UNIVERSIDADE DE BRASÍLIA
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DEPARTAMENTO DE ENFERMAGEM

USE OF PHOTOBIOMODULATION THERAPY TO PREVENT OR TREAT ACUTE RADIATION DERMATITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

BEATRIZ REGINA LIMA DE AGUIAR

Brasília - DF

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Trabalho de Conclusão de Curso (TCC), apresentado ao curso de graduação em Enfermagem da Universidade de Brasília – UnB, *campus* Darcy Ribeiro, como requisito para obtenção do título de Bacharel em Enfermagem.

Orientadora: Profa. Dra. Elaine Barros Ferreira

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BANCA EXAMINADORA

Profa. Dra. Elaine Barros Ferreira
Orientadora

Profa. Dra. Paula Elaine Diniz dos Reis
Membro Efetivo

Enfa. MSc. Amanda Gomes de Menêses
Membro Efetivo

Enfa. MSc. Priscila de Souza Maggi Bontempo
Membro Suplente

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“Conheça todas as teorias, domine todas as técnicas,

mas ao tocar uma alma humana, seja apenas outra alma humana”

(Carl G. Jung)

Use of photobiomodulation therapy to prevent or treat acute radiation dermatitis: A systematic review and meta-analysis

Abstract

Purpose: To evaluate the effects of the use of PBMT, such as laser and other light therapies, to prevent and/or treat RD. **Methods:** A systematic review was conducted using databases CINAHL, Cochrane CENTRAL, LILACS, PubMed, Scopus, and Web of Science. Google Scholar, Open Grey, and ProQuest were used to gray literature search. We followed the PRISMA methods for conduction of systematic review. The risk of bias of included studies was assessed using the Cochrane Collaboration Risk of Bias Tool (RoB tool) and while the quality of evidence for each outcome was assessed using the GRADEpro software. **Results:** A total of 7 articles were included in this systematic review. Six them were performed in breast cancer patients (receiving doses > 40 Gy) and one in head and neck cancer patients (receiving 30-32 Gy). Most of the articles included (n = 6) showed results indicating the benefit of using PBMT, either for the prevention or the treatment of RD, and only one of the studies included did not reduce the incidence of RD or the interruptions in radiotherapy. Patients receiving PBMT developed more RD grade 1 than the control group (RR 1.55, 95% CI 1.14–2.10, I^2 = 51%). However, PBMT appears to have potential to prevent RD grade 2 (RR 0.33, 95% CI 0.09–1.23, I^2 = 85%) and RD grade 3 (RR 0.21, 95% CI 0.05-0.94, I^2 = 0%). **Conclusions:** The PBMT showed positive results for the prevention of RD, especially for grade 3. However, there were no sufficient evidence to support the indication of PBMT for the prevention or treatment of RD, due to the methodological weaknesses of the evaluated studies and the poor quality of evidence.

Keywords: Radiotherapy. Radiodermatitis. Laser therapy. Low-level light therapy. Photobiomodulation.

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No entanto, para facilitar a leitura do manuscrito, figuras e tabelas foram inseridas ao longo do texto.

Introduction

Radiation dermatitis (RD) is one of the main reactions resulting from exposure to ionizing radiation, affecting about 90 to 95% of patients undergoing radiotherapy (RT) [1-4]. The skin is a highly proliferating tissue and has the ability to balance cell death and renewal [4]. Continuous and subsequent exposure to the ionizing radiation beam favors the development of an inflammatory reaction by damage to the epidermal basal cells, endothelial cells and vascular components that together cause the loss of skin self-renewal property [2, 4-6].

Acute RD manifests as erythema, hyperpigmentation, dry or moist desquamation [4, 7]. These manifestations may cause discomfort and pain influencing the patient's quality of life and, depending on the severity of the injury, the therapeutic protocol may be interrupted [2, 4, 8].

The *Multinational Association of Supportive Care in Cancer* (MASCC) [9] has developed guidelines for the skin care of patients undergoing RT, but there is still no consensus in the literature on the most effective approach to the prevention and treatment of RD [4-6, 8]. There is also no significant evidence that topical pharmacological or non-pharmacological therapies are effective in preventing acute RD [10].

Low-Level Light Therapy (LLLT), also known as Photobiomodulation Therapy (PBMT) is the application of low-power light sources in the visible and infrared spectrum that is capable of stimulating healing and decreasing the intensity of inflammation and pain [3, 5, 6]. Recent studies have evaluated the use of PBMT as a tool to prevent and/or treat of RD [4-6].

