The role of photobiomodulation therapy in the care of cancer patients: review of the literature

J. Robijns, MSc¹,², S. Censabella, PhD³, P. Bulens, MD²,³, A. Maes, MD²,³, L. Noé, MD²,³, M. Brosens, MD²,³, L. Van den Bergh, MD, PhD²,³, S. Claes³, J. Mebis, MD, PhD¹,³

SUMMARY
Photobiomodulation therapy is based on the application of visible and/or (near-)infrared light on the target tissue. We performed a review of 34 articles on the use of photobiomodulation therapy in the management of cancer related lymphoedema, oral mucositis, radiodermatitis, chemotherapy-induced peripheral neuropathy, osteonecrosis of the jaw, and xerostomia/hyposalivation. The findings suggest that photobiomodulation therapy is a promising option for the management of these cancer therapy-related side effects. (BELG J MED ONCOL 2017;11(8):364-374)

INTRODUCTION
Cancer therapy ranging from surgery, chemotherapy (CTx), radiotherapy (RT) to targeted systemic therapies (e.g. hormone- and/or immunotherapy) can cause serious side effects. The severity of the side effects depends on the cancer type and site, the therapy characteristics, and the individual patient susceptibility. The patients' quality of life can seriously be affected by these side effects and therefore effective supportive care strategies are necessary.¹ The use of photobiomodulation therapy (PBMT), also known as low-level laser therapy (LLLT), was introduced in 1967 by Mester et al.² It's based on the application of visible and/or (near-)infrared light by laser diodes (LDs) and/or light-emitting diodes (LEDs) on target tissue.³ Several studies have demonstrated that PBMT is able to stimulate the wound healing process, reduce inflammation, and relieve pain.⁴ For the last twenty years, the use of PBMT for the management of cancer therapy-related side effects has been investigated in several clinical trials. However, for a lot of clinicians this new and emerging therapeutic option is still unknown.⁵ The aim of this review was to summarise all the available clinical trials that examined the applicability of PBMT in the domain of cancer related lymphoedema (CRL), oral mucositis (OM), radiodermatitis (RD), chemotherapy-induced peripheral neuropathy (CIPN), osteonecrosis of the jaw (ONJ), and xerostomia/hyposalivation.

PBMT – CELLULAR AND TISSUE MECHANISM
The basic mechanism behind PBMT is quite complex and is still not completely clear. Several studies demonstrated that the light is absorbed by endogenous chromophores in the target cells. The main chromophore is cytochrome c ox-
The treatment of CRL is focused on preventing disease progression and reducing the symptoms. Complete decongestive therapy (CDT) is the main treatment option for CRL.10 PBMT can also prevent the formation of fibrotic tissue.11 A meta-analysis of nine studies by Smoot et al. demonstrated moderate evidence for the effectiveness of LD-PBMT in the reduction of arm swelling and pain in women with BCRL (Table 1). Additionally, these studies showed that the combination of PBMT with CDT is more effective in reducing the arm volume than with CDT alone.11 A recent randomised, placebo-controlled clinical trial (RCT) with 40 BC patients confirmed the results of the meta-analysis.12 Up to now, there was only one case-control study that showed a beneficial effect of LD-PBMT in the management of CRL in HNC patients.13 A task force consisting of an international multidisciplinary panel of clinicians and researchers with expertise in the area of supportive care in cancer and/or the use of PBMT, developed guidelines for the management of complications related to cancer therapy. They suggested using a LED- or LD-PBMT device (wavelength 750-830 nm, power density 20–80 mW/cm², fluence 3 J/cm²) two to three times a week to treat CRL until symptoms improve. They suggested applying it on the edematous area and the regional lymphatic chain.1

PBMT IN THE SUPPORTIVE CARE OF CANCER PATIENTS

Cancer-related lymphoedema (CRL)

