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Review

Tumor safety and side effects of photobiomodulation therapy used for prevention and management of cancer treatment toxicities. A systematic review

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ABSTRACT

Photobiomodulation therapy (PBMT), also known as low-level laser therapy (LLLT), has been increasingly used for the treatment of toxicities related to cancer treatment. One of the challenges for the universal acceptance of PBMT use in cancer patients is whether or not there is a potential for the light to stimulate the growth of residual malignant cells that evaded oncologic treatment, increasing the risk for tumor recurrences and development of a second primary tumor. Current science suggests promising effects of PBMT in the prevention and treatment of breast cancer-related lymphedema and oral mucositis, among other cancer treatment toxicities. Nevertheless, this seems to be the first systematic review to analyze the safety of the use of PBMT for the management of cancer-related toxicities. Scopus, MEDLINE/PubMed, and Embase were searched electronically. A total of 27 articles met the search criteria. Selected studies included the use of PBMT for prevention and treatment of oral mucositis, lymphedema, radiodermatitis, and peripheral neuropathy. Most studies showed that no side effects were observed with the use of PBMT. The results of this systematic review, based on current literature, suggest that the use of PBMT in the prevention and management of cancer treatment toxicities does not lead to the development of tumor safety issues.

Introduction

Photobiomodulation therapy (PBMT), also known as low-level laser therapy (LLLT), is the use of red or near infrared (NIR) light to heal, restore, and stimulate multiple physiological processes as well as to repair damage caused by injury or disease [1]. In this paper, PBMT is used to refer to either LLLT or Light Emitting Diode (LED). Both therapies have been shown as promising treatment options to promote tissue repair [2]. Introduced in 1928, the LED has been employed since the early 1990s for therapeutic purposes in inflammatory, traumatic, infectious, and autoimmune lesions. Furthermore, the laser, which emerged in the late 1960s, has been used in the treatment of wound healing, pain relief, and inflammation in a wide range of orthopedic conditions. Its use in dentistry, however, began 30 years later [2].

In the last 20 years, the use of PBMT in the supportive care of cancer patients has increased. The treated cancer therapy-related side effects

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include oral mucositis (OM), lymphedema, neuropathy, and radiodermatitis [3–8]. However, some results of in vitro and in vivo studies investigating the effects of PBMT on the proliferation of cancer cells raised concerns regarding the oncological safety of the use of PBMT in cancer patients [9–13]. These studies were experimental in nature and did not consider the effects of the immune system present in humans. Two recently published studies evaluating the safety of PBMT in head and neck (H&N) cancer patients, although retrospective in design, did not show any negative signal that would favor the development of tumor recurrences and/or new primary tumors [14,15].

Several cellular effects secondary to PBMT have been demonstrated in a variety of cell types (e.g. fibroblasts, lymphocytes, osteoblasts, stem cells, and smooth muscle cells) and in vitro studies [16–23]. These effects are the result of primary reactions involving absorption of specific wavelengths of light by components of the mitochondrial respiratory chain, such as cytochromes, cytochrome *c* oxidase, and flavin dehydrogenases. The light absorption modifies the reduction-oxidation reaction (REDOX) status of the cytoplasm and mitochondria, leading to increased levels of adenosine triphosphate (ATP). These primary reactions stimulate a cascade of secondary reactions at the cellular level that involves intracellular signaling, leading to stimulation of cytokine reactions, nitric oxide (NO) production [13], release of growth factors [24–26], up-regulation of ATP [27,28], increased metabolism, change in REDOX signaling, increased reactive oxygen species (ROS), and cell proliferation [29]. In addition, stimulation of lymphocytes and local fluid circulation have been reported [29,30].

The aim of the present systematic review was to evaluate the current literature regarding the tumor safety of PBMT use in the prevention and/or treatment of complications related to antineoplastic therapies. The conflicting results regarding the effects of laser on cancer cells, the lack of prospective human clinical studies designed to investigate the safety of PBMT in cancer patients, and the increased use of PBMT in cancer facilities raised the question whether PBMT can be considered safe.

Materials

A systematic literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol for this systematic review was registered in the International Prospective Register of Systematic Review (PROSPERO) database (registration number CRD42018094364) to avoid duplicate publications of systematic reviews and to enable comparison among methods as they are reported in the review protocol.

