Selting K, Dittus D, Döring M, Handgretinger R, Barth M. Laser therapy - a new treatment option on oral mucositis. Bone Marrow Transplant. 2014;49(Suppl 1):S399.	Germany
Lang-Bicudo L, Eduardo Fde P, Eduardo Cde P, Zezell DM. LED phototherapy to prevent mucositis: a case report. Photomed Laser Surg. 2008 Dec;26(6):609-13. doi: 10.1089/pho.2007.2228.	Brazil
Quinn A, Holeva K, Clump D. Light years ahead: Use of low level laser therapy for oral mucositis. Oncol Nurs Forum. 2015;42(2):E173.	USA
Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya GA. Low level helium neon laser therapy for chemoradiotherapy induced oral mucositis in oral cancer patients - a randomized controlled trial. Oral Oncol. 2012 Sep;48(9):893-7. doi: 10.1016/j.oraloncology.2012.03.008.	India
Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya AG, Vadhiraja BM. Low level laser therapy for concurrent chemoradiotherapy induced oral mucositis in head and neck cancer patients - a triple blinded randomized controlled trial. Radiother Oncol. 2012 Sep;104(3):349-54. doi: 10.1016/j.radonc.2012.06.011.	India
Pereira EM, De Almeida Lawall M, Vieira CL, Veras GR. Low level laser therapy in oral mucositis: A case report. Head Neck. 2015;37(Suppl 1):E142.	Brazil
Cauwels RGEC, Martens LC. Low level laser therapy in oral mucositis: a pilot study. Eur Arch Paediatr Dent. 2011;12(2):118-23.	Belgium
Bensadoun RJ, Franquin JC, Ciais G, Darcourt V, Schubert MM, Viot M, et al. Low-energy He/Ne laser in the prevention of radiation-induced mucositis: A multicenter phase III randomized study in patients with head and neck cancer. Support Care Cancer. 1999 Jul;7(4):244-52. doi: 10.1007/s005200050256.	France
Jaguar GC, Prado JD, Nishimoto IN, Pinheiro MC, de Castro DO Jr, da Cruz Perez DE, et al. Low-energy laser therapy for prevention of oral mucositis in hematopoietic stem cell transplantation. Oral Dis. 2007 Nov;13(6):538-43. doi: 10.1111/j.1601-0825.2006.01330.x.	Brazil
Kuhn A, Porto FA, Miraglia P, Brunetto AL. Low-level infrared laser therapy in chemotherapy-induced oral mucositis: a randomized placebo-controlled trial in children. J Pediatr Hematol Oncol. 2009 Jan;31(1):33-7. doi: 10.1097/MPH.0b013e318192cb8e.	Brazil
Kuhn A, Vacaro G, Almeida D, Machado Á, Braghini PB, Shilling MA, et al. Low-level infrared laser therapy for chemo- or radiotherapy-induced oral mucositis: a randomized, placebo-controlled study. J Oral Laser Applications. 2007;7:175-81.	Brazil
Amadori F, Bardellini E, Conti G, Pedrini N, Schumacher RF, Majorana A. Low-level laser therapy for treatment of chemotherapy-induced oral mucositis in childhood: a randomized double-blind controlled study. Lasers Med Sci. 2016 Aug;31(6):1231-6. doi: 10.1007/s10103-016-1975-y.	Italy
Abramoff MM, Lopes NN, Lopes LA, Dib LL, Guilherme A, Caran EM, et al. Low-level laser therapy in the prevention and treatment of chemotherapy-induced oral mucositis in young patients. Photomed Laser Surg. 2008 Aug;26(4):393-400. doi: 10.1089/pho.2007.2144.	Brazil
Antunes HS, de Azevedo AM, da Silva Bouzas LF, Adão CA, Pinheiro CT, Mayhe R, et al. Low-power laser in the prevention of induced oral mucositis in bone marrow transplantation patients: a randomized trial. Blood. 2007 Mar 1;109(5):2250-5. doi: 10.1182/blood-2006-07-035022.	Brazil
Medeiros NJ, Medeiros NF, Santos CC, Parente GV, Carvalho JN. Low-power laser therapy in chemical-induced oral mucositis: a case study. Braz J Otorhinolaryngol. 2013 Nov-Dec;79(6):792. English, Portuguese. doi: 10.5935/1808-8694.20130143.	Brazil
Libik TV, Gileva OS, Danilov KV, Grigorev SS, Pozdnyakova AA. Management of cancer therapy-induced oral mucositis pain and xerostomia with extra- and intra oral laser irradiation. AIP Conference Proceedings. 2017;1882:020044. doi: 10.1063/1.5001623.	Russia
Gobbo M, Verzegnassi F, Ronfani L, Zanon D, Melchionda F, Bagattoni S, et al. Multicenter randomized, double-blind controlled trial to evaluate the efficacy of laser therapy for the treatment of severe oral mucositis induced by chemotherapy in children: laMPO RCT. Pediatr Blood Cancer. 2018 Aug;65(8):e27098. doi: 10.1002/pbc.27098.	Italy
Whelan HT, Connelly JF, Hodgson BD, Barbeau L, Post AC, Bullard G, et al. NASA light-emitting diodes for the prevention of oral mucositis in pediatric bone marrow transplant patients. J Clin Laser Med Surg. 2002 Dec;20(6):319-24. doi: 10.1089/104454702320901107.	USA
Eduardo Fde P, Bezinelli LM, de Carvalho DL, Lopes RM, Fernandes JF, Brumatti M, et al. Oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation: clinical outcomes in a context of specialized oral care using low-level laser therapy. Pediatr Transplant. 2015 May;19(3):316-25. doi: 10.1111/petr.12440.	Brazil
Montmaneix N, Chausset A, Sozeau C, Merlin E, Duclos C. Paediatric experience in low-level laser therapy in the prevention of oral mucositis. Bone Marrow Transplant. 2011;46(1):S417.	France
Ribeiro da Silva VC, da Motta Silveira FM, Barbosa Monteiro MG, da Cruz MMD, Caldas Júnior AF, Pina Godoy G. Photodynamic therapy for treatment of oral mucositis: Pilot study with pediatric patients undergoing chemotherapy. Photodiagnosis Photodyn Ther. 2018 Mar;21:115-120. doi: 10.1016/j.pdpdt.2017.11.010.	Brazil
Wong SF, Wilder-Smith P. Pilot study of laser effects on oral mucositis in patients receiving chemotherapy. Cancer J. 2002 May-Jun;8(3):247-54. doi: 10.1097/00130404-200205000-00008.	USA
Soto M, Lalla RV, Gouveia RV, Zecchin VG, Seber A, Lopes NN. Pilot study on the efficacy of combined intraoral and extraoral low-level laser therapy for prevention of oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation. Photomed Laser Surg. 2015 Nov;33(11):540-6. doi: 10.1089/pho.2015.3954.	Brazil