Lymphoedema is a common side-effect in patients treated for breast cancer (BC) and head and neck cancer (HNC). In approximately 20% of BC patients, lymphoedema can develop in the upper extremity after BC treatment. Patients with breast cancer-related lymphoedema (BCRL) have to cope with pain and a diminished arm mobility leading to decreased daily functional activity.9 Lymphoedema in HNC patients can develop externally, on the face and/or neck, or internally at the pharynx or larynx. A study by Deng et al. with 81 HNC patients, showed that 75% of the patients developed CRL (10% external, 39% internal, and 51% both types). External CRL may affect the patient’s body image, while internal CRL may cause breathing, swelling, and speaking problems.9 The treatment of CRL is focused on preventing disease progression and reducing the symptoms. Complete decongestive therapy (CDT) is the main treatment option for CRL.10

PBMT FOR THE MANAGEMENT OF CRL

The effectiveness of PBMT for the management of BCRL has already been demonstrated in several studies and in 2006 it was accepted as treatment option by the Food and Drug Administration (FDA).13 The beneficial effect of PBMT on BCRL is explained by the fact that it is able to stimulate the lymph flow and increase the number of lymph vessels. In addition, PBMT can also prevent the formation of fibrotic tissue.11 A meta-analysis of eleven RCTs in HNC patients showed that LD-PBMT reduced the OM incidence, severity, duration, and the associated pain.15 Oberoi et al. performed another systematic review with meta-analysis of eighteen RCTs in which they showed that prophylactic use of LD-PBMT reduced severe OM and its associated pain in patients treated for HNC or undergoing hematopoietic stem cell transplantation (HSCT).16 In 2014, the MASCC/ISOO panel developed clinical practice guidelines in which they included the use of PBMT in the prevention and management of OM based...
TABLE 1. Summary of clinical studies investigating the use of PBMT for the management of CRL.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Publication type</th>
<th>Study type</th>
<th>Sample size + cancer type</th>
<th>Treatment groups</th>
<th>PBMT device</th>
<th>Wave-length (nm)</th>
<th>Power (mW)</th>
<th>Energy density (J/cm²)</th>
<th>Laser schedule</th>
<th>Evaluation schedule</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philip</td>
<td>1998</td>
<td>Full article</td>
<td>Single group</td>
<td>10 BC</td>
<td>LD-PBMT</td>
<td>Scanning Space Mild MS-UF LD</td>
<td>904</td>
<td>10-14</td>
<td>NA</td>
<td>16 sessions over 10 weeks</td>
<td>Pre-treatment during treatment: biweekly Post-treatment: final treatment, 1, 3, 6, 30-36 months</td>
<td>42% reduction in arm volume after PBMT. The arm tissue (except the upper arm) softened. Subjective symptoms improved (e.g., pain, cramps, heaviness, mobility).</td>
</tr>
<tr>
<td>Carati</td>
<td>2003</td>
<td>Full article</td>
<td>Double-blind, single crossover RCT</td>
<td>64 BC</td>
<td>LD-PBMT + Sham laser</td>
<td>Direct contact: Thor LD Corp LTU 904H LD</td>
<td>904</td>
<td>5</td>
<td>NA</td>
<td>3×/week for 3 weeks; two cycles (18 sessions) 8-weeks between cycle washout period</td>
<td>Pre-treatment Post-treatment cycle 1: immediately (final treatment) and week 9 Post-treatment cycle 2: weeks 18 and 22</td>
<td>PBMT reduced effectively the arm volume, extracellular fluid and tissue stiffness in 35% of the patients.</td>
</tr>
<tr>
<td>Kaviani</td>
<td>2006</td>
<td>Full article</td>
<td>Double-blinded RCT</td>
<td>11 BC</td>
<td>LD-PBMT + Sham laser</td>
<td>Noncontact mode applied 1 cm above skin; Mustang-524 Ga-As LD</td>