Several systematic reviews have been published to evaluate the use of PBMT in the management of oral mucositis (OM) [11, 12] and lymphedema induced by RT [13]. However, there is no systematic review evaluating the effects of this therapy on acute RD specifically.

Thus, this study aims to present the scientific evidence available in the literature on the use of PBMT to prevent and/or treat RD in cancer patients undergoing RT.

Methods

We perform and report this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) [14]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO).

Study design and eligibility criteria

We considered eligible for this systematic review randomized or non-randomized clinical trials, and comparative studies that performed to evaluate the effect of PBMT in the prevention and/or treatment of acute RD in cancer patients undergoing RT. The research question and inclusion criteria were performed according to the acronym PICOS (Population, Intervention, Control, Outcome and Study Design). There was no restriction on year of publication.

Studies were excluded if the following conditions occurred: (1) Studies with patients who do not have cancer; (2) Studies evaluating the use of ultraviolet light therapy; (3) Studies in which there is no correlation between PBMT and acute RD; (4) Chronic RD; (5) Other non-radiotherapy-induced skin lesions; (6) Studies with non-individualized data for RD; (7) *In vitro* or *in vivo* animal studies; (8) Non-comparative studies, reviews, letters, chapters, personal opinions, and conference summaries; (9) Studies that did not report sufficient information; (10) Language restrictions (studies not using alpha-roman alphabet).

Search strategy

Search strategy was conducted in seven electronic databases: CINAHL, Cochrane CENTRAL, LILACS, LIVIVO, PubMed, Scopus, and Web of Science. The search in the gray literature was performed using Google Scholar, OpenGrey, and Proquest. The search strategy can be accessed in Appendix 1.

The search was performed on June 4th in all databases. EndNoteBasic® software, Thomson Reuters, USA, was used to collect references and remove duplicates. A manual search was performed on the reference list of the selected studies to check if any article was missed in the electronic search.

Study selection

Two reviewers (B.R.L.A. and E.B.F.) independently screened the titles and abstracts of studies using Rayyan software [15]. Those studies that met the inclusion criteria were selected. The same reviewers independently read all the full studies selected initially and defined the studies included in this revision according to the inclusion and exclusion criteria. All conflicts were discussed between the two reviewers (B.R.L.A. and E.B.F.), and when necessary a third reviewer (P.E.D.R.) was consulted and had the final decision.

Data collection process and items

Two reviewers (B.R.L.A. and E.B.F.) independently performed the extraction of the following data from the selected studies: authors, year of publication, country, type of cancer, dose of RT, scale evaluating the degree of RD, sample size – intervention and control group, type of intervention (prophylactic or therapeutic), detailed PBMT protocol for each study, institutional skin care and study considerations (main results, secondary outcomes).

Risk of bias in individual studies

The methodologic quality of included studies was individually assessed by two investigators (B.R.L.A. and E.B.F.) independently using the Cochrane risk of bias tool [16]. The risk of bias tool considered the following aspects of studies in its assessment: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting, other bias. These aspects were evaluated for the risk of bias as low risk, high risk or unclear (no information, or uncertainty about potential bias). Disagreements were resolved by consensus or discussion with a third author (P.E.D.R.).

Summary measures

The primary outcome was PBMT capability to prevent or to treat the severity of acute RD. The secondary outcome was the reduction of pain.

Synthesis of results

Meta-analysis was performed with the Cochrane review manager software (RevMan 5.3; The Nordic Cochrane Centre). Between-study heterogeneity was assessed by I^2 value.

Risk of bias across studies

We performed the evaluation of the studies regarding clinical heterogeneity (cancer type), methodological heterogeneity (type of study, scale used to evaluate RD, protocol of PBMT), and statistical heterogeneity (regarding the results obtained).

Confidence in cumulative evidence

Two authors (B.R.L.A. and E.B.F.) independently evaluated the quality of evidence of studies contributing data to each outcome according to the five GRADE categories (study limitations/risk of bias, consistency of effect, imprecision, indirectness, and publication bias). Disagreements were resolved by consensus or discussion with a third author (P.E.D.R.) [17, 18].

