Low-level laser therapy for oral mucositis in children with cancer:
a meta-analysis & systematic review considering safety and efficacy

Melody G Redmana,b, Katherine Harrisc, Bob S Phillipsd

a: Sheffield Children’s NHS Foundation Trust, UK;
melody.redman@nhs.net
b: Clinical Genetics Department, Chapel Allerton Hospital, Chapeltown Road, Leeds, LS74SA
c: LPOOL; katherineharris@doctors.org.uk, postal address
d: Centre for Reviews and Dissemination, University of York, Heslington, York, YO10 5DD, UK; bob.phillips@york.ac.uk

**Corresponding Author:** Melody G Redman; Clinical Genetics Department, Chapel Allerton Hospital, Chapeltown Road, Leeds, LS74SA, melody.redman@nhs.net

**Competing interests**: The authors have no competing interests to declare.

**Funding:** The public and patient involvement work referred to in this article was supported by the National Institute for Health Research (NIHR) Design Service Yorkshire and the Humber Public Involvement Funds [Call 34]. Additionally, the NIHR funded some of MR & BP’s time which was spent on this work.

**Highlights:**

* Trials considering Low-Level Laser Therapy (LLLT) used a vast range of protocols.
* 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.

**Keywords: (Up to ten from the Medical Subject Headings from Index Medicus)**Neoplasms; Low-Level Light Therapy; Stomatitis; Systematic Review **Acknowledgements:** The authors wish to thank Jessica Morgan for general support, the patients who contributed to our public and patient involvement (PPI) work, and the NIHR for their funding support to enable PPI to take place. We also thank the 26 authors who responded to our requests for further information, with a special thanks to Brian Hodgson and Francesca Amadori for providing detailed unpublished information. We thank Noel Aruparayil, Alexander Cary, and Kirill Horoshenkov for their help with translating papers. We thank Sofia Dias for her advice on statistics.

# Abstract

**Aim**
To assess the efficacy of oral low-level laser therapy (LLLT) in the reduction of oral mucositis experienced by children and young people with cancer undergoing chemotherapy.

**Methods**
A systematic review was undertaken to consider the efficacy of oral LLLT for oral mucositis in children with cancer, and the safety of oral LLLT in any age with cancer (PROSPERO registration: CRD420180997772). 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 considers 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 understand the true effect. 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 2,712 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.

# Introduction

Inflammation and ulceration of the mouth (oral mucositis) is a significant and distressing side effect of chemotherapy and haematopoietic stem cell transplants (HSCT). Oral mucositis can cause pain, problems with nutrition, 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]

Patients and parents emphasised the distress caused by oral mucositis and the need for new treatments for children and young people (CYP). 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 hospital, and asked her mum, “Can’t you just put me to sleep for three months…?”. NICE guidance exists for the use of low-level laser therapy (LLLT) – also known as photobiomodulation (PBM) – 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]

Chemotherapy that CYP undergo is often multi-agent and multi-day - different to adults. CYP are more prone to oral mucositis than adults.[7] Tools from adult oncology are not always directly transferable to paediatric oncology;[8] acceptance and compliance with treatments may not be the same.

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...”[9]

LLLT is only being used for CYP in one centre in the whole of England or Wales.[10] Therefore, we sought to undertake a systematic review.

## Objectives:

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

# Methods

The review protocol was registered on PROSPERO international database [CRD420180997772]. It used approaches based on established methodology systematic review handbooks [11,12].