<td>890</td>
<td>10</td>
<td>1.5</td>
<td>3×/week x 3 weeks; 2 cycles with an 8 week inter-cycle washout period (18 sessions)</td>
<td>Pre-treatment Post-treatment cycle 1: immediately (final treatment) and week 9 Post-treatment cycle 2: weeks 18 and 22</td>
<td>In both groups the arm circumference decreased, but no significant difference between the groups.</td>
</tr>
<tr>
<td>Kuzanoglu</td>
<td>2009</td>
<td>Full article</td>
<td>RCT, blinded, alternating allocation</td>
<td>50 BC</td>
<td>LD-PBMT + educ + educ</td>
<td>Electronica Laser PAGANI LS774 Ga-As LD</td>
<td>904</td>
<td>NA</td>
<td>1.5</td>
<td>3×/week x 4 weeks (12 sessions) 4 weeks (20 sessions)</td>
<td>Pre-treatment Post-treatment cycle 1: immediately 3, 6, and 12 months</td>
<td>Arm circumference and pain score reduced in both groups, but the long-term results were better in the PBMT group.</td>
</tr>
<tr>
<td>Lau</td>
<td>2009</td>
<td>Full article</td>
<td>Single-blinded RCT</td>
<td>21 BC</td>
<td>LD-PBMT + educ + educ + Wallact + educ</td>
<td>Scanning 50 cm above skin; Comby 3 Terza Serie, Model D LD</td>
<td>808</td>
<td>905x2</td>
<td>NA</td>
<td>2</td>
<td>3×/week x 4 weeks (12 sessions)</td>
<td>Pre-treatment Post-treatment: immediately</td>
</tr>
<tr>
<td>Dirican</td>
<td>2011</td>
<td>Full article</td>
<td>Single group</td>
<td>9 BC</td>
<td>LD-PBMT</td>
<td>Direct contact: Plan Corp LTD 904H LD</td>
<td>904</td>
<td>5</td>
<td>NA</td>
<td>3×/week; two 3-week cycles; 8-week hiatus between cycles (18 sessions)</td>
<td>Pre-treatment Post-treatment immediately for each cycle</td>
<td>Combination of PBMT with CB showed benefits in the reduction of arm volume, pain and scar mobility.</td>
</tr>
<tr>
<td>Omar</td>
<td>2011</td>
<td>Full article</td>
<td>Double-blind RCT with placebo group</td>
<td>17 BC</td>
<td>LD-PBMT</td>
<td>Direct contact: Plan Corp LTD 904H LD</td>
<td>904</td>
<td>5</td>
<td>NA</td>
<td>12 weeks (36 sessions)</td>
<td>Pre-treatment Post-treatment during treatment: weeks 4 and 8 Post-treatment: immediately and 4 weeks</td>
<td>Significant reduction in arm volume. Significant increase in shoulder mobility and handgrip strength in 93% of patients.</td>
</tr>
<tr>
<td>Rinder</td>
<td>2013</td>
<td>Full article</td>
<td>RCT</td>
<td>46 BC</td>
<td>LD-PBMT</td>
<td>Direct contact: Plan Corp LTD 904H LD</td>
<td>904</td>
<td>5</td>
<td>NA</td>
<td>Average number of sessions: PBMT: 10 MLD: 8 PBMT: 10</td>
<td>Pre-treatment Post-treatment: immediately</td>
<td>Arm volume reduced in all groups, but no significant difference between the groups. No differences in quality of life. Skin quality improved in all groups.</td>
</tr>
<tr>
<td>Lee</td>
<td>2013</td>
<td>Full article</td>
<td>Case control study</td>
<td>1 HNC</td>
<td>LD-PBMT</td>
<td>-104 Diode Cluster Probe (lymphatic pathways) -904-904 (lymphatic areas)</td>
<td>NA</td>
<td>5–10</td>
<td>1.5</td>
<td>Daily over 3 weeks</td>
<td>Pre-treatment, weekly during PBMT and 3 month after the end of PBMT</td>
<td>Significant reduction in oedema and improvement in swelling.</td>
</tr>
<tr>
<td>Stoog</td>
<td>2016</td>
<td>Full article</td>
<td>Double-blind RCT with placebo group</td>
<td>40 BC</td>
<td>LD-PBMT</td>
<td>Cluster laser device, non-contact mode: “TIME: LAS VITA”</td>
<td>980</td>
<td>640</td>
<td>4.89</td>
<td>2x/week x 4 weeks</td>
<td>Pre-treatment Post-treatment: immediately 1–3 months</td>
<td>50% reduction in median pain score. Increase in mean quality of life and grip strength in PBMT group. No statistically significant difference between the groups.</td>
</tr>
</tbody>
</table>