Inclusion criteria

Only human clinical studies (retrospective and prospective) regarding treatment and/or prevention of toxicities associated with oncological treatment, and information about safety of PBMT were included.

Exclusion criteria

Case-control studies, cohort studies, case reports, case series, animal studies, in vitro studies, letters to editors, editorials, review articles, commentaries, monographs, conference papers, unpublished data, studies published in a language other than English, and studies without information about safety or side effects of PBMT in the treatment of toxicities induced by antineoplastic therapies were excluded.

Search strategy

Electronic and systematic searches of scientific studies that evaluated the effect of PBMT in cancer patients for prevention and/or treatment of toxicities induced by antineoplastic therapies were conducted without restriction in publication year (last search was February, 20th 2017). Therein, Medline/PubMed (https://www.ncbi.nlm.nih.gov/pubmed), EMBASE (https://www.embase.com/login), and Scopus (https://www.scopus.com) were screened. The following keywords were used: “low-level laser therapy”, “photobiomodulation”, “oral mucositis”, “lymphedema”, “radiodermatitis”, “xerostomia”, “hyposalivation”, “trismus”, “peripheral neuropathy”, and “osteoradionecrosis”. Multiple synonyms, abbreviations, and related keywords for each of these terms were used for searching, linked in independent strategies by the Boolean operator “AND”. All publications presented in these databases containing a combination of controlled, pre-defined Medical Subject Headings (MeSH) and free terms related to PBMT in head and neck squamous cell carcinoma (HNSCC), using Boolean operators (OR, AND) to combine searches, were retrieved. The process was repeated in each database to ensure that any relevant result was not missed during the identification phase, adapted to the rules of syntax of each electronic database. Additional manual searches were conducted by reading the reference lists from all selected studies to detect other potentially eligible reports that could meet the inclusion criteria. Furthermore, key authors/co-authors were identified among the included studies, which allowed for verification of extra database searches filtered by author/co-author name.

Study selection

All titles were systematically organized in Microsoft Office Excel 2016 (Microsoft Corporation, Redmond, Washington, USA). The titles were verified, and the duplicates excluded. Later, titles and abstracts were screened and read completely for possible inclusion on the qualitative synthesis of this review. The studies were classified into the following categories: duplicated, language other than English, in vitro, animal studies, no follow-up information, and safety. The studies assessed for eligibility were detailed and reviewed in full text version by two independent reviewers (AS and MP). The studies that omitted relevant methodological information were also excluded from the current review. When discrepant ratings occurred between the reviewers, a final decision was made by a third reviewer (CM) in order to achieve consensus.

Data extraction

Methodological information extracted from included studies were: (1) first author, (2) year of publication, (3) size of the sample, (4) study type, (5) treatment design (parameters of PBMT), (6) mean follow-up, and (7) outcomes.

Risk of bias assessment

To assess the risk of bias, eight methodological aspects were verified according to the Cochrane Handbook for Systematic Reviews of Interventions, which are randomization, allocation concealment, blinding of participants, blinding of outcome assessment, blinding of outcome assessment (all-cause mortality), incomplete outcome data (short-term), incomplete outcome data (long-term), and selective reporting. Aspects such as randomization, method of randomization, and blinded participants and operators were checked. If each item was present in the selected article, it was judged as “low risk of bias” (green circle). If one or more items were not present in the selected article, the paper was judged as “high risk of bias” (red circle). If this information was not available, the paper was classified as “undefined risk of bias” (yellow circle).

Data analysis

Due to a great variation of the PBMT protocols used in the included studies, it was not possible to perform a meta-analysis. Therefore, this