Eligibility criteria

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

**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  |
| **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 mucositisTiming and intensity of oral pain and ChIMES scoreAcceptability, effectiveness, and adherence to oral low-level laser therapySymptoms, other than pain, considered important to the paediatric populationDuration of action of oral low-level laser therapyOral temperatureAny adverse events.**Additional outcomes:**Interruptions to cancer treatmentOral pain on a 0 (no pain) to 10 (maximum pain) scaleQuality of lifeNormalcy of diet (days of total parenteral nutrition)Duration of hospitalisation (days). |
| **Study design** | Must be an RCT  |

 **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 |

Search strategy
The databases and sources searched included: 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. A 32-step search strategy was used for EMBASE, MEDLINE® and AMED. Alternative search strategies were used for other sources. The search strategy ran from the earliest date available until 28/06/2020, including an update search. Searches were not restricted by age or language. Published and unpublished studies were considered. All studies included for efficacy analysis had their reference lists reviewed. Additional unpublished material was sought from authors and experts in the field.

Data collection
Two reviewers (MR & KH) individually screened all search results. Full texts were obtained and screened where there was any uncertainty about whether the study should be included. Where there was any disagreement about study inclusion, a third reviewer (BP) was consulted. Non-English studies were screened by experienced clinicians and/or academics (see acknowledgments).

Where studies were selected for inclusion, data extraction was either performed by KH or MR and then checked by the other. An example data extraction form is provided in Supplementary Figure 1. Studies are referred to by their first author.

Risk of bias
To assess the efficacy of LLLT, any RCTs that qualified for inclusion were analysed for quality at a study level using the Cochrane risk of bias tool.[12 p.37] When considering the adverse events associated with LLLT, studies were scrutinised using guidance provided by Loke.[13]

Statistical analysis
Meta-analysis was performed using RevMan 5.4[14] where outcome measures were comparable. Pooling was not performed where there was substantial heterogeneity (I2 ≥ 50%).[11 p.10.10.2] The Mantel–Haenszel method was used as there were few events.[11 p.10.4.1] Multivariate and repeated measures analyses were considered,[15,16] but the paucity of data precluded their use.

# Results

**Figure 1: An adapted PRISMA Flow Diagram[17] 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.**
**Figure 2: An adapted PRISMA Flow Diagram[17] 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.**

Records identified through database searching
(n = 3,069 + 706 = 3,775)

## Screening

## Included

## Eligibility

## Identification

Additional records identified through other sources
(n = 1,153 + 794 = 1,947)

Records after duplicates removed
(n = 3,390 + 1,303 = 4,693)

Records screened
(n = 3,390 + 1,303 = 4,693)

Records excluded
(n = 4,521)

Full-text articles assessed for eligibility
(n = 115 + 57 = 172)

Full-text articles excluded, with reasons
(n = 158)

Studies included in qualitative synthesis
(n = 14 + 0 = 14)

Studies included in quantitative synthesis (meta-analysis)
(n = 5)

Records identified through database searching
(n = 3,069 + 706 = 3,775)

## Screening

## Included

## Eligibility

## Identification

Additional records identified through other sources
(n = 1,153 + 794 = 1,947)

Records after duplicates removed
(n = 3,390 + 1,303 = 4,693)

Records screened
(n = 3,390 + 1,303 = 4,693)

Records excluded
(n = 4,453)

Full-text articles assessed for eligibility
(n = 159 + 81 = 240)

Full-text articles excluded, with reasons
(n = 115)

Studies assessed as possible to include in qualitative synthesis
(n = 102 + 23 = 125)

Studies included in quantitative synthesis (meta-analysis)
(n = 60 + 15 = 75)

Figures 1 & 2 demonstrate adapted PRISMA diagrams,[17] outlining the flow of studies analysed and included. 14 RCTs (n>416 CYP) were included in the narrative synthesis of LLLT efficacy.[18-31] Five RCTs (n=380 CYP) were included for meta-analysis.[19,20,23,25,26] Ahmed[19] informed us that nearly half of their patients were below aged 17 (personal correspondence, 2020), and the other patients were young adults; we included these in the meta-analyses. 75 studies were included for safety analysis (see Supplementary Table 1 for full list). Relevant ongoing trials considering efficacy (four RCTs) or potentially safety (nine additional trials) can be found in Supplementary Table 2.