Partially adapted from Robjins et al. (2017).6

Abbreviations: BC, breast cancer; HNC, head and neck cancer; CRL, cancer-related lymphedema; RCT, randomised controlled trial; LD, laser diode; PBMT, photobiomodulation therapy; MLD, manual lymphatic drainage; CB, compression bandaging; educ, education; CG, compression garment; IC, intermittent compression; NA, not available; ref, reference; UE, upper extremity.
on a meta-analysis performed by Migliorati et al. Following these guidelines, PBMT is recommended for the prevention of OM in patients receiving high-dose CTx in case of HSCT. In addition, they suggested using PBMT for the prevention of OM in HNC patients undergoing RT without concomitant CTx. The European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) also recommend the use of LD-PBMT in patients receiving high-dose CTx or chemoradiotherapy (CRT) before HSCT. The guidelines of Zecha et al. proposed to use PBMT both in a preventive and therapeutic manner (wavelength 630-830 nm, power density 20-80 mW, energy density 2-4 J/cm²). The prophylactic use of PBMT can start before or on the first day of CTx/RT and continue during all days of the therapy on each site of the mucosal surface that is at risk. Once OM has developed PBMT is recommended two to three times a week up to daily until the symptoms improve.

Radiodermatitis (RD)

RD affects up to 95% of the patients undergoing RT. RD is an inflammatory skin reaction that is characterised by red rash, dry desquamation and in some cases moist desquamation. The severity of the skin reactions depends on different therapy- and patient-related factors. RD is a distressing and painful side effect of RT, which can lead to problems in the patients’ daily life (e.g. washing practices, getting dressed, household activities, hobbies). Rarely, the skin reactions become too severe, leading to interruption of RT for a short period of time. Existing treatment options for RD include different topical agents such as moisturising creams/gels and wound dressings. The MASCC panel developed clinical practice guidelines for the prevention and treatment of RD. However, the available evidence is still to weak to support a general consensus on the management of RD.

**PBMT for the prevention and management of RD**

The research on the use of PBMT for the prevention and management of RD in cancer patients is limited (Table 3). Schindl et al. introduced it in the late 1990’s, by performing a case report study in which they treated three breast patients with RT-induced skin ulcers after mastectomy. Re-
Results showed that LD-PBMT was able to improve the wound healing process of the skin ulcers. Furthermore, there were two studies that investigated the use of LED-PBMT for the prevention of RD. A study by Deland et al. showed that LED treatments reduced the incidence of RD in breast cancer patients. In contrast, Fife et al. was not able to replicate these results in a RCT. A possible explanation for the different results is the use of different treatment and assessment parameters in both studies. A more recent study by our research group showed that LD-PBMT is an effective treatment for acute RD in breast cancer patients. PBMT prevented the aggravation of acute RD and reduced the impact of it on the patients’ quality of life.

Zecha et al. suggested using LED- or LD-PBMT (wavelength 630–680 nm; power density 20-150mW/cm²; energy density 2–4 J/cm²) in a prophylactic (daily from the first day of RT) or a therapeutic regime (minimum three times a week) on the cutaneous surfaces of the irradiated area (Figure 1).

Chemotherapy-induced peripheral neuropathy (CIPN)
Neurotoxic chemotherapeutic substances (e.g. platinum agents, taxanes, vinca alkaloids, thalidomide, and bortezomib) can lead to chemotherapy-induced peripheral neuropathy (CIPN). It affects approximately 68.1% of the patients when measured in the first month after CTx, 60.0% at three months and 30.0% at six months or more. The risk for developing CIPN is determined by the type of CTx agents, the administration time, and the cumulative dose. Most patients with CIPN develop sensory dysfunctions. Sometimes motor dysfunctions such as muscle weakness and/or autonomic neuropathy can also establish. The underlying mechanism causing CIPN is still unclear but is known that chemotherapeutic agents can damage the peripheral and/or central nerve system, affecting the communication in the nerve tracts. Patients with CIPN have to cope with functional problems during their daily life. In severe cases of CIPN, CTx dose reductions, changes in the CTx dosing or even a CTx termination need to be performed, leading to diminished overall survival.