Results

Study selection

A total of 793 references were identified for review, of which 252 were excluded due to duplication and 541 citations was analyzed. After triage of the titles and abstracts, 29 full text articles were chosen for evaluation. Following the review of the full papers, an additional 22 papers were excluded, as they did not meet the eligibility criteria. Therefore, seven articles were included [19-25], being that two articles [23, 24] correspond to complementary data analysis of the same study, totaling 7 articles included in this systematic review, corresponding to 6 studies. The study selection process can be seen in Figure 1.

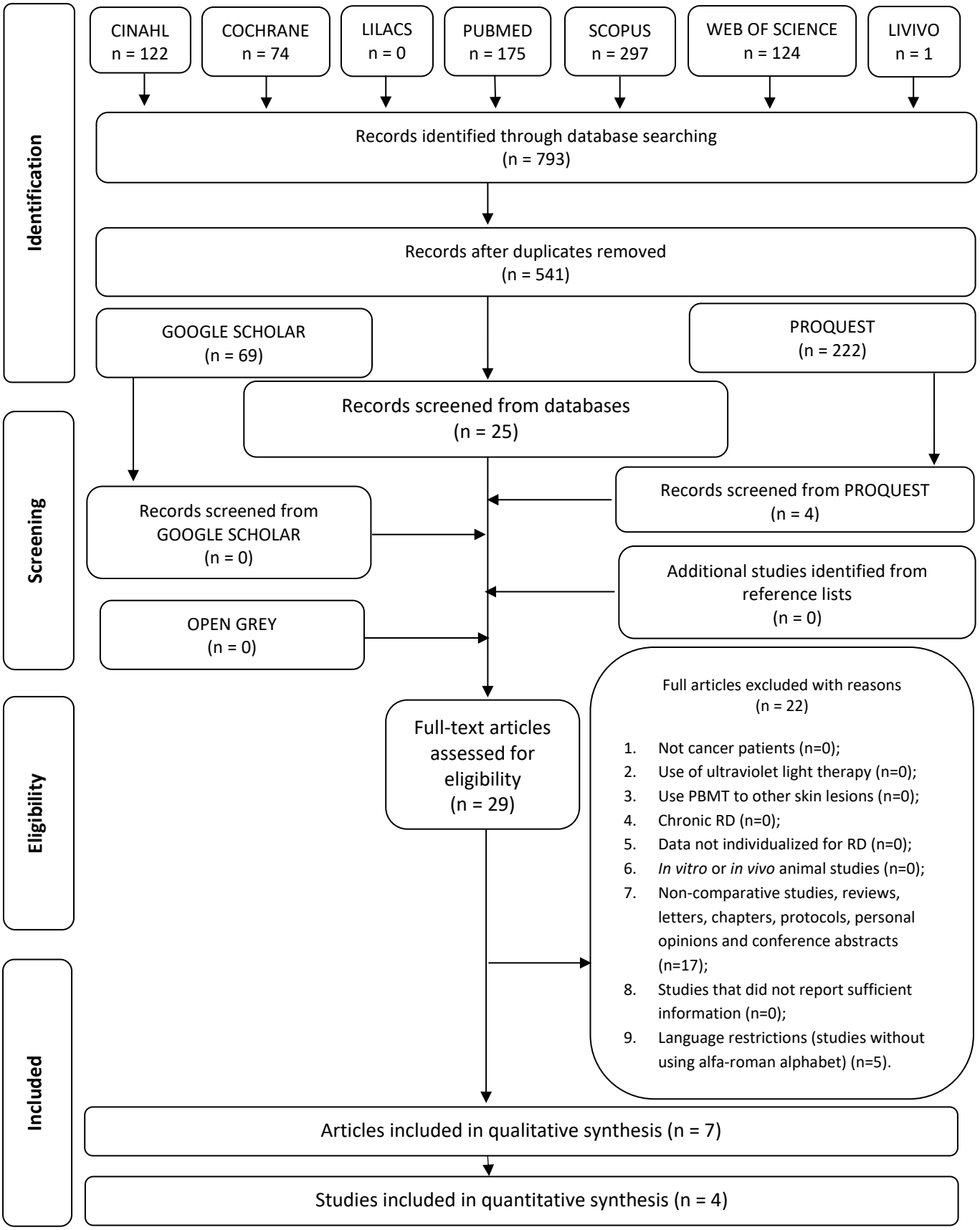

Fig. 1 Flow diagram of literature search and selection process. Adapted from PRISMA [14]

All analyzes of the articles included in this systematic review were performed considering that Robijns et al. [23] and Robijns et al. [24] are two articles that present complementary information from the same study. Robijns et al. [24] developed a secondary analysis of the Robijns et al. [23] but the primary outcome we are evaluating in this systematic review is the same among them.