Unable to obtain further information from authors
(n = 50)

Results demonstrate that LLLT may reduce the severity of oral mucositis, and the level of oral pain, but further RCTs are needed to understand the true effect. 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 2,712 patients of all ages who had undergone LLLT) demonstrated minor and infrequent adverse reactions, but most studies had significant areas of weakness in quality.

# Quality of studies

Within the included RCTs for assessing efficacy, there is a significant risk of performance bias as the outcome assessors were generally not blinded. For several RCTs, insufficient data were provided to assess selection bias (see Figures 3 & 4).

**[COLOUR] Figure 3: Risk of bias graph: assessment of each risk of bias item presented as percentages across all included studies.**


**[COLOUR] Figure 4 - Risk of bias summary: assessment of each risk of bias item for each included study. (? = unclear; + = low risk, - = high risk)**



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

# Efficacy of LLLT

Intra-oral LLLT was used by all studies, except Hodgson[26] who used extra-oral LLLT. Studies considered prevention and/or treatment of oral mucositis. Protocols of LLLT administration varied widely (see Supplementary Table 3); wavelengths ranged from 632.8nm to 955nm. Energy delivery ranged from 1.5 J/cm2 to 8 J/cm2. LLLT was applied daily (apart from in two studies[18,24]), but duration of the intervention ranged from 4 to 15 days.

Two scales were used to assess oral mucositis grading: World Health Organization (WHO) oral mucositis scale/common toxicity criteria or National Cancer Institute Common Terminology Criteria (NCI CTC).[32 p.3-4] Hodgson[26] provided us with unpublished data using both grading systems, which allowed us to validate combining the grades for meta-analysis (see Supplementary Table 4). Patients aged >18, or undergoing HSCT with no cancer diagnosis, were removed from the unpublished dataset of Hodgson[26] and Amadori[20]. Abramoff[18] included patients up to 23 years old; it was not possible to obtain the breakdown of data and thus all these are included.

To enable meta-analysis, three different timepoints were used since different studies considered different timepoints, and low-grade (0-2) and high-grade (3-4) oral mucositis results were grouped together.

 **GRADE OF ORAL MUCOSITIS**LLLT non-significantly reduced severe oral mucositis at all timepoints (Day 3-5: Odds Ratio [OR] 0.73 with 95% CI 0.33–1.61. Day 7-10: OR 0.35 with 95% CI 0.12–1.03. Day 11-17: OR 0.36 with 95% CI 0.09–1.39) (see Figure 5) but these results are heterogenous and change over time (see Figure 6).

**Figure 5: Forest plot of comparison: Odds ratio comparing likelihood of patients developing grade 3+ oral mucositis in laser group and control group.**
**Key:** **Each study is labelled by its main author & 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% confidence interval (CI). M-H=Mantel–Haenszel meta-analysis method; random=random-effects model; CI=confidence interval (the bracketed region denotes upper and lower ends); I2 represents heterogeneity between the RCTs; 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 odds ratio, with its breadth including the CIs.**



**[COLOUR] Figure 6: Graph comparing the odds ratio of developing oral mucositis grade 3 or more in the laser group compared to control group**