To date, there is still no effective treatment for CIPN. Currently, the main focus in the management of CIPN is reducing the symptoms by medication and/or physical therapy.

PBMT AND CIPN
The use of PBMT for the management of CIPN has only been investigated in three clinical trials (Table 4). Yamada et al. investigated the use of LD-PBMT in a single-arm, prospective study with 34 female BC patients undergoing taxane-based...
CTx. The patients evaluated the effectiveness of the treatment by using a 10-point scale Brief Pain Index (BPI) questionnaire before and after each laser session. At the end of the trial the BPI score of the patients ameliorated with an average of four points.²⁸ In a more recent, prospective cohort study with pre- and post-intervention design by Hsieh et al., seventeen patients with gastrointestinal cancer were treated with LD-PBMT. Results revealed that after twelve sessions of PBMT, the patients’ neurotoxicity symptoms were diminished and moreover their cold and mechanical allodynia was resolved.²⁹ Argenta et al. enrolled 70 patients treated with CTx for cancer of different aetiology in a randomised-control, crossover trial to determine if LD-PBMT (eighteen sessions) with or without physiotherapy reduced the symptoms of CIPN compared to a sham treatment. This study demonstrated that LD-PBMT could reduce the CIPN associated symptoms effectively.³⁰ These findings indicate that LD-PBMT might be an effective therapeutic option for CIPN. However, it was not taken up in the guidelines developed by Zecha et al.¹ Our research unit is now performing a RCT investigating the effectiveness of PBMT in the prevention of CIPN in breast cancer patients undergoing taxane treatment.

Osteonecrosis of the jaw (ONJ)
Patients with bone metastases or multiple myeloma are generally treated with bisphosphonates (BP) or denosumab. These treatments inhibit bone turnover by inducing osteoclastic apoptosis and inhibiting the osteoblast-mediated osteoclastic activity. A serious side effect is osteonecrosis of the jaw (ONJ), which occurs in 0.8% to 12% of the patients.³¹ ONJ is a serious and painful side effect.³² Each case of ONJ needs to be evaluated and treated individually. The American Association of Oral and Maxillofacial Surgeons (AAOMS) developed guidelines based on the stage of the disease, good oral hygiene, pharmacological therapy (e.g. antibiotics, pain medication) and, in case of exposed bone, surgical removal is recommended.³²

PBMT FOR THE TREATMENT OF ONJ
PBMT is known to have bio stimulatory effects that can up-regulate the production and mineralisation of the bone.³³ Additionally, PBMT also has anti-bacterial effects and is proangiogenic.³⁴ A recent review by Latifyan et al., summarised the results of seven clinical trials that investigated the efficiency of PBMT for the treatment of ONJ (Table 5).³⁵ They showed that

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**TABLE 3. Summary of clinical studies investigating the use of PBMT for the management of RD in cancer patients.**

<table>
<thead>
<tr>
<th>First author (ref.)</th>
<th>Year</th>
<th>Publication type</th>
<th>Study type</th>
<th>Sample size</th>
<th>PBMT device</th>
<th>Wavelength (nm)</th>
<th>Power (mW)</th>
<th>Energy density (J/cm²)</th>
<th>Laser schedule</th>
<th>Evaluation schedule</th>
<th>Assessment scale</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schindl²²</td>
<td>1999</td>
<td>Full article</td>
<td>Case report</td>
<td>3</td>
<td>HeNe LD</td>
<td>632.8</td>
<td>30</td>
<td>30</td>
<td>3 times/week until wound closure</td>
<td>Weekly and at 36 months follow-up</td>
<td>NA</td>
<td>Accelerated wound healing.</td>
</tr>
<tr>
<td>DeLand²³</td>
<td>2007</td>
<td>Full article</td>
<td>Prospective study with a retrospective control group</td>
<td>47</td>
<td>LED</td>
<td>590</td>
<td>NA</td>
<td>0.15</td>
<td>Daily after each RT session</td>
<td>Weekly</td>
<td>NCI CTC</td>
<td>Significantly reduced incidence of RD.</td>
</tr>
<tr>
<td>File²⁴</td>
<td>2010</td>
<td>Full article</td>
<td>Prospective, double-blind RCT with a placebo group</td>
<td>33</td>
<td>LED</td>
<td>590</td>
<td>NA</td>
<td>NA</td>
<td>Daily before and after each RT session + 7 additional daily treatments after the end of RT</td>
<td>Baseline, weekly during RT and 2-6 weeks after the end of RT</td>
<td>NCI CTC</td>
<td>No significant effects.</td>
</tr>
<tr>
<td>Censabella²⁵</td>
<td>2016</td>
<td>Full article</td>
<td>Prospective quasi-experimental study with control and PBMT group</td>
<td>79</td>
<td>LD</td>
<td>808-906</td>
<td>60</td>
<td>4</td>
<td>2 times/week after the RT session starting at fraction 20 of RT</td>
<td>Baseline, fraction 20 of RT and at the end of RT</td>
<td>RTOG</td>
<td>Significantly reduced incidence of RD grade.</td>
</tr>
</tbody>
</table>