Study characteristics

The studies that met the eligibility criteria were published between 2007 and 2017 in the English language. Five studies evaluate PBMT in breast cancer patients undergoing external boost RT [19-24] and only one study evaluates PBMT in head and neck cancer patients undergoing RT [25]. The treatment was performed using three-dimensional intensity-modulated radiation therapy (IMRT) in two studies [19, 25], the other four studies used three-dimensional conformal radiation therapy [20-24]. The synthesis of articles included are listed in Table 1. Control groups in all articles received institutional skin care and the experimental group received PBMT associated with the institutional skin care. The protocols of the PBMT of the studies included are described in Table 2. Between the studies in breast cancer patients, 4 aimed to compare the effectiveness of PBMT to prevent RD [19, 20, 22-24], whereas Robijns [23] and Robijns [24] are 2 articles that correspond of the same study, and one study evaluated the effectiveness of this therapy to treat RD [21]. The study in head and neck cancer patients evaluated the potential of PBMT to treat RD [25].

Table 1 Summary of descriptive characteristics of included studies (n=6)

Author, Year, Country	Cancer type	RT Total Dose	Scale of RD	Experimental Group (n)	Control Group (n)	Type of intervention	Main results
DeLand et al., 2007 [19] EUA	Breast	50.4 Gy + 12.6–18 Gy ("boost")	NCI	ISC + #1 protocol (19)	ISC (28)	P	RD grade / EG n (%) / CG n (%): 0: 7 (36.8) / - ; 1: 11 (57.9) / 4 (14.3) ; 2: 1 (5.3) / 18 (64.3) ; 3: - / 6 (21.4) ; IT: 1 (5.3) / 19 (67.9). Grades were significantly lower (p<0.0001) in the EG
Fife et al., 2010 [20] EUA	Breast	45- 50.4 Gy + 10.8-15.4 Gy ("boost")	NCI	ISC + #2 protocol (18)	ISC (15)	P	RD grade / EG n (%) / CG n (%): 0: - / 1 (6.6) ; 1: 6 (33.3) / 4 (26.7) ; 2: 12 (66.6) / 9 (60.0) ; 3: - / 1 (6.6) ; IT: 2 (11.1) / 1 (6.6). RD grades were not significantly lower (p>0.05) in the EG
Censabella et al, 2016 [21] Belgium	Breast	50 Gy + 16 Gy ("boost")	RTOG	ISC + #3 protocol (38)	ISC (41)	T	RD grade / EG n (%) / CG n(%): 0: - / - ; 1: 37 (97.4) / 29 (70.7) ; 2: 1 (2.6) / 12 (29.3) ; 3: - / - ; IT: - / - . EG: RD remained stable (p= 0.22); 1 patient had grade 2 RD (p<0.005). CG: RD severity progressed with significant increase to grade 2 (p= 0.01)

Table 1 (continuation)

Strouthos et al, 2017 [22] Belgium	Breast	50.4 Gy + 10.8- 16.2 Gy ("boost")	CTCAE 4.0	ISC + #4 protocol (25)	ISC (45)	P	RD grade 0 1 2 3 IT	EG n (%) - 22 (88) 3 (12) - -	CG n (%) - 25 (55.6) 18 (40) 2 (4.4) 2 (4.4)
							RD grade was significantly lower in the EG compared to the CG (p= 0.0211)		
Robijns et al, 2018 [23, 24] Belgium	Breast	50 Gy + 16Gy ("boost")	RTOG	ISC + #5 protocol (60)	ISC (60)	P	RD grade 0 1 2 3 IT	EG n (%) - 56 (93.3) 4 (6.7) - -	CG n (%) - 42 (70) 16 (26.7) 2 (3.3) -
							RD grade was significantly lower in the EG compared to the CG (p= 0.004)		
Zhang et al., 2018 [25] China	H&N	30-32 Gy	RTOG	ISC + #6 protocol (30)	ISC (30)	T	RD grade 0 1 2 3 IT	EG n (%) 18 (60) 12 (40) - -	CG n (%) 2 (6.7) 19 (63.3) 9 (30) -
							RD grade was significantly lower in the EG compared to the CG (p= 0.000)		

Cancer type: H&N= Head and Neck; RT Total Dose: RT= Radiotherapy; Gy= Gray; Scale of RD: RD= Radiation Dermatitis; NCI= Terminology Criteria for Adverse Events on Skin; RTOG= Radiotherapy Oncology Group; CTCAE=Common Terminology Criteria for Adverse Events; Experimental/Control Group: ISC= Institutional Skin Care; Type of Intervention: P= Prevention; T= Treatment; Main Results: RD= Radiation Dermatitis; EG= Experimental Group; CG= Control Group; IT= Interruption Treatment.