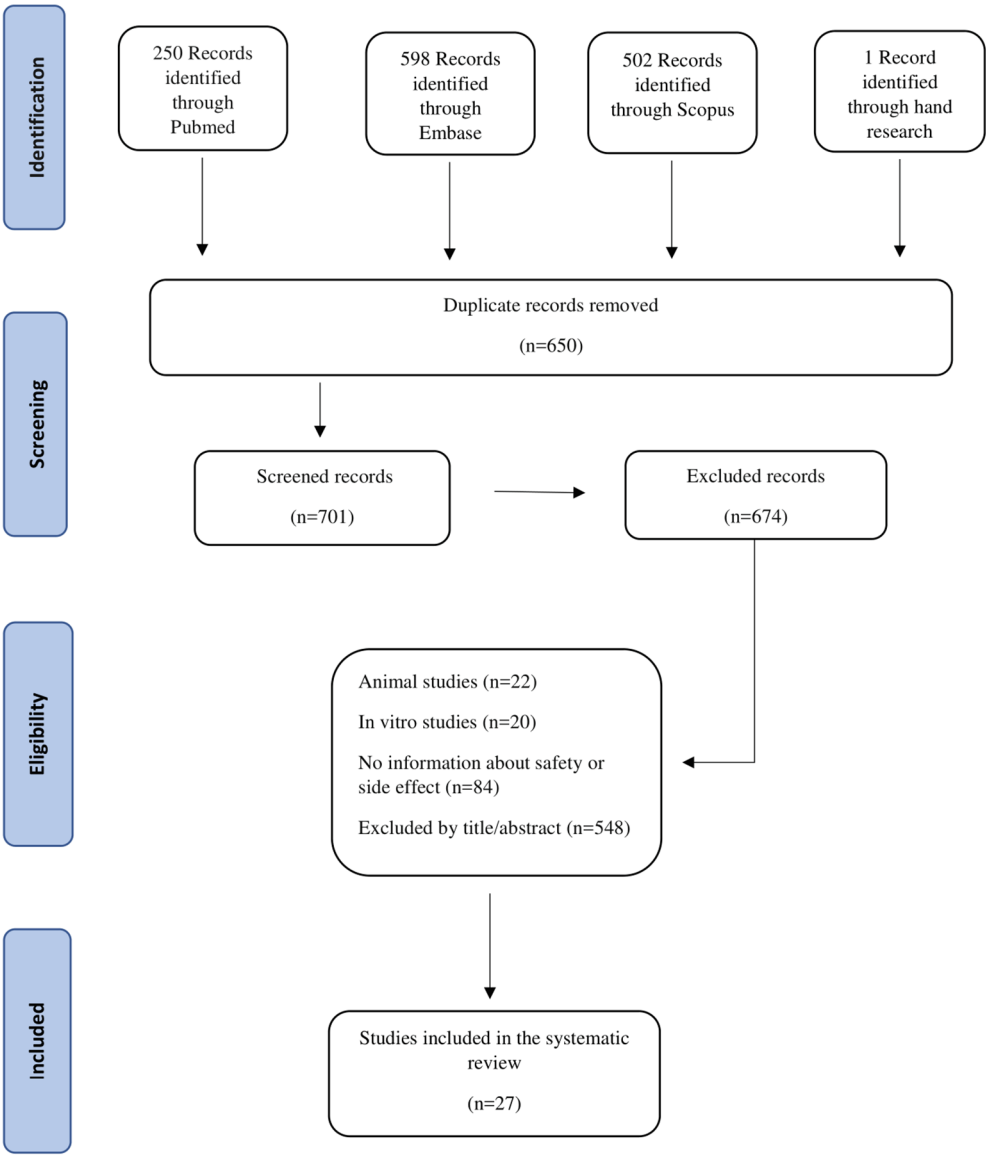

Fig. 1. Flow diagram of literature search.

systematic review presented a detailed qualitative synthesis of the results from the included studies.

Results

Search and study selection

A flow diagram that summarizes the selection process of the studies is shown in Fig. 1. In total, 1350 studies were identified through the search strategies on the databases and one study through the manual search. After the first review process, 650 studies were eliminated due to duplication. Later, 548 studies were excluded by the title, and 124 studies were excluded because they did not meet the inclusion criteria. Twenty-two from the remaining 126 studies were excluded because they were animal studies, and 20 were in vitro. Another 84 studies did not have information about side effects or safety of PBMT. Finally, 27 studies with all the inclusion criteria were included in the present systematic review.