Bezinelli LM, Eduardo FP, Neves VD, Correa L, Lopes RM, Michel-Crosato E, et al. Quality of life related to oral mucositis of patients undergoing haematopoietic stem cell transplantation and receiving specialised oral care with low-level laser therapy: A prospective observational study. Eur J Cancer Care (Engl). 2016 Jul;25(4):668-74. doi: 10.1111/ecc.12344.	Brazil
Eduardo FP, Bezinelli L, Luiz AC, Correa L, Vogel C, Eduardo CP. Severity of oral mucositis in patients undergoing hematopoietic cell transplantation and an oral laser phototherapy protocol: a survey of 30 patients. Photomed Laser Surg. 2009 Feb;27(1):137-44. doi: 10.1089/pho.2007.2225.	Brazil
Curra M, De Campos Baldin JJCM, Carvalho ALH, Martins MAT, Daudt LE, Gaio EJ, et al. Severity of oral mucositis in patients undergoing hematopoietic stem cell transplantation and correlation with oral status. Head Neck. 2015;37(Suppl 1):E157.	Brazil
Chor A, de Azevedo AM, Maiolino A, Nucci M. Successful treatment of oral lesions of chronic lichenoid graft-vs.-host disease by the addition of low-level laser therapy to systemic immunosuppression. Eur J Haematol. 2004 Mar;72(3):222-4. doi: 10.1046/j.0902-4441.2003.00202.x.	Brazil
Silva GB, Mendonça EF, Bariani C, Antunes HS, Silva MA. The prevention of induced oral mucositis with low-level laser therapy in bone marrow transplantation patients: a randomized clinical trial. Photomed Laser Surg. 2011 Jan;29(1):27-31. doi: 10.1089/pho.2009.2699.	Brazil
Genot-Klastersky MT, Klastersky J, Awada F, Awada A, Crombez P, Martinez MD, Jaivenois MF, Delmelle M, Vogt G, Meuleman N, Paesmans M. The use of low-energy laser (LEL) for the prevention of chemotherapy- and/or radiotherapy-induced oral mucositis in cancer patients: results from two prospective studies. Support Care Cancer. 2008 Dec;16(12):1381-7. doi: 10.1007/s00520-008-0439-8.	Belgium
Corti L, Chiarion-Sileni V, Aversa S, Ponzoni A, D'Arcais R, Pagnutti S, et al. Treatment of chemotherapy-induced oral mucositis with light-emitting diode. Photomed Laser Surg. 2006 Apr;24(2):207-13. doi: 10.1089/pho.2006.24.207.	
de Fátima Lima Ferreira M, de Carvalho FB, de Oliveira SCPS, Monteiro JSC, Santos GMP, Gesteira MFM, et al. Use of laser photomodulation in the evolution of oral mucositis associated to cyclophosphamide, methotrexate, 5-fluouracil - CMF in 5 fluouracil + adriamycin + cyclophosphamide - FAC chemotherapy protocols in patients with breast cancer. Proc SPIE 8569, Mechanisms for Low-Light Therapy VIII, 85690O. 2013. doi: 10.1117/12.2005274	Brazil
Khouri VY, Stracieri ABPL, Rodrigues MC, de Moraes DA, Pieroni F, Simões BP, et al. Use of therapeutic laser for prevention and treatment of oral mucositis. Braz Dent J. 2009;20(3):215-20. doi: 10.1590/S0103-64402009000300008.	Brazil
Guedes CDCFV, de Freitas Filho SAJ, de Faria PR, Loyola AM, Sabino-Silva R, Cardoso SV. Variation of Energy in Photobiomodulation for the Control of Radiotherapy-Induced Oral Mucositis: A Clinical Study in Head and Neck Cancer Patients. Int J Dent. 2018 Feb 22;2018:4579279. doi: 10.1155/2018/4579279.	Brazil
Moskvin S, Pritiko D, Sergeenko E, Lukash E, Gusev L. A brief literature review and own clinical experience in prophylaxis of oral mucositis in children using low level laser therapy. Biomedicine (Taipei). 2019 Mar;9(1):1. doi: 10.1051/bmdcn/2019090101.	Russia
Rezk-Allah SS, Abd Elshaf HM, Farid RJ, Hassan MAE, Alsirafy SA. Effect of Low-Level Laser Therapy in Treatment of Chemotherapy Induced Oral Mucositis. J Lasers Med Sci. 2019 Spring;10(2):125-130. doi: 10.15171/jlms.2019.20.	Egypt
Giacco CA, Castro S, Fluck V, Martinez JE, Higuera J. Evaluation of patients with oral mucositis following oncological treatment and treated with low intensity laser. Biocell. 2019;43(Suppl 3):A91.	Argentina
Lavaee F, Amanati A, Ramzi M, Naseri S, Shakiba Sefat H. Evaluation of the effect of photodynamic therapy on chemotherapy induced oral mucositis. Photodiagnosis Photodyn Ther. 2020 Jun;30:101653. doi: 10.1016/j.pdpdt.2020.101653.	Iran
Legouté F, Bensadoun RJ, Seegers V, Pointreau Y, Caron D, Lang P, et al. Low-level laser therapy in treatment of chemoradiotherapy-induced mucositis in head and neck cancer: Results of a randomised, triple blind, multicentre phase III trial. Radiat Oncol. 2019 May 22;14(1):83. doi: 10.1186/s13014-019-1292-2.	France
Pires Marques EC, Piccolo Lopes F, Nascimento IC, Morelli J, Pereira MV, Machado Meiken VM, et al. Photobiomodulation and photodynamic therapy for the treatment of oral mucositis in patients with cancer. Photodiagnosis Photodyn Ther. 2020 Mar;29:101621. doi: 10.1016/j.pdpdt.2019.101621.	Brazil
Rupel K, Zupin L, Colliva A, Kamada A, Poropat A, Ottaviani G, et al. Photobiomodulation at multiple wavelengths differentially modulates oxidative stress in vitro and in vivo. Oxid Med Cell Longev. 2018 Nov 11;2018:6510159. doi: 10.1155/2018/6510159.	
Pinheiro SL, Bonadiman AC, Borges Lemos ALDA, Annicchino BM, Segatti B, Pucca DS, et al. Photobiomodulation therapy in cancer patients with mucositis: a clinical evaluation. Photobiomodul Photomed Laser Surg. 2019 Mar;37(3):142-150. doi: 10.1089/photob.2018.4526.	Brazil
El Mobadder M, Farhat F, El Mobadder W, Nammour S. Photobiomodulation Therapy in the Treatment of Oral Mucositis, Dysphagia, Oral Dryness, Taste Alteration, and Burning Mouth Sensation Due to Cancer Therapy: A Case Series. Int J Environ Res Public Health. 2019 Nov 15;16(22):4505. doi: 10.3390/ijerph16224505.	Lebanon
Noirrit-Esclassan E, Valera MC, Vignes E, Munzer C, Bonal S, Daries M, et al. Photobiomodulation with a combination of two wavelengths in the treatment of oral mucositis in children: The PEDIALASE feasibility study. Arch Pediatr. 2019 Jul;26(5):268-274. doi: 10.1016/j.arcped.2019.05.012.	France
Nunes LFM, de Arruda JAA, Souza AF, Silva RCC, Lanza CRM, Kakehasi FM, et al. Prophylactic photobiomodulation therapy using 660 nm diode laser for oral mucositis in paediatric patients under chemotherapy: 5-year experience from a Brazilian referral service. Lasers Med Sci. 2020 Oct;35(8):1857-1866. doi: 10.1007/s10103-020-03060-9.	Brazil