**Table 3: Effect of LLLT on grade of oral mucositis**

|  |  |
| --- | --- |
| **RCT** | **Effect of LLLT on grade of oral mucositis** |
| Abramoff 2008[18] | For those receiving 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 to 27% in the placebo group. (p=0.03).  |
| Ahmed 2015[19] | 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 to 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 2016[20] | No statistically significant change. Day 4, oral mucositis median grade=2 for both laser and sham group. 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 2018[21] | 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 1997[22] | Only 2 patients aged 17 out of group of 30 patients. Distribution of daily mucositis index statistically significantly lower in laser group compared to sham group on days 2-7 (inclusive) after bone marrow transplantation. |
| Cruz 2007[23] | 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 2013[24] | 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 2018[25] | On day 7, of those receiving LLLT, one patient developed grade 4 oral mucositis, and 2 patients developed grade 3. Of those receiving 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 2012[26] | As displayed in the meta-analysis, odds ratio 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 day 8-10 (OR=1.25, 95% CI 0.23 to 6.71) and 15-17 (OR=3.29, 95% CI 0.12 to 89.81). None of these were statistically significant. |
| Khouri 2009[27] | Unable to ascertain how many patients were children and met full inclusion criteria. Mean grade of oral mucositis in laser group was 1.75±0.45, compared to 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 2009[28] | Statistically significant reduction of oral mucositis in laser group (32% patients grade >0) compared to placebo group (94% patients grade >0) on day 7 after oral mucositis diagnosis (p=0.001) |
| Salvador 2017[29] | 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 2011[30] | 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 2015[31] | 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). |

 **ORAL PAIN**
Three studies had extractable data on oral pain. Median results from Gobbo[25] and Ahmed[19] were converted to estimates of means using an online tool.[33] Similarly to observed grade of mucositis, there may be a trend towards less pain experienced from Day 7 onwards after LLLT had been commenced, however, this is not statistically significant (see Figures 7 and 8). Further narrative synthesis is provided in Supplementary Table 5.

**Figure 7: Forest plot comparing the standardised mean difference in oral pain out of a 10 point scale.**
**[COLOUR] Figure 8: Graph comparing standardised mean difference in self-reported oral pain in laser group compared to control group.**

**USE OF ANALGESIA**Three RCTs[20,23,25] considered the use of analgesia. It was not possible to perform meta-analysis, however a summary is presented in Table 5.

**Table 5: Effect of LLLT on use of analgesia**

|  |  |
| --- | --- |
| **RCT** | **Effect of LLLT on use of analgesia** |
| Amadori 2016[20] | Children treated with LLLT requested less additional analgesia (morphine, tramadol or paracetamol) than those receiving the sham protocol (p<0.05). |
| Cruz 2007[23] | 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[25] | No statistically significant difference between the use of analgesics in the laser group compared to the control group. |

**NUTRITION**Three RCTs[22,23,26] considered the impact on diet, but no difference was found between the two groups in the studies (see Table 6).

 **Table 6: Effect of LLLT on nutrition**

|  |  |
| --- | --- |
| **RCT** | **Effect of LLLT on diet** |
| Cowen 1997[22] | 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[23] | 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[26] | 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).  |

 **Other outcome measures**One RCT looked at interruptions to cancer treatment; results are awaiting publication.[21] None of the RCTs looked at duration of hospitalisation. One study looked at quality of life,[31] but these results cannot be extracted for children alone. Supplementary Table 6 outlines other outcome measures reported in the RCTs.

Safety of LLLT
As oral mucositis is an adverse event associated with chemo/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 events, attempts were made to contact authors. Adverse reactions or adverse device effects which could be related to LLLT specifically were sought.

125 studies were identified which would be expected to provide some information on the safety of LLLT (see Figure 2). However, despite attempts to contact authors, data were unavailable on adverse device effects or adverse reactions from 50 of these potential studies (these 50 studies combined would have provided further information on at least 1,459 individuals who have undergone LLLT).

Of the 75 studies (encompassing 2,712 patients who had undergone LLLT) where sufficient data were available to identify any adverse reactions (either from the papers or from the authors), 24 studies were known to include children. In most manuscripts the documentation of how adverse events have been monitored is limited, which in turn affects the quality assessment for the majority of the 75 studies. The quality assessments[13] indicate that all of the studies included have significant areas of weakness, with the majority of studies unclear on how information about adverse events due to LLLT was collected. 69.3% of the quality assessment questions considered were either ‘unclear’, or ‘not applicable’. Additionally, 22.3% of the quality assessment questions were answered as ‘no’. This demonstrates that the vast majority of studies provided insufficient assurance of quality of consideration of adverse device events or adverse reactions.