All of the included studies evaluated the safety of PBMT for prevention and treatment of toxicities induced by cancer treatments [3,5,14,15,31–53]. In terms of follow-up and clinical outcomes assessed, 4 studies evaluated tumor safety issues of PBMT for more than 24 months of treatment conclusion [14,15,42,43]; 6 studies evaluated PBMT side effects from 1 to 24 months [3,32,34,35,38,45]; 8 studies evaluated PBMT side effects for less than 1 month [36,37,39,41,44,48,51,53]; 4 studies evaluated PBMT side effects during the course of radiotherapy (RT) [5,33,40,47]; and 5 studies evaluated PBMT side effects until complete wound healing or neutrophil recovery [31,39,46,49,50].

Study characteristics

Table 1 presents the main characteristics of the included studies.

Risk of bias

Twenty-one (77.7%) studies were considered to have low risk of bias for random sequence generation [3,14,31,32,34,36–43,45–50,52,53], 11 (40.7%) for allocation concealment [3,34,36,37,40,42,43,46,49,52,53], 19 (70.3%) for blinding of participants and personnel [3,14,31–34,36–38,40,41–43,45–48,52,53], 20 (74.0%) for blinding of outcome assessor (patient reported outcomes) [3,14,31–34,

Table 1
Baseline characteristics of studies included in the systematic review.

Study	Sample size	Study type	Use of PBMT	Treatment design	Mean follow-up	Side effect (*) or tumor safety (**) outcomes
Carati et al. [34]	64	Double-blind, single crossover, randomized clinical trial	Lymphedema	Wavelength 904 nm, dose of 1.5 J/cm^2. Laser applied 3 times per week for 3 weeks	26–30 weeks	There were no adverse reactions or side effects reported among any participants*
Kaviani et al. [45]	11	Double-blind, randomized clinical trial	Lymphedema	Wavelength 890 nm, dose of 1.5 J/cm^2. Laser applied 3 times per week for 3 weeks. After an 8-week interval, the same treatment protocol was repeated for another 3-week period (18 treatment sessions)	22 weeks	None of the participant reported any adverse reaction or side effects*
Antunes et al. [32]	94	Prospective, randomized, double-blind, placebo-controlled clinical trial	Oral mucositis	Wavelength 660 nm, 100 mW, dose of 4 J/cm^2. Applied daily for 5 consecutive days (Monday to Friday), lasted on average 45.7 days	18 months	LLLT was well-tolerated, and no toxicity (side effect) was observed during application*
Antunes et al. [14]	94	Prospective, randomized, double-blind, placebo-controlled clinical trial	Oral mucositis	Wavelength 660 nm, 100 mW, dose of 4 J/cm^2. Applied daily, for 5 consecutive days (Monday to Friday) lasted on average 45.7 days	41.3 months	LLLT treatment had a significant positive impact on the response to cancer treatment and on progression-free survival**
Brandão et al. [15]	152	Retrospective study	Oral mucositis	Wavelength 660 nm, 40 mW, 0.4 J, dose of 10 J/cm^2. Applied daily for 5 consecutive days (Monday to Friday) throughout radiation therapy	40.8 months	PBMT is a safe clinical modality for prevention of OM in OSCC patients**
Gouvêa Lima et al. [42]	75	Prospective, randomized, double-blinded clinical trial	Oral mucositis	Wavelength 660 nm, 10 mW, dose of 2.5 J/cm^2. Applied daily before each radiation fraction	24 months	No difference was detected in disease control or survival between placebo and laser group**