Minicucci EM, Cruz AR, Simoes CC, Gomes DO, Felipe DF. Protocol and preliminary results of symptoms and control of mucositis in patients submitted to autologous stem cell transplantation. Support Care Cancer. 2019;27(Suppl 1):S128.	Brazil
Bourbonne V, Otz J, Bensadoun RJ, Dissaux G, Lucia F, Leclere JC, et al. Radiotherapy mucositis in head and neck cancer: prevention by low-energy surface laser. BMJ Support Palliat Care. 2019 Sep 16:bmjspcare-2019-001851. doi: 10.1136/bmjspcare-2019-001851.	France
Soares RG, Farias LC, da Silva Menezes AS, de Oliveira E Silva CS, Tabosa ATL, Chagas PVF, et al. Treatment of mucositis with combined 660- and 808-nm-wavelength low-level laser therapy reduced mucositis grade, pain, and use of analgesics: a parallel, single-blind, two-arm controlled study. Lasers Med Sci. 2018 Nov;33(8):1813-1819. doi: 10.1007/s10103-018-2549-y.	Brazil
Genot-Klastersky MT, Paesmans M, Ameye L, Kayumba A, Beauvois S, Dragan T, et al. Retrospective evaluation of the safety of low-level laser therapy/photobiomodulation in patients with head/neck cancer. Support Care Cancer. 2020 Jul;28(7):3015-3022. doi: 10.1007/s00520-019-05041-3.	Belgium

Supplementary Table 6: Trials to consider for future systematic reviews/meta-analyses

Title	Contact	URL	Date of registration/start	Reason for consideration
Divergent Low Level Laser Therapy as novel treatment for oral mucositis in pediatric cancer patients	Tissing, WJE	https://apps.who.int/trialsearch/Trial2.aspx?TrialID=NTR5659	2016-01-19	Children, RCT
Low-level Laser Therapy in the Prevention of Chemotherapy-induced Mucositis in Children and Young Adults Treated for a Tumoral Disease (MUCILA)	Roussy, G	https://clinicaltrials.gov/ct2/show/NCT03983369	2018-09-12	Children and young adults, multicenter RCT
Oral Manifestations in Children With Cancer	Gurgel, BCV	https://clinicaltrials.gov/ct2/show/NCT02662465	2016-01-25	RCT including age 1-25
Effectiveness of Diode low-level laser therapy on treatment of mucositis induced by chemoradiotherapy in H&N cancer patients referring to Guilan(Rasht) dental college:A single- blind randomized clinical trial	Barati, S	http://en.irct.ir/trial/33928	2018-12-03	Any age, single blind randomised trial
Prevention of Oral Mucositis Using Photobiomodulation Therapy	Mandrell, B	https://clinicaltrials.gov/ct2/show/NCT04227340	2020-01-13	Feasibility study, children. May provide further safety information.
Low-Level Laser Therapy for Prevention of Oral Mucositis	Clump, DA	https://clinicaltrials.gov/ct2/show/NCT02682992	2016-02-17	Adults only – safety information
LiTEFORM. Lite Therapy Effectiveness For ORal Mucositis Trial. A randomised controlled trial of the clinical and cost effectiveness of Low Level Laser in the management of Oral Mucositis in Head and Neck cancer irradiation	Nugent, M	https://www.icrpartnership.org/project/114786	2017-01-01	Adults only – safety information
Effectiveness of Low Energy Laser Treatment in Oral Mucositis Induced by Chemotherapy and Radiotherapy in Head and Neck Cancer	Lagares, D	https://clinicaltrials.gov/ct2/show/NCT01876407	2013-06-12	Adults only – safety information