Partially adapted from Robijns et al. (2017)⁶
Abbreviations: RD, radiodermatitis; HeNe, Helium Neon; LED, Light Emitting Diode; NA, not available; RT, radiotherapy; NCI CTC, National Cancer Institute Common Toxicity Criteria; RTOG, Radiation Therapy Oncology Group; RD, radiodermatitis; ref, reference; LD, laser diode; PBMT, photobiomodulation therapy; RCT, randomised controlled trial.
the overall response rate was 55% in PBMT treated patients, which was significantly higher than in the control group (30%). The studies revealed that PBMT was able to improve ONJ by improving the healing process of the lesions and reducing the accompanied pain.35

Zecha et al. also formulated some clinical guidelines on a therapeutic base in which they recommended to use LD- or LED-PBMT two to three times a week up to daily by using an extra- (wavelength 750–830 nm; power density 20–80mW; energy density 6 J/cm²) or intra-oral device (wavelength 630–680; power density 20–200mW; energy density 6 J/cm²) on five or more points (1 cm apart) along lingual and buccal aspects of the maxilla and/or mandible depending on site and size of region affected.1

Hyposalivation and xerostomia

RT to the head and neck region destroys the function of the salivary glands leading to hyposalivation (i.e. reduced saliva production), which is accompanied by xerostomia (i.e. subjective oral dryness). Other cancer therapies (e.g. CTx, immunotherapy, radioactive iodine treatment and total body irradiation/HSCT) can also induce hyposalivation and xerostomia, although to a minor severity. Hyposalivation increases the risk of oral infections and can lead to teeth damage, oral mucosal discomfort, pain, and eating problems. Consequently, patients with hyposalivation cannot fully perform their daily activities and have diminished general well being.36

Intensity-modulated radiation therapy (IMRT) has the greatest potential to spare the salivary gland tissue and prevent the development of hyposalivation. Furthermore, good oral hygiene and dental care is recommended before, during, and after treatment.