Silva et al. [49]	42	Randomized clinical trial	Oral mucositis	Wavelength 660 nm, 40 mW, dose of 4 J/cm^2. Daily sessions began on D-4 and continued through to D + 4. There was a total of nine treatment days	D-2 until the wounds healed or until neutrophil recovery	The laser application was well-tolerated, and no side effects occurred*
Schubert et al. [48]	70	Randomized, double-blind, placebo-controlled	Oral mucositis	Wavelength 650 nm, 40 m, energy of density of 2 J/cm^2 and 780 nm; 60 mW, energy of density of 2 J/cm^2. Laser therapy starting on the first day of HCT conditioning and continued for 3 days post-transplant (ending on day + 2 post-transplant)	21 days	LLLT appears to be safe and without side effects*
Guedes et al. [43]	58	Prospective, randomized, double-blind	Oral mucositis	Wavelength 660 nm, 25 mW, 6.3 J/cm^2 and 660 nm, 100mW, 33 J/cm^2. Laser was applied from the first to the last day of radiotherapy or until resolution of persistent OM lesions	24 months	Tumor recurrence was found in 14 (24%) cases and did not vary significantly between the groups**
Freitas et al. [39]	40	Prospective	Oral mucositis	Wavelength 660 nm, 40 mW, 6.6 J/cm^2. Treatment was administered for 10 consecutive days, with exception of weekends	10 days	Laser and LED irradiations were well tolerated, and no adverse/side effects were reported*
Vitale et al. [53]	16	Randomized, double- blind clinical trial	Oral mucositis	Soft laser: wavelength between 660 and 810 nm. Diode laser GaAlAs: wavelength 970 nm, 3.2 W. Laser therapy was started 3–6 days after the end of CT and/or HSCT. Performed once a day, for 4 consecutive days	11 days	Absence of side effects*
Gautan et al. [40]	121	Randomized, double-blinded clinical trial	Oral mucositis	Wavelength 632.8 nm, 24 mW, dose of 3.5 J/cm^2. Applied daily for 6.5 weeks	6.5 weeks	LLLT can be considered as a safe modality for treating CRT-induced OM*
Elad et al. [36]	20	Placebo-controlled, randomized, and double-blind	Oral mucositis	165–200 mW/cm^2, each additional exposure was 15 s longer until the exposure duration reached 90 s. Treatment started on the first day of conditioning therapy, continuing until day 28	Day 21 post-HSCT	LLLT is safe and effective for the prevention of oral mucositis in patients undergoing HSCT*
Kuhn et al. [46]	21	Placebo-controlled, randomized trial	Oral mucositis	Wavelength 830 nm, 100 mW, dose of 4 J/cm^2. Laser therapy started on day 1 of treatment and was made available 7 days a week, until the end of the treatment	Daily until complete healing of the lesions	Laser was well-tolerated, and there were no adverse side effects attributable to its use*
Arora et al. [33]	24	Randomized controlled trial	Oral mucositis	Wavelength 632.8 nm, 10 mW, dose of 1.8 J/cm^2. One time per day for 33 days	6.5 weeks	There were no adverse effects noted with the use of 60-mW He-Ne laser*
Genot-Klastersky et al. [41]	62	2 prospective clinical trials	Oral mucositis	Laser combining a visible 100 mW laser and an IR laser with power from 50, 250, and 500 mW, dose of 2 J/cm^2. Three sessions were delivered per week	Mean of 21 days	LLLT is an effective and safe approach to prevent or treat oral mucositis resulting from cancer chemotherapy*