Low-Level Laser Therapy for Prevention of Oral Mucositis	Kim, H	https://clinicaltrials.gov/ct2/show/NCT02723604	2016-03-30	Adults only – safety information
Photobiomodulation to Demonstrate Safety and Reduce the Incidence of Oral Mucositis in Adult Head & Neck Cancer Patients	Kothari, V	https://clinicaltrials.gov/ct2/show/NCT03972527	2019-06-03	Adults only – safety information
Head and neck cancer/Oral Mucositis	Unknown	https://www.centerwatch.com/clinical-trials/listings/221549/head-and-neck-canceroral-mucositis-4/?section=elg	Unknown	Adults only – safety information
Evaluation of Low-Level Laser Therapy Efficacy in Pain Management of Grade 2 Oral Mucositis Induced by Radiotherapy or Chemoradiotherapy: a Study in Patients With Upper Aerodigestive Tract Cancer (ESMULLLAT)	Vigarios, E	https://clinicaltrials.gov/show/NCT03955224	2019-05-20	Adults only – safety information
Effect of photobiomodulation on the severity of oral mucositis and molecular changes in head and neck cancer patients undergoing radiotherapy: a study protocol for a cost-effectiveness randomized clinical trial	Martins, AFL	https://doi.org/10.1186/s13063-019-3196-8	2017-08	Adults only – safety information

Supplementary Table 7: Protocols used by the studies included in the efficacy comparison (Empty fields indicate information not available)

Author & Year	**Hodgson 2012**	**Salvador 2017**	**Amadori 2018**	**Ahmed 2015**	**Cruz 2007**	***Kuhn 2009***	**Amadori 2016**	**Abramoff 2008**	**Gobbo 2018**	**Cowen 1997**	**Fani 2013**	**Silva 2015**	**Silva 2011**	**Khouri 2009**
Study	Amelioration of oral mucositis pain by NASA near-infrared light-emitting diodes in bone marrow transplant patients	Effect of photobiomodulation therapy on reducing the chemo-induced oral mucositis severity and on salivary levels of CXCL8/interleukin 8, nitrite, and myeloperoxidase in patients undergoing hematopoietic stem cell transplantation: a randomized clinical trial	Effectiveness of low-level laser therapy in the prevention and treatment of chemotherapy-induced oral mucositis in children	Evaluation of Low Level Laser Therapy in the Management of Chemotherapy-Induced Oral Mucositis in Pediatric and Young Cancer Patients : a Randomized Clinical Trial	Influence of low-energy laser in the prevention of oral mucositis in children with cancer receiving chemotherapy	Low-level infrared laser therapy in chemotherapy-induced oral mucositis: a randomized placebo-controlled trial in children.	Low-level laser therapy for treatment of chemotherapy-induced oral mucositis in childhood: a randomized double-blind controlled study.	Low-level laser therapy in the prevention and treatment of chemotherapy-induced oral mucositis in young patients	Multicenter randomized, double-blind controlled trial to evaluate the efficacy of laser therapy for the treatment of severe oral mucositis induced by chemotherapy in children: laMPO RCT.	Low energy Helium-Neon laser in the prevention of oral mucositis in patients undergoing bone marrow transplant: results of a double blind randomized trial.	The effect of the low-level laser on prevention of chemotherapy-induced oral mucositis in patients with acute leukemia	The Impact of Low-Level Laser Therapy on Oral Mucositis and Quality of Life in Patients Undergoing Hematopoietic Stem Cell Transplantation Using the Oral Health Impact Profile and the Functional Assessment of Cancer Therapy-Bone Marrow Transplantation Que	The Prevention of Induced Oral Mucositis with Low-Level Laser Therapy in Bone Marrow Transplantation Patients: A Randomized Clinical Trial	Use of therapeutic laser for prevention and treatment of oral mucositis
No of children	29	***unknown***	***unknown***	***unknown***	60	21	123	13	101	2	***unknown***	***unknown***	***unknown***	***unknown***

Prevention and or Treatment	Prevention/treatment	Prevention/treatment	Prevention/treatment	Prevention/treatment	Prevention	Treatment	Treatment	Prevention/treatment	Treatment	Prevention	Prevention	Prevention	Prevention	Prevention/treatment
Intra oral or extra oral	Extraoral	Intraoral	Intraoral	intraoral	intraoral	intraoral	intraoral	intraoral	intraoral	intraoral	intraoral	intraoral	intraoral	intraoral
Country	USA	Brazil	Italy	Iraq	Brazil	Brazil	Italy	Brazil	Italy	France	Iran	Brazil	Brazil	Brazil
Laser details														
Laser used	LED device (Warp 75, Quantum Devices, Barneveld, WI)	InGaAlP laser diode (Twin laser, MMOptics Ltda., São Carlos, SP, Brazil)	diode laser	iLase™ (BIOLASE, Inc., Irivine, CA92618 USA, continuous infrared AlGalnAs diode)	MMOptics laser	GaA1As laser [Dental Manufactory Company (DMC) Equipment (Sao Carlos, SP, Brazil)]	diode laser (DioBeam 830, CMS Dental, Copenhagen, Denmark).	AsGaAl diode laser (THERA LASER; DMC Equipments Ltda. São Carlos, Brazil)	diode laser device (class IV, K-Laser Cube series, Eltech K-Laser, Via Castagnole 20/H, Treviso, Italy)	He-Ne laser. prototype purchased from Fradama S.A., Geneva, Switzerland.	A diode laser (Aluminum Gallium Indium; Azor-2k-02, Russia)	InGaAlP diode laser	InGaAlP diode laser	indium gallium aluminum phosphide (InGaAlP) AND and gallium aluminum arsenide (GaAlAs) lasers
Wavelength	670 (±10)nm	660 nm	830nm	940±15nm	780nm	830nm	830nm	685nm	660 and 970nm combined wavelengths	632.8nm	660nm	660nm	660nm	660nm and 780 nk
Fluence								72 J/cm2	36.8 J/cm2					
Energy delivery (density)	4 J/cm2	4 J/cm2	Prophylactic - 2.2 J/cm2; Therapeutic - 4.5 J/cm2	4.2 J/cm²	4J/cm2	4 J/cm2	4.5 J/cm2		8 J/cm2	1.5 J/cm2	1.5 J per point	4 J/cm2	4 J/cm2	6.3 J/cm2