**PBMT FOR THE TREATMENT OF HYPOSALIVATION AND XEROSTOMIA**

To date, there were only a small number of studies investigating the use PBMT for the management of hyposalivation (Table 6). Cowen et al. performed a placebo-controlled RCT with 30 patients that underwent HSCT to investigate the efficiency of LD-PBMT. Xerostomia and the ability to swallow improved in the patients that were treated with LD-PBMT.37 Simoes et al. reported on a prospective study with two patient groups of which one group was treated once a week with LD-PBMT
<table>
<thead>
<tr>
<th>First author (ref.)</th>
<th>Year</th>
<th>Publication type</th>
<th>Study type</th>
<th>Sample size</th>
<th>Treatment</th>
<th>PBMT device</th>
<th>Wave-length (nm)</th>
<th>Power (mW)</th>
<th>Energy density (J/cm²)</th>
<th>Laser schedule</th>
<th>Evaluation schedule</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiero⁵⁵</td>
<td>2009</td>
<td>Full article</td>
<td>Three groups; pretest-posttest</td>
<td>49</td>
<td>-LD-PBMT (n=10)</td>
<td>Er:YAG laser</td>
<td>880</td>
<td>NA</td>
<td>27-54</td>
<td>3 applications</td>
<td>12—80 months follow up period</td>
<td>CR=6; PR=4</td>
</tr>
<tr>
<td>Scoletta⁵⁵</td>
<td>2010</td>
<td>Full article</td>
<td>Single group; pretest-posttest</td>
<td>20</td>
<td>LD-PBMT</td>
<td>Er:YAG laser</td>
<td>904</td>
<td>7</td>
<td>28.4</td>
<td>10 sessions over a period of 20 days</td>
<td>1h before the laser procedure and 28 days after</td>
<td>Significant decrease in pain score, clinical size, oedema, and presence of pus and fistulas.</td>
</tr>
<tr>
<td>Atalay⁵⁵</td>
<td>2011</td>
<td>Full article</td>
<td>RCT</td>
<td>20</td>
<td>-Laser surgery + LD-PBMT (n=10)</td>
<td>Nd:YAG laser</td>
<td>950</td>
<td>250</td>
<td>6.25</td>
<td>5 sessions over a period of 10 days</td>
<td>Every other day for the first 10 days and monthly for the next 6 months</td>
<td>No significant difference between the groups.</td>
</tr>
<tr>
<td>Romeo⁵⁵</td>
<td>2011</td>
<td>Full article</td>
<td>Single group; pretest-posttest</td>
<td>7</td>
<td>LD-PBMT</td>
<td>Nd:YAG laser</td>
<td>1064</td>
<td>NA</td>
<td>14.37</td>
<td>Weekly during 2 months</td>
<td>NA</td>
<td>Significant difference in NRS score.</td>
</tr>
<tr>
<td>Vescovi ³⁵</td>
<td>2012</td>
<td>Full article</td>
<td>Five groups; pretest-posttest</td>
<td>190</td>
<td>-Medical therapy</td>
<td>InGaAlP LD</td>
<td>660</td>
<td>40</td>
<td>6</td>
<td>Daily until mucosal healing</td>
<td>Followed until mucosal wound healing was clinically observed or weekly during the first month</td>
<td>CR=12; PR=2</td>
</tr>
<tr>
<td>Martins³⁵</td>
<td>2012</td>
<td>Full article</td>
<td>Three groups; pretest-posttest</td>
<td>22</td>
<td>-Clinical protocol (n=3)</td>
<td>GaAlAs LD</td>
<td>808</td>
<td>500</td>
<td>5</td>
<td>Five sessions on post-operative day 1, 3, 5, 7, and 10</td>
<td>Before the start of laser and follow-up (6-25 months)</td>
<td>CR=4; PR=7</td>
</tr>
</tbody>
</table>

Partially adapted from Robijns et al. (2017)⁵

Abbreviations: ONJ, osteonecrosis of the jaw; PBMT, photobiomodulation therapy; PRP, platelet-rich plasma; LD, CR, complete remission; PR, partial remission; NRS, numerical rating scale; NA, not available; ref, reference; LD, laser diode.
and the other one three times a week. Results showed that xerostomia improved in both groups, although it was better in the group that received LD-PBMT three times a week.38 In a double-blind RCT by Arbabi-Kalati et al., they demonstrated that LD-PBMT can reduce the incidence of severe xerostomia.39 Oton-Leite et al. enrolled 60 HNC patients receiving RT in a RCT investigating the effect of LD-PBMT on oral complications. They were able to demonstrate that the salivary flow of the patients treated with LD-PBMT significantly improved.40 A recent study by Saleh et al. in HNC patients, found no significant improvement of hyposalivation and xerostomia after LD-PBMT treatment. This might be due to fibrosis and acinar atrophy of the glandular tissue.41

The guidelines by Zecha et al. suggested the use of an extra-(wavelength 750-830 nm; power density 20-80mW; energy density 3 J/cm²) and/or intra-oral LED/LD-PBMT device (wavelength 630-680 nm; power density 20-150mW; energy density 3 J/cm²) starting the first day of RT and continuing daily during RT for the prevention of xerostomia and hyposalivation by targeting the major and minor salivary glands.1

**CONCLUSION**

Based on evidence collected in this review, PBMT has the potential to become a new preventive and therapeutic option for a broad range of acute and chronic side effects associated with cancer therapy. Especially for the prevention and management of OM, the use of PBMT has already been accepted in the general treatment guidelines developed by the MAS-

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**TABLE 6.** Summary of clinical studies investigating the use of PBMT for the management of xerostomia/hyposalivation in cancer patients.