(*continued on next page*)

Table 1 (*continued*)

Study	Sample size	Study type	Use of PBMT	Treatment design	Mean follow-up	Side effect (*) or tumor safety (**) outcomes
Jaguar et al. [44]	24	Placebo-controlled trial	Oral mucositis	Wavelength 660 nm, 10 mW, 2.5 J/cm^2. Treatment started from the beginning of the conditioning regimen up to day + 2	Beginning of the conditioning regimen to the thirtieth day after stem cell transplantation (day + 30)	The laser therapy applications were well-tolerated, and no side effects were observed*
Fife et al. [38]	33	Prospective, randomized, double-blind, controlled study	Radiodermatitis	Wavelength 590 nm, dose of 1.5 J/cm^2. Applied daily before and after each radiation session	11 weeks	No adverse events were observed with LED treatment *
Simões et al. [50]	39	Comparative study	Oral mucositis	Low power PBMT: wavelength 660 nm, 40 mW, energy density of 6 J/cm^2. The treatment was done once a week. In the combined protocol: low power as described above and the high power PBMT was 808 nm, 10 J/cm^2. The irradiations were done three times a week	The time for complete mucosal healing was recorded	Laser irradiations were well-tolerated with no detectable adverse side effects*
Antunes et al. [31]	38	Randomized, placebo-controlled, prospective clinical trial	Oral mucositis	Wavelength 660 nm, 46.7 mW, and energy density of 4 J/cm^2. One time per day, every day until neutrophil recovery	D-7 until neutrophil recovery	The treatment was well-tolerated, and no toxicity was recorded*
Lima et al. [5]	25	A prospective, comparative and non-randomized study	Oral mucositis	Wavelength 830 nm, 15 mW, 12 J/cm^2. Laser applications daily since the first day of RT up to the end of the therapy	7 weeks	The laser did not cause adverse effects*
DeLand et al. [35]	47	Placebo-controlled	Radiodermatitis	Wavelength 590 nm, standard 100-pulse, 250 ms per pulse at a fluence of 0.15 J/cm^2. LED administered daily, 1 h before RT	6 months	No adverse effects associated with LED treatment were observed*
Li et al. [47]	32	Clinical evaluation study	Lymphedema	Wavelength 750 nm–100 μm, frequency range of 400–3 THz, and photon energy range of 12.4 meV–1.7 eV. Five days per week for 4 weeks	20 days	Procedure is safe and effective*
Argenta et al. [3]	70	Randomized, double-blinded, sham-controlled, crossover trial	Peripheral neuropathy	Wavelengths 800–970 nm. Three times per week for six weeks	16 weeks	There were no observed complications among patients treated with PBMT*
Storz et al. [52]	40	Double-blind, placebo-controlled trial	Lymphedema	980 nm, 40 mW, energy density of 4.89 J/cm^2. Two times a week for four weeks	12 weeks	Neither adverse events nor any harm was related to this study*
Soto et al. [51]	12	Randomized, double-blind clinical trial	Oral mucositis	Intraoral: 685 nm, 35 mW, total energy per point of 0.35 J. Extraoral: 830 nm, power 80 mW, energy per point 2.4 J. Laser therapy began on the 1st day of the conditioning regimen and ended on the day of healing of the ulcers	22 days	There were no adverse events associated with the use of laser therapy in this study*
Ferreira et al. [37]	35	Randomized clinical trial	Oral mucositis	Wavelength 650 nm, 100 mW, energy per point of 2 J. Applied daily from first to fifth day of pre-transplant conditioning	15 days	LLLT is safe and effective*

PBMT = photobiomodulation therapy; LLLT = low level laser therapy; LED = light emitting diode; OM = oral mucositis; OSCC = oral squamous cell carcinoma; CRT = chemoradiotherapy; HSCT = hematopoietic stem cells transplantation; IR = infrared; RT = radiotherapy.

* Studies based on short-term follow-up that evaluated PBMT side effect outcomes.