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.’[34] However, they discuss adverse events found in the treatment (LLLT) group of ten patients (they report two patients with a traumatic ulcer from self-biting and one patient with HSV-1 positive ulceration), and go on to explain that the oral adverse events are typical of HSCT.[34] Additionally this complicates the quality assessment of studies as definitions and monitoring methods regarding adverse events may be related to the cancer treatment and not to the LLLT. One study looked at 22 children undergoing LLLT and found adverse device events in 2 children, and 1 issue with tolerability: one child was found to have some slight gingival bleeding after vomiting flowing laser treatment, and one other child had a blood spot on the palate, however this was attributed to mucositis rather than LLLT.[35] The same study also found that a 4-year old boy refused to wear protective glasses, which are a necessary precaution for the LLLT procedure.[35] 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.[36] However, Antunes et al published a retrospective matched case-control study, comparing those who had received LLLT with those who had not; this did not show any reduction in survival.[37] Additionally Genot et al retrospectively reviewed 361 patients and found that for the 62% who received LLLT, there was no statistically significant impact on overall survival, time to local recurrence or progression-free survival.[38] Fischlechner et al also considered overall survival and found no difference between 126 patients who had received LLLT and 126 matched controls.[39]

# Additional analyses

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

# Discussion

14 studies (n>416 CYP) were considered in the narrative synthesis around LLLT efficacy, and 5 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 led to 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 are needed to understand the true effect. Future RCTs should include protocols considering LLLT for both prevention and treatment, and should compare LLLT to sham therapy, ensuring appropriate blinding.

Heterogeneity between the RCTs was anticipated given a vast range of LLLT protocols used including different LLLT settings, durations, starting points of treatment, and outcomes assessed (see Supplementary Table 3). Some simplifications were made to pool the data, such as combining NCI & WHO oral mucositis grades, and presenting efficacy over a group of days rather than identical time points.

This systematic review has highlighted some challenges on assessing the efficacy of LLLT. As there are many differences in the protocols of the LLLT devices used, it is not clear what the optimal protocol is, or the significance of different alternative parameters. This is in-keeping with existing literature reflecting the challenges of assessing medical devices.[40]

The meta-analyses demonstrated that LLLT may reduce the correlated outcomes of severe mucositis and oral pain. However, these findings are heterogenous, not statistically significant, and further research is needed. 75 studies (encompassing 2,712 patients of all ages who had undergone 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.
 **Further work**Whilst this review was robust in nature and included grey literature, there is currently insufficient data available to draw any firm conclusions about the role of LLLT in children with cancer. Ongoing and unreported trials (see Supplementary Table 2) should be considered for inclusion in any future systematic review. A large multi-centre RCT is recommended to truly evaluate its role in prevention and treatment of oral mucositis in children with cancer.

# 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 severity of oral mucositis and associated pain. LLLT protocols vary greatly between institutions, and clarity around the optimal delivery protocols is needed. Further research is needed to assess if LLLT is an efficacious tool for the prevention or treatment of oral mucositis in children with cancer.

# References

[1] Cheng KKF, Lee V, Li CH, Yuen HL, Epstein JB. Oral mucositis in pediatric and adolescent patients undergoing chemotherapy: the impact of symptoms on quality of life. Support Care Cancer 2012;20(10):2335-42.

[2] Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, et al. Perspectives on cancer therapy‐induced mucosal injury. Cancer 2004;100(S9):1995-2025.

[3] He M, Zhang B, Shen N, Wu N, Sun J. A systematic review and meta-analysis of the effect of low-level laser therapy (LLLT) on chemotherapy-induced oral mucositis in pediatric and young patients. Eur J Pediatr 2018;177(1):7-17.

[4] Sonis ST, Oster G, Fuchs H, Bellm L, Bradford WZ, Edelsberg J, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. J Clin Oncol 2001;19(8):2201-5. doi: 10.1200/JCO.2001.19.8.2201.