<table>
<thead>
<tr>
<th>First author (ref.)</th>
<th>Year</th>
<th>Publication type</th>
<th>Study type</th>
<th>Sample size</th>
<th>Treatment</th>
<th>PBMT device</th>
<th>Wave-length (nm)</th>
<th>Power (mW)</th>
<th>Energy density (J/cm²)</th>
<th>Laser schedule</th>
<th>Evaluation schedule</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowen37</td>
<td>1997</td>
<td>Full article</td>
<td>Double-blind, placebo-controlled RCT</td>
<td>30</td>
<td>-LD-PBMT -Sham laser</td>
<td>HeNe LD</td>
<td>632.8</td>
<td>60</td>
<td>1.5</td>
<td>5 consecutive days before the HSCT</td>
<td>First and last session of PBMT</td>
<td>Xerostomia and ability to swallow improved.</td>
</tr>
<tr>
<td>Simoes38</td>
<td>2010</td>
<td>Full article</td>
<td>Prospective, two-group study</td>
<td>22</td>
<td>-LD-PBMT 3x/week -LD-PBMT 1x/week</td>
<td>AlGaP LD</td>
<td>660</td>
<td>40</td>
<td>6</td>
<td>Started within the first 2 weeks of RT until complete healing of OM</td>
<td>First and last session of PBMT</td>
<td>Xerostomia improved in both groups, but was better in the group 3x/week.</td>
</tr>
<tr>
<td>Arbabi-Kalati39</td>
<td>2013</td>
<td>Full article</td>
<td>Double-blind randomized trial</td>
<td>48</td>
<td>-LD-PBMT -Sham laser</td>
<td>LD</td>
<td>630</td>
<td>30</td>
<td>5</td>
<td>Before each CTx session</td>
<td>Before the CTx and every 2 weeks until the end of CTx</td>
<td>Severe xerostomia (grade 3) was prevented.</td>
</tr>
<tr>
<td>Oton-Leite40</td>
<td>2013</td>
<td>Full article</td>
<td>Double-blind, placebo-controlled RCT</td>
<td>60</td>
<td>-LD-PBMT -Sham laser</td>
<td>InGaAP diode laser</td>
<td>685</td>
<td>36</td>
<td>2</td>
<td>A week before RT and daily for 5 consecutive days before each session of RT until the end of RT</td>
<td>1 week after starting RT, at the 15th RT session and at the final RT session</td>
<td>Significantly higher SFR in the PBMT group.</td>
</tr>
<tr>
<td>Saleh41</td>
<td>2014</td>
<td>Full article</td>
<td>Double-blind, placebo-controlled RCT</td>
<td>23</td>
<td>-LD-PBMT -Sham-laser</td>
<td>GaAlAs diode</td>
<td>830</td>
<td>100</td>
<td>71</td>
<td>2x/week for 6 weeks</td>
<td>Before the start of PBMT, at the 6th session of PBMT and at the last session (12)</td>
<td>No significant increase of SFR or decrease of xerostomia.</td>
</tr>
</tbody>
</table>

Abbreviations: CTx, chemotherapy; RT, radiotherapy; LD, laser diode; PBMT, photobiomodulation therapy; HSCT, hematopoietic stem cell transplantation; OM, oral mucositis; SFR, salivary flow rate; ref, reference; RCT, randomised controlled trial.
For the other applications, more RCTs with larger patient populations are necessary to confirm the promising results of the current trials. In the future trials more attention needs to be paid towards the identification of the most effective PBMT parameters for each individual medical condition. Finally, more research is needed to evaluate any potential side effects of PBMT that might influence tumour behaviour and/or proliferation.

REFERENCES