** Studies based on long-term follow-up that evaluated tumor safety outcomes.

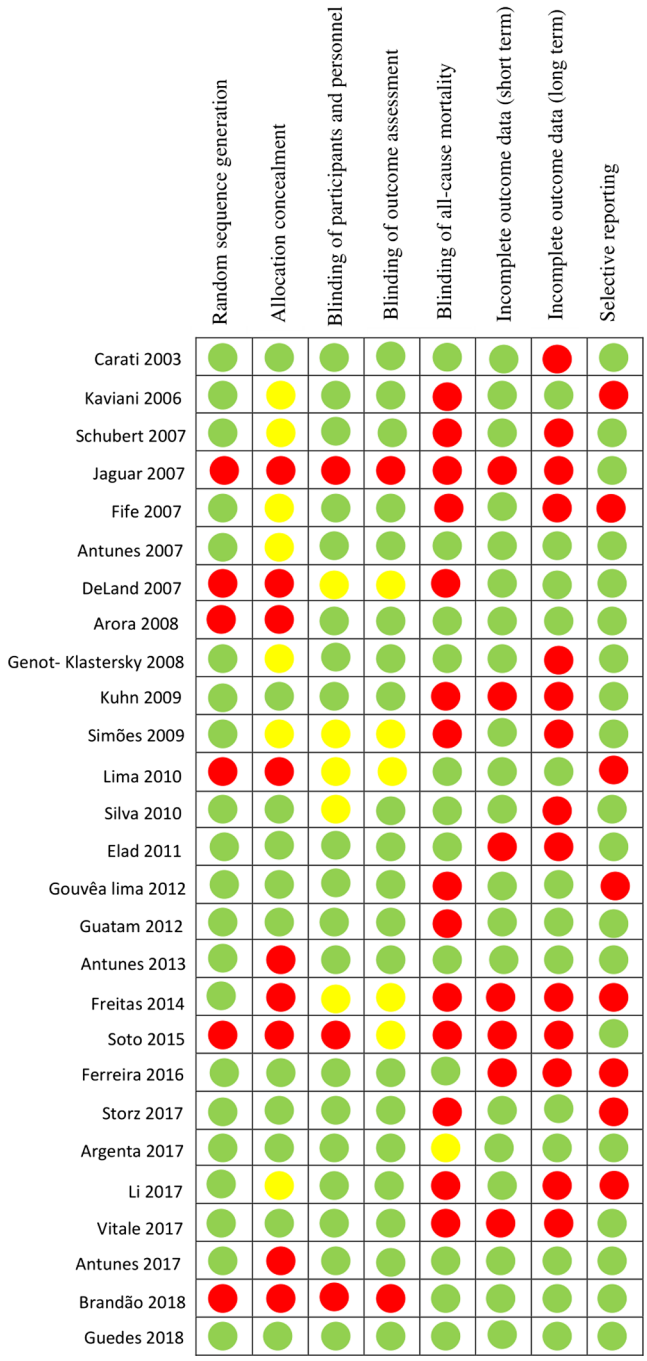

Fig. 2. Risk of bias of the selected articles. If the item was present in the selected article, it was judged as "low risk of bias" (green circle). If the item was not presented in the selected article, the paper was judged as "high risk of bias" (red circle). If this information was not available, the paper was classified as "undefined risk of bias" (yellow circle) for the item. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

36–38,40–43,45–49,52,53], 12 (44.4%) for blinding of outcome assessor (all-cause mortality) [5,14,15,31–34,36,37,41,43,49], 21 (77.7%) for incomplete outcome data (short-term) [3,5,14,15,31–35,38,40–45,47–50,52], 13 (48.1%) for incomplete outcome data (long-term) [3,5,14,15,31–33,35,40,42,43,45,52], and 19 (70.3%) for selective outcome reporting [3,14,15,31–36,40,41,43,44,46,48–51,53] (Fig. 2).

Synthesis of results

Table 1 presents the mean follow-up of each study, which in many cases may be considered a limiting factor when evaluating the safety of PBMT use in cancer patients. Only four studies reported a long follow-up time (more than 2 years) [14,15,42,43]. In contrast, most studies included in the review were double-blinded, placebo controlled, which makes the study more reliable with a placebo group for comparison of outcomes, and the evaluators and patients were blinded to the treatment protocol, which decreases the chance of bias [3,14,31–38,40–46,48,49,51–53].

The studies that evaluated the efficacy of PBMT for the prevention and treatment of lymphedema presented variable follow-up times from 20 days to 30 weeks [34,45,47,52]. This is a relevant limitation of the studies for the evaluation of the short- and long-term safety of the use of PBMT in cancer patients (chance of tumor recurrence or second primary tumor). Despite the short follow-up time, 3 (out of 5 selected studies) were double-blinded and placebo controlled trials.

Among the 20 studies that evaluated the use of PBMT for prevention and treatment of OM, 3 were in patients of H&N cancer submitted to RT [33,43,50], 6 studies in patients of H&N cancer submitted to chemoradiotherapy [5,14,15,32,39–42], and 9 studies in hematopoietic stem cell transplantation patients [31,36,37,44,46,48,49,51,53]. The follow-up time for patients varied from 10 days up to 41.3 months. In some studies, the follow-up was performed only during cancer treatment [5,31–33,36,37,39–41,44,46,48–51,53], while in other studies, a long post-cancer treatment follow-up period (more than 2 years) was performed—all of these with variable results [14,15,42,43]. One study reported a higher rate of tumor recurrence in the laser group [43]. Other studies did not show differences in tumor recurrence between groups [15,42]. Moreover, another study showed better survival rates and disease-free survival in the laser group when compared to placebo [14]. The studies that evaluated the effect of PBMT to prevent radiodermatitis and to manage chemotherapy-induced peripheral neuropathy did not show significant impact on tumor outcomes [3,35,38].