[5] National Institute for Health and Care Excellence. Low-level laser therapy for preventing or treating oral mucositis caused by radiotherapy or chemotherapy, https://www.nice.org.uk/guidance/ipg615/chapter/2-The-condition-current-treatments-and-procedure; 2018 [accessed 21 Sept 2020].

[6] Zadik Y, Arany PR, Fregnani ER, Bossi P, Antunes HS, Bensadoun R-J, et al, on behalf of The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of photobiomodulation for the management of oral mucositis in cancer patients and clinical practice guidelines. Support Care Cancer 2019;27(10):3969-83. doi: 10.1007/s00520-019-04890-2.

[7] Sonis ST. Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity. Oral Oncol 1998;34(1):39-43.

[8] Phillips RS, Bhuller K, Sung L, Ammann RA, Tissing WJ, Lehrnbecher T, et al. Risk stratification in febrile neutropenic episodes in adolescent/young adult patients with cancer. Eur J Cancer 2016 Sep;64:101-6. doi: 10.1016/j.ejca.2016.05.027.

[9] Sung L, Robinson P, Treister N, Baggott T, Gibson P, Tissing W, et al. Guideline for the prevention of oral and oropharyngeal mucositis in children receiving treatment for cancer or undergoing haematopoietic stem cell transplantation. BMJ Support Palliat Care 2017 Mar;7(1):7-16. doi: 10.1136/bmjspcare-2014-000804.

[10] Redman M, Harris K, Morgan JE, Phillips R. Recommended technology to relieve oral mucositis not yet available for children or young people in England or Wales. Arch Dis Child 2019;104:1238.

[11] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0. Cochrane. www.training.cochrane.org/handbook; 2019 [accessed 21 Sept 2020].

[12] Centre for Reviews and Dissemination, University of York. Systematic Reviews: CRD’s guidance for undertaking reviews in health care. York: York Publishing Services Ltd; 2009.

[13] Loke YK, Price D, Herxheimer A, Cochrane Adverse Effects Methods Group. Systematic reviews of adverse effects: framework for a structured approach. BMC Med Res Methodol. 2007;7:32. doi: 10.1186/1471-2288-7-32.

[14] Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020.

[15] Mawdsley D, Bennetts M, Dias S, Boucher M, Welton NJ. Model-Based Network Meta-Analysis: A Framework for Evidence Synthesis of Clinical Trial Data. CPT Pharmacometrics Syst Pharmacol 2016;5(8):393-401.

[16] Pedder H, Dias S, Bennetts M, Boucher M, Welton NJ. Modelling time-course relationships with multiple treatments: Model-based network meta-analysis for continuous summary outcomes. Res Synth Methods 2019;10(2):267-86.

[17] Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;6(7):e1000097. doi: 10.1371/journal.pmed.1000097

[18] Abramoff MMF, Lopes NNF, Lopes LA, Lauria L, 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;26(4):393-400. doi: 10.1089/pho.2007.2144

[19] Ahmed KM, Hussein SA, 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.

[20] 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;31(6):1231-36. doi: 10.1007/s10103-016-1975-y.

[21] Amadori F, Bardellini E. Effectiveness of lllt in the prevention and treatment of chemotherapy-induced oral mucositis in children. Support Care Cancer (2018;26( 2Suppl 1):S139. doi: 10.1007/s00520-018-4193-2.

[22] Cowen D, Tardieu C, Schubert M, Peterson D, Resbeut M, Faucher C, et al. Low energy Helium-Neon laser in the prevention of oral mucositis in patients undergoing bone marrow transplant: results of a double blind randomized trial. Int J Radiat Oncol Biol Phys 1997;38(4):697–703. Doi: 10.1016/S0360-3016%2897%2900076-X

[23] Cruz LB, Ribeiro AS, Rech A, Rosa LGN, Castro Jr CG, Brunetto AL. Influence of low-energy laser in the prevention of oral mucositis in children with cancer receiving chemotherapy. Pediatr Blood Cancer 2007;48(4):435-40. doi: 10.1002/pbc.20943.