Table 2 Photobiomodulation therapy protocols for radiation dermatitis in the included studies (n=6)

Author, Year, Country		Protocol											
		PBMT source	**Wavelength (nm)**	**Peak radiant power (W)**	**Energy density (J/cm^2)**	**Spot size (cm^2)**	**Exposure duration (seconds)**	**Pulse (n)/ duration on and/or off**	**Power density (irradiance; mW/cm^2)**	**Points irradiated**	**Distance from the tissue (cm)**	**Frequency**	**Duration**
DeLand et al., 2007 [19] EUA	#1	LED Gentle Waves	590	-	0.15	-	<60	100 / 250 ms	-	whole breast and scar	in contact with the breast tissue	1 time/day (1 hour after RT)	Beginning with the onset of RT, 33–38 PBMT treatments approximately 7-week.
Fife et al., 2010 [20] EUA	#2	LED Gentle Waves	590	-	0.15	-	35	100 / 250 ms on and 100 ms off	-	whole breast and scar	2.0	2 times/day (before and after each RT session)	Beginning with the onset of RT + seven daily treatments were given over the next 2 weeks
Censabella et al, 2016 [21] Belgium	#3	Laser diode (MLS ® IV laser M6)	905 808	25 1.1	4.0	19.635	Whole breast: 384 ± 93 Axilla: 153 ± 41 Inframammary fold: 120 ± 39	100-ns single pulse Continuous pulse	168	whole breast, axilla, and/or inframammary fold	5.0	2 times/ week	Beginning from fraction 20 (40 Gy) of RT, with a total 6 sessions
Strouthos et al, 2017 [22] Belgium	#4	69 diode Laser	660 850	1,39	0.15	-	240-300	100 / 250 ms	44.6	breast fold and axilla	-	2 times/ week (20–30 min prior to RT)	beginning simultaneous with RT

Table 2 (continuation)

Robijns et al, 2018 [23, 24] Belgium	#5	Laser diode (MLS ® IV laser M6)	905 808	25 1.1	4.0	19.625	Whole breast: ±420-720 Axilla: ±68 Inframammary fold: ±103	100-ns single pulse Continuous pulse	168	whole breast, axilla, and/or inframammary fold	5.0	2 times/ week	Biweekly from the first until the last day of RT over a period of 7 weeks 14 sessions in total
Zhang et al., 2018 [25] China	#6	Red Light Phototherapy	-	-	-	-	600	-	-	-	15-20	2 times/day	-

Protocol: PBMT= Photobiomodulation Therapy; RT= Radiation Therapy; Gy= Gray.

Risk of bias within studies

According to the RoB tool, the majority of the studies were moderate to high for risk of bias. Only 3 [20, 23-25] in 6 studies mentioned random sequence generation, but only one study of them described how it was performed [23, 24]. Three studies not described any blindness so that both performance and detection bias were high [19, 21, 25]. Attrition and reporting bias were low because outcomes in all 6 studies were clear and sufficient. The details can be found in Figure 2.