Number of irradiated points	2	10		10	5		5	18	9	15	12	10	10	
Energy delivered	12 J/cm2/treatment	12.8 J/day						2 J per point of application	8J/ area	54 J/session		12.8 J/day	12.8 J/day	
Spot size		0.04 cm2	1 cm2				1 cm2	600 micrometer spot	1 cm2		2mm	0.04 cm2	0.04 cm3	
Time spent at each point (seconds)	80 s	4s	Prophylactic - 15s; Therapeutic - 30s	30s			30s	54 s	25 s	10s	60s	4s	4s	10s
Power density	~50 mW/cm2													
Power		40mw	150mW	0.3mW 'output power' (sounds wrong??)	60mW	100mW	150mW	35mW	3.2W Peak	60mW	25 mW	40mW	40mW	25 mW
Frequency of LLLT	daily	daily	daily	daily	daily	daily	daily	alternate days	daily	daily	twice weekly	daily	daily	daily (different laser on alternate days)

Duration of LLLT	15 days	from the first day of the conditioning regimen and continued every day until the seventh post-transplant day (D+7)	5 days	3 weeks	5 days	5 days	4 days	5 days (prophylactic); 5 days MINIMUM (therapeutic)	4 days	5 days (d-5 to d-1)	1 month	1st day of the conditioning regimen through to the 7th day after transplantation (D + 7	Daily sessions began on D-4 and continued through to D+4.	Prevention: 1st day of conditioning until clinical manifestation of oral mucositis. Treatment: started from initial clinical manifestations of mucositis with follow-up until D+15 after transplantation

Supplementary Table 8: Merging WHO and NCI CTC grading systems

Merging of WHO and NCI CTC grades
Different authors used different grading scales for the severity of oral mucositis. Hodgson et al[1] provided us with unpublished baseline data for their patients, including each time WHO & NCI CTC grades measured. This gave us 157 NCI CTC measurements to compare with 157 WHO measurements in our population of children with cancer. Comparing the frequency of measurements of different grades, we used Spearman's rank correlation co-efficient. This demonstrated Spearman's p = 0.7 [95% CI -0.477, 0.978], p value = 0.233[2]. There is a strong correlation between these results – even though the description of the grades has some differences, operationally they are similar, with no statistically significant difference between them. Therefore, we chose to combine WHO & NCI CTC grades for the meta-analysis. Both WHO & NCI CTC grades define grade 3 as severe.[3] For the meta-analysis, we compared those with grade ≥3 (severe to life-threatening) mucositis with grade ≤2 (none to moderate) mucositis to enable exploration of the outcome measure of severity of oral mucositis.
1 - Hodgson BD, Margolis DM, Salzman DE, et al. Amelioration of oral mucositis pain by NASA near-infrared light-emitting diodes in bone marrow transplant patients. Support Care Cancer. 2012;20(7):1405-1415. doi:10.1007/s00520-011-1223-8. 2 - Statistical software used: Correlation test. Langtest web application. Available from: http://langtest.jp/shiny/cor/ [cited 25th August 2020]. 3 – National Institute for Health and Care Excellence. IP overview: Low-level laser therapy for preventing or treating oral mucositis caused by radiotherapy or chemotherapy. Available from: https://www.nice.org.uk/guidance/ipg615/documents/overview [cited 14th Feb 2021].

Supplementary Table 9: Narrative synthesis considering effect of LLLT on oral pain

RCT	Effect of LLLT on oral pain
Abramoff 2008	Authors state pain relief in the group receiving therapeutic laser, but statistical analysis is not performed.
Ahmed 2015	(Note: Some patients were adults). Prophylactic laser reduced oral pain on day 12 (laser median = 2.5, sham median = 4, p=0.032), 14 (laser median = 0, sham median = 3, p=0.008), and 16 (laser median = 0, sham median = 2, p=0.001) of treatment. At days 6, 18 and 20 of treatment, the median score of pain for both groups was 0. At days 8 (laser median = 1.5, sham median = 2, p=0.458) and 10 (laser median =2, sham median =4, p=0.051), there was no statistically significant difference in scores.
Amadori 2016	Median Visual Analogue Scale scores of oral pain lower in the laser group at day 4 (laser group = 1, sham group = 2, p=0.002) and day 7 (laser group median= 0, sham group median = 1, p=0.0005). No difference at day 1 (laser group median = 4, sham group median= 4, p = 0.9)
Amadori 2018	Abstract reports reduction in OM pain in groups receiving LLLT as treatment of OM. Further details not yet published or available.