Discussion

This seems to be the first systematic review evaluating the body of evidence about the safety of PBMT use in the prevention and management of toxicities related to cancer treatment. Based on this systematic review, it is evident that the data available in the literature are poor and that the safety of this technology needs to be more effectively studied.

Twenty of the included studies were related to OM prevention or treatment. From these, only 4 were specifically designed to evaluate the tumor safety of PBMT use in the treatment and prevention of OM and were based on longer follow-up periods (24 months or more) [14,15,42,43]. The other 16 studies were mainly based on short-term follow-up periods and designed to show the efficacy of PBMT in the prevention and treatment of OM, as referred to the safety of the technology and the absence of adverse events/side effects during the treatment. However, this was not the main objective of the studies. Despite the fact that these 16 studies showed a high risk of bias, mainly due to the short follow-up period, none of them recorded any evidence regarding a negative impact of PBMT on side effect outcomes of cancer patients [5,31–33,36,37,39–41,44,46,48–51,53].

The safety of PBMT in cancer patients has been recently questioned. Some studies suggest that the PBMT use is able to influence the cellular metabolic processes to the point of stimulating the proliferation of malignant cells and to modulate the tumor microenvironment in order to increase the tumor volume [54,55]. On the other hand, studies by other authors suggest that PBMT induces apoptosis and cell death in malignant neoplastic cells in a dose-dependent manner, lacking the potential to activate residual malignant cells [13,56,57]. In the study of Guedes et al. [43], where two different laser protocols were used

(0.25 J and 1.0 J), they showed tumor recurrence rate in 14 cases (24%), but with no statistical difference between the groups and no control group to compare the results. This result must be considered cautiously because of the limited extension of follow-up (2 years) [43]. Similarly, Brandão et al. [15] showed rates of local regional recurrence of 29.6% and second primary tumors in the oral cavity of 12.5% in patients treated with PBMT. Furthermore, their study also had no control group for comparison of results, but it had a longer mean follow-up (40.8 ± 11.7 months) [15]. The rates of local regional recurrence and second primary tumors were very similar, sometimes even better when compared with other studies that use traditional methods of treatment of oral squamous cell carcinoma (OSCC) without PBMT [58,59].

Contrastingly, two studies showed that the use of PBMT in the prevention and treatment of OM was associated with better cancer prognosis (disease-free survival) for patients with H&N carcinomas [14,32]. In these studies, evaluation of patients treated with PBMT showed that there was no significant difference in patients with tumor recurrence or second primary tumors between the laser-treated group and the placebo group. The authors attributed it to the improved quality of life, enabling compliance with cancer treatment regimens as well as better overall general health, which likely led to the improved response to therapy.

Four articles in this systematic review were designed to evaluate the efficacy of the PBMT in the management of lymphedema related to post-mastectomy. All of these studies were based on short-term follow-up periods and allowed the assessment of adverse events/side effects related to the PBMT. In 2 articles, PBMT was applied for 3 weeks, and the follow-up time was 26–30 weeks [34] and 22 weeks [45]. In 1 article, the follow-up was 4 weeks [47], while in another study, it was 12 weeks [52]. None of the papers showed adverse reactions/side effects related to the use of PBMT. However, no studies showed a follow-up long enough to ensure no long-term deleterious effects on the profiling of malignant cells [34,45,47,52].

Only two clinical trials that used PBMT for the treatment of radiodermatitis were selected. In both studies, no adverse effects associated with laser treatment were observed, and all patients completed the trial [35,38]. As with lymphedema-related studies, neither study had a follow-up long enough to ensure the long-term safety of the technology. Only one study related to PBMT safety in the treatment of peripheral neuropathy associated with chemotherapy was found [3]. In this clinical trial, patients who used PBMT had a significant reduction in neuropathy symptoms. After 16 weeks of follow-up, it was concluded that the use of PBMT is safe and effective for the treatment of peripheral neuropathy.

Conclusion

Based on the results of this systematic review, it is suggested that the use of PBMT to prevent and/or treat complications associated with cancer treatment is safe. Future studies using similar protocols of PBMT application and with long-term follow-up are needed to confirm the safety of PBMT use in cancer patients. Additionally, further prospective studies with long-term follow-up are necessary to support the findings of the present review.

Conflict of interest statement

None to declare.

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