[24] Fani MM, Azar MR, Ramzi M, Azad A, Hajizadeh E, Nasrabadi NI, et al. The effect of the low-level laser on prevention of chemotherapy-induced oral mucositis in patients with acute leukemia. J Dent Lasers 2013;7(1):22-6. doi: 10.4103/0976-2868.118439.

[25] 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. Pediat Blood Cancer 2018; 65(8):e27098. doi: 10.1002/pbc.27098

[26] 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;20(7):1405-15. doi: 10.1007/s00520-011-1223-8.

[27] Khouri VY, Stracieri AB, Rodrigues MC, Moraes DA, Pieroni F, Simões BP, et al Use of therapeutic laser for prevention and treatment of oral mucositis. Braz Dent J 2009;20:215-20.

[28] 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;31(1):33-7. doi: 10.1097/MPH.0b013e318192cb8e.

[29] 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;32(8):1801-10. doi: 10.1007/s10103-017-2263-1.

[30] Silva GBL, Mendonça EF, Bariani C, Antunes HS, Silva MAG. The prevention of induced oral mucositis with low-level laser therapy in bone marrow transplantation patients: a randomized clinical trial. Photomed Laser Surg 2011;29(1):27-31. doi: 10.1089/pho.2009.2699.

[31] Silva GBL, Sacono NT, Othon-Leite AF, Mendonça EF, Arantes AM, Bariani C, et al. Effect of low-level laser therapy on inflammatory mediator release during chemotherapy-induced oral mucositis: a randomized preliminary study. Lasers Med Sci 2015;30(1):117-26. doi: 10.1007/s10103-014-1624-2.

[32] Interventional procedure overview of low-level laser therapy for preventing or treating oral mucositis caused by radiotherapy or chemotherapy. National Institute for Health and Care Excellence. Available from: https://www.nice.org.uk/guidance/ipg615/documents/overview

[33] Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. Department of Mathematics, Hong Kong Baptist University, http://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html; [accessed 21 Sept 2020].

[34] Elad S, Luboshitz-Shon Noa, Cohen T. A randomized controlled trial of visible-light therapy for the prevention of oral mucositis. Oral oncol 2011;47(2):125-30.

[35] 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 Pédiatrie 2019;26(5):268-74. doi: 10.1016/j.arcped.2019.05.012.

[36] Kreisler M, Christoffers AB, Willershausen B, d’Hoedt B. Low-level 809 nm GaAlAs laser irradiation increases the proliferation rate of human laryngeal carcinoma cells in vitro. Lasers Med Sci 2003;18(2):100-3. doi: 10.1007/s10103-003-0265-7.

[37] Antunes HS, Herchenhorn D, Small IA, Araujo CMM, Viegas CMP, de Assis Ramos G, et al. Long-term survival of a randomized phase III trial of head and neck cancer patients receiving concurrent chemoradiation therapy with or without low-level laser therapy (LLLT) to prevent oral mucositis. Oral Oncol 71:11-5. doi: 10.1016/j.oraloncology.2017.05.018.

[38] Genot MT, Klastersky J, Lalami Y, Paesmans M, Kayumba A, Ameye L, et al. 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(Suppl 1):S125.

[39] Fischlechner R, Kofler B, Schartinger VH, Dudas J, Riechelmann H. Does low-level laser therapy affect the survival of patients with head and neck cancer? Lasers Med Sci 2020. doi: 10.1007/s10103-020-03073-4.

[40] Rothery C, Claxton K, Palmer S, Epstein D, Tarricone R, Sculpher M. Characterising Uncertainty in the Assessment of Medical Devices and Determining Future Research Needs. Health Econ 2017;26(S1):109-23. doi: 10.1002/hec.3467.