Cowen 1997	Only 2 patients aged 17 - unable to distil results. Laser application had reduced pain scores on the threshold of statistical significance: mean pain score 12.7 ± 1.3 for laser patients; 20.3 ± 2.5 for control patients (p=0.05).
Gobbo 2018	No reduction in self-reported pain at day 4: laser group median = 4, IQR 2-6; control group median 5, IQR 3-7 (p=0.07). Statistically significant reduction in self-reported pain score at day 7: laser group median = 1, IQR 0-3; control group median 2.5 IQR 1-5 (p=0.006). and day 11: laser group median = 0, IQR 0-1; control group median 1, IQR 0-3 (p=0.01).
Hodgson 2012	Unpublished data used as in meta-analysis. No statistically significant difference. Standardised mean difference 0.50 (95% CI of -0.38 to 1.38) on days 3-5, 0.02 (95% CI of -0.80 to 0.84) on days 8 to 10, and -0.06 (95% CI of -0.88 to 0.76) on days 11-14.

Supplementary Table 10: Effect of LLLT on use of analgesia

RCT	Effect of LLLT on use of analgesia
Amadori 2016]	Children treated with LLLT requested less additional analgesia (morphine, tramadol or paracetamol) than those receiving the sham protocol (p<0.05).
Cruz 2007	No statistically significant difference between the mean amount of days where 'painkillers' were used in the laser group compared to the control group.
Gobbo 2018	No statistically significant difference between the use of analgesics in the laser group compared to the control group.

Supplementary Table 11: Effect of LLLT on nutrition

RCT	Effect of LLLT on diet
Cowen 1997	There was no significant difference between the laser and control group of mean duration of parenteral nutrition (p value not provided; only 2 of 30 patients were children)
Cruz 2007	There was no significant difference between the laser and control group of food intake (kcal) at Day 1 (p=0.207), 8 (p=0.522), or 15 (p=0.876).
Hodgson 2012	This RCT compared patients' ability to tolerate normal/soft/liquid/no diet. Using unpublished data provided by the author and comparing each of the 7 time-points of measurement, there was no significant difference between the laser and control groups (p=0.3239).

Supplementary Table 12: Outcome measures considered where not covered elsewhere

Study	Outcome measure
Hodgson 2012	Incidence and duration of erythema and ulceration, WHO pain assessment
Salvador 2017	Salivary samples
Cruz 2007	Drugs used (antibiotics/antivirals/antifungals) White cell count Buccal health Tooth brushes sessions Nutritional status
Kuhn 2009	Mean duration of OM
Abramoff 2008	changes in granulocyte levels; oesophagitis (NCI criteria)
Gobbo 2018	White cell count/neutrophil count Admission to hospital because of OM alone
Cowen 1997	Use of narcotics, daily scores of saliva production
Silva 2017	Progression of oral mucositis

Supplementary Figure 1: Data extraction form

Laser Therapy in Children with Cancer: Data Extraction Form

Protocol

Melody Redman, Katherine Harris, Bob Phillips. Low level laser therapy to prevent or treat oral mucositis in children with cancer. PROSPERO 2018 CRD42018099772 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018099772

Source

First Author/Editor	Title	Year	Source (e.g. Journal, Trial Registry)

Eligibility for Efficacy/Safety

Criteria		Yes/No/Unclear	Comments
Received laser therapy as an intervention			
For efficacy: Patients <18 with any form of cancer			
For efficacy: Randomised Control Trial (RCT)			
Outcome(s)	oral mucositis, oral pain, etc		
	adverse events		

IF YES TO ALL THE ABOVE, PROCEED.
IF NO TO RCT OR AGE<18, BUT OUTCOMES INCLUDE ADVERSE EVENTS, PROCEED BUT STATE TYPE OF TRIAL IN COMMENTS SECTION.
IF UNCLEAR, AWAIT DISCUSSION WITH SECOND REVIEWER.
IF STUDY IS TO BE EXCLUDED, PLEASE RECORD WHY:

References to this data

If this source has been identified through other methods or the data has been used in other studies, please link the papers in *RevMan 5.3* and list below:

Code	First Author/Editor	Year		Source (e.g. Journal, Trial Registry)

Quality Assessment

If RCT, use Cochrane Risk of Bias tool (Higgins J Green S Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration 2011 https://handbook-5-1.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm).

If other, use BMC Medical Research Methodology (Loke Y, Price D, Herxheimer A, the Cochrane Adverse Effects Methods Group. Systematic reviews of adverse effects: framework for a structured approach. BMC Medical Research Methodology. 2007 Jul 5;7(1):32.)

Trial demographics

	Comments
Number of participants	
Age of participants (average and range e.g. median = 7 years; range = ages 3-17)	
Gender distribution (%, raw numbers e.g. 70 males (50%), 70 females (50%))	
Cancer details (e.g. type: leukaemia, staging)	
Country of study	
Other information	

Trial characteristics

Characteristic	**Comments (state if unclear)**

Single centre or multi-centre	
Eligibility criteria (include definition)	
Method of randomization and how many participants randomized	
Distribution of participants across intervention groups (e.g. Group A = 20, Group B = 22)	
Number of participants who received intended treatment	
Number of participants who were analysed	
Number of participants who experienced an adverse effect	
Form of laser therapy used	
Single or multi-therapy	
Frequency and method of administration (including duration of each session of oral laser therapy)	

Overall duration of treatment	
Setting in which laser therapy administered (e.g. hospital, home)	
Comparator (e.g. nothing, other treatment)	
Median/mean (range) length of follow-up reported in this paper	
Statistical technique used	
Time-points when outcomes were measured during the study (e.g. 3 days, 5 days, 10 days…)	
Time-points reported in the study (e.g. <1 week, <2weeks)	
Type of analysis in study (e.g. intention to treat)	
Other	

Primary outcomes for the review

Outcome	**Reported**	**Comments**
Severity of oral mucositis	**Yes / No**	
Timing and intensity of oral pain (+/-ChIMES score)	**Yes / No**	

Acceptability / adherence to oral low level laser therapy	**Yes / No**	
Symptoms, other than pain, considered important to the paedialow level laser therapytric population	**Yes / No**	
Duration of action of oral low level laser therapy	**Yes / No**	
Oral temperature	**Yes / No**	
Adverse events or reactions	**Yes / No**	

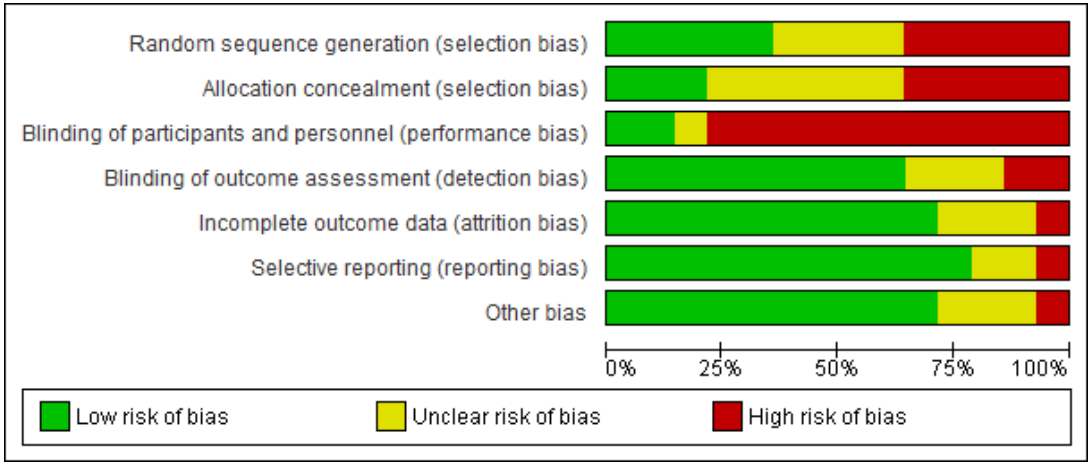
Secondary outcomes for the review

Outcome	**Reported**	**Comments**
Interruptions to cancer treatment	**Yes / No**	
Oral pain on a 0 (no pain) to 10 (maximum pain) scale	**Yes / No**	
Quality of life	**Yes / No**	
Normalcy of diet (days of total parenteral nutrition - TPN)	**Yes / No**	
Duration of hospitalisation (days)	**Yes / No**	
Other	**Yes / No**	

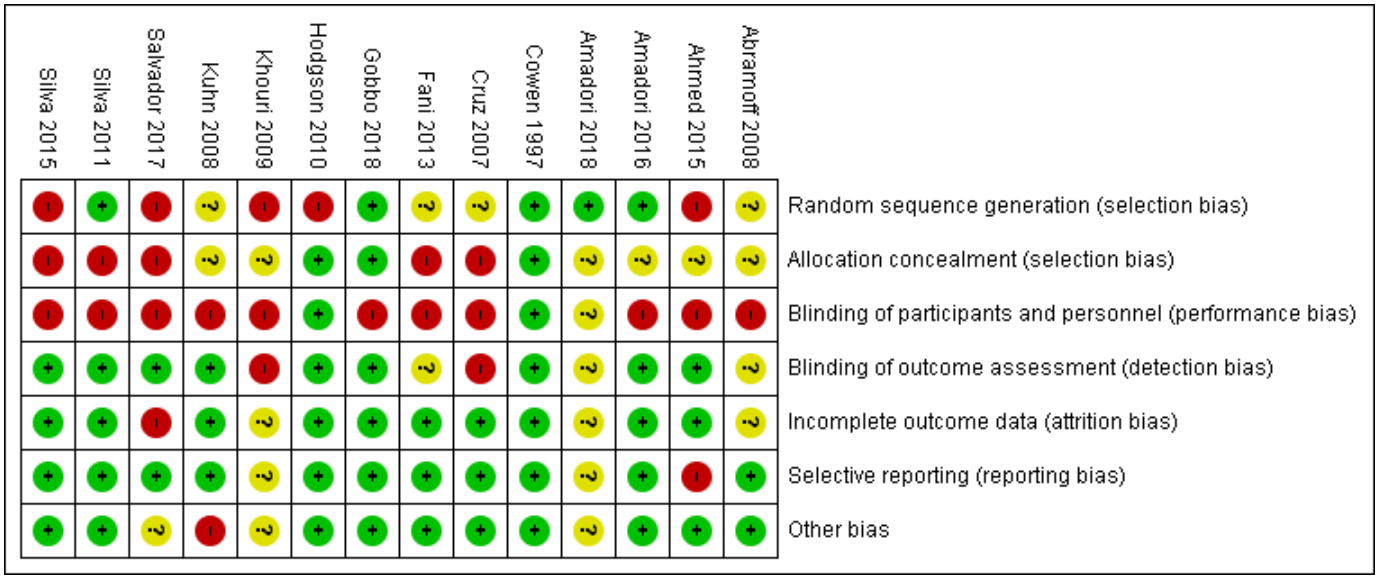
				Code of paper		
				Outcome(s) of interest and definition in study		
				Measurement tool		
				n	**Continuous data**	**Intervention group**
				Mean (SD)		
				Events/number	**Dichotomous data**	
				n	**Continuous data**	**Control group**
				Mean (SD)		
				Episodes or people	**Dichotomous data**	
				SD or SE	**Details if outcome only described in text**	
				Length of follow up		
				Yes/No/ Unclear	**Participants blinded**	***Assessing risk of bias***
				Yes/No/ Unclear	**Assessor blinded**	
				Yes/No/ Unclear	**Blinding of researcher**	
				Other comments		

On assessment of the reference list, are there any potentially relevant studies that haven't been included from the search strategy? Or are there any sources of unpublished data mentioned? If so, list below.			
First Author/Editor	**Title**	**Year**	**Source (e.g. Journal, Trial Registry)**
Contact details for unpublished data			
Any other comments			

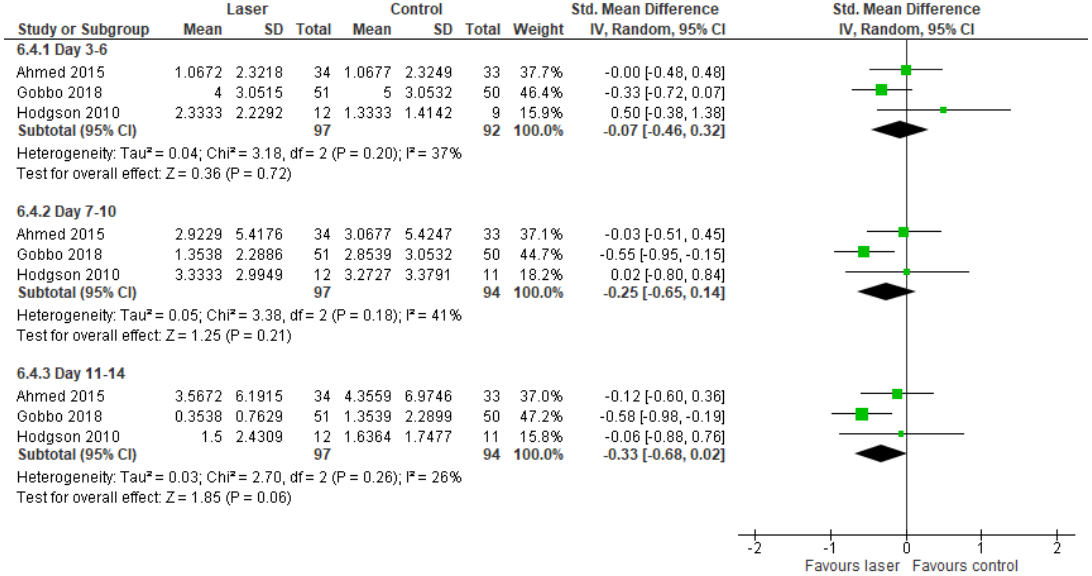
Supplementary Figure 2: Risk of bias graph: assessment of each risk of bias item presented as percentages across all included studies



Supplementary Figure 3: Risk of bias summary: assessment of each risk of bias item for each included study. (? = unclear; + = low risk, - = high risk)

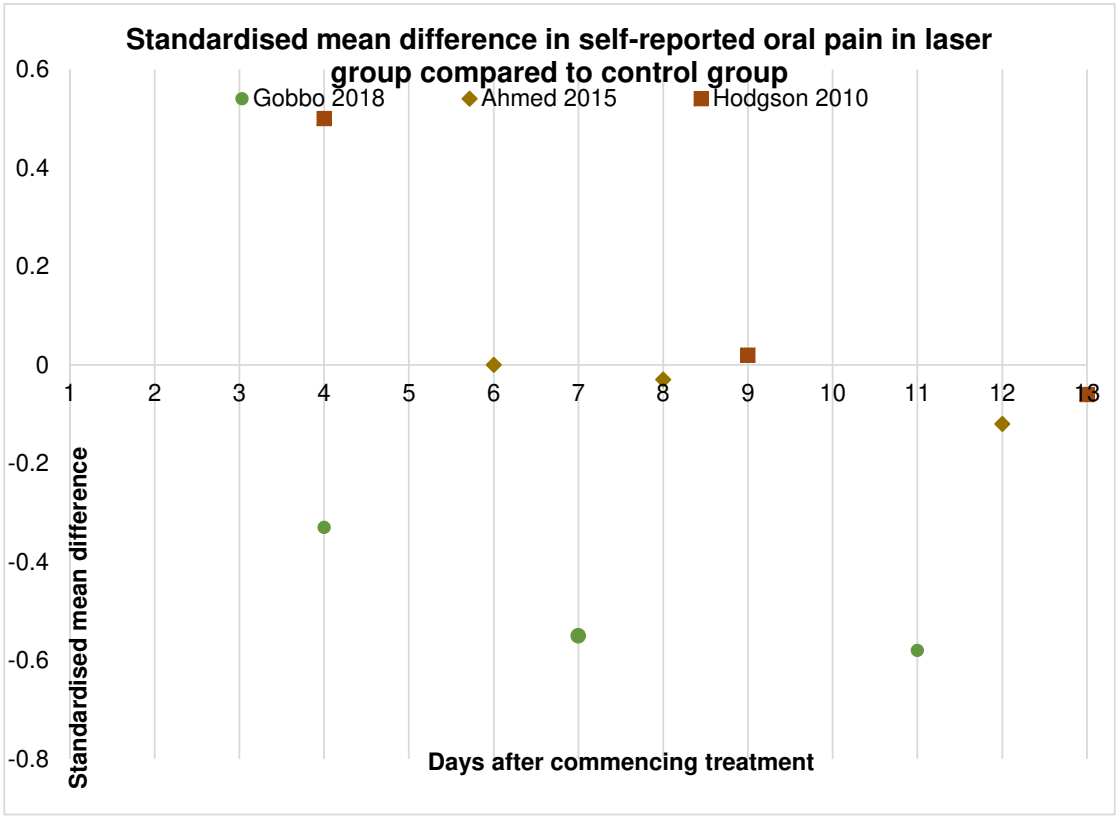


Supplementary Figure 4: Forest plot comparing the standardised mean difference[3] in oral pain out of a 10 point scale



[3] Standardised mean differences were used to allow comparison between different pain scales (some pain scales allowed responses up to 5 and some allowed responses up to 10).

Supplementary Figure 5: Graph comparing standardised mean difference[4] in self-reported oral pain in laser group compared to control group



[4] Standardised mean differences were used to allow comparison between different pain scales (some pain scales allowed responses up to 5 and some allowed responses up to 10).