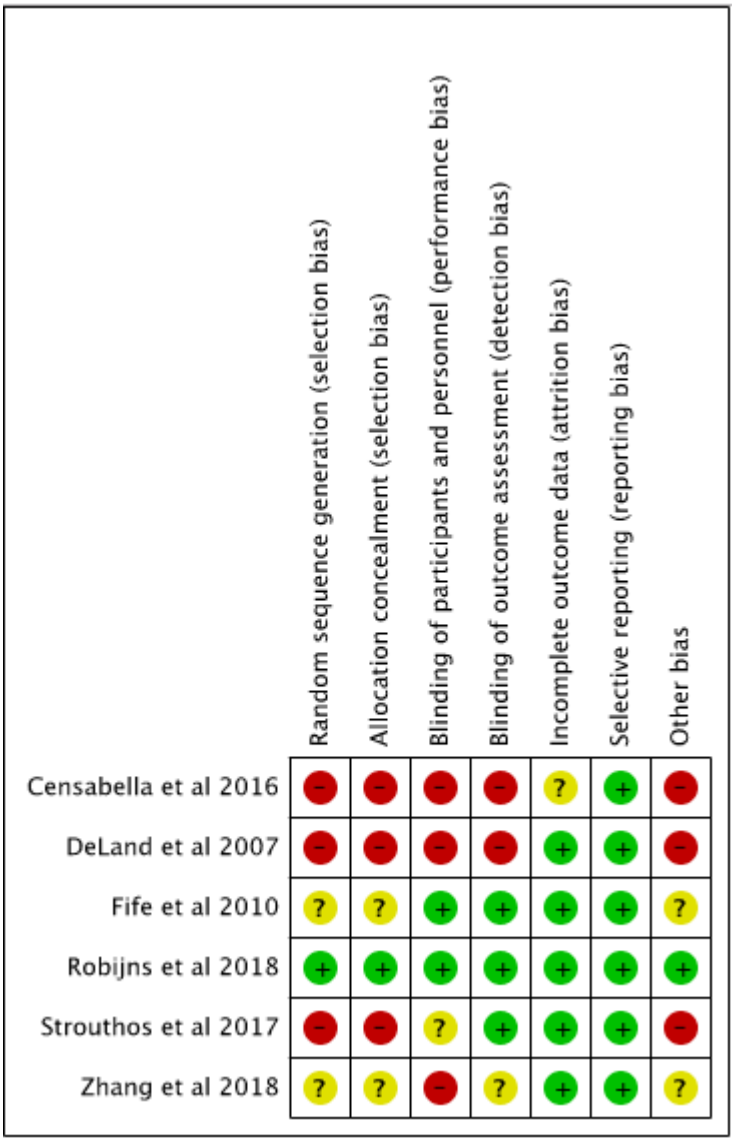

Fig. 2 Risk of bias assessment for individual studies

Results of individual studies

De Land et al. [19] compared the prospective effects of PBMT on RD prevention with the control group composed of retrospective patient data with characteristics similar to the experimental group. All patients underwent mastectomy, and some had received chemotherapy before RT. RT was performed with photons and boost with electrons. All patients in both groups applied Aquaphor® 3-4 times/daily during RT, and the experimental group received PBMT protocol #1 daily, described in Table 2. The degree of RD in the experimental group was evaluated by a nurse through photographs taken weekly, on the last day of RT, 3 months and 6 months after RT following the criteria for adverse skin effects of The National Cancer Institute (NCI). RD data from the control group were obtained from annotations on a weekly evaluation graph. The degrees of RD were significantly lower ($p < 0.0001$) in the experimental group. The only patient in the experimental group who discontinued treatment had long-term erythema and an inframammary skin infection by *C. albicans*.

Fife et al. [20] conducted a study similar to De Land et al. [19], in which both groups used Aquaphor® 3-4 times/day during RT, and the experimental group performed additional protocol #2 PBMT. Protocol #2 resembles protocol #1, as can be seen in Table 2, differing only in the frequency and duration of PBMT. In this study the patients underwent mastectomy or previous lumpectomy and received photon beam RT followed by a boost electron, and in mastectomized patients, they used bolus to treat the chest wall. Patients in both groups used eye protectors to blind them and the control group received a sham treatment in which the PBMT machine was positioned under the patient's skin for the same duration as the experimental group, but the light delivery button was not activated. The degree of RD was monitored weekly until the sixth week after termination of RT, the outcome was assessed by observing photographs at week 5 of RT, and a blinded dermatologist following the National Cancer Institute (NCI) criteria classified RD. One patient in the study received bilateral breast RT with right breast PBMT and simulated treatments for the left breast, but both breasts developed grade 2 skin reactions. There was no statistical significance of lower incidence on RD degree when RT was administered in with PBMT ($p > 0.05$). There was no significant difference in discomfort, pain, convenience, or satisfaction with treatment between the two groups ($p > 0.05$).

In the DERMIS pilot study by Censabella et al. [21], patients received photon or electron boost and patients who used RT bolus or who underwent concomitant chemotherapy were excluded from the study. In contrast, patients who had previously had chemotherapy or who were on hormone therapy or immunotherapy were included. All patients included in the study received the standard institutional skin care protocol (use of Flamigel® from the beginning of RT three times daily and use of Mepilex® or Mepilex Lite® as a secondary dressing in case of painful RD or dry peeling). Patients in the experimental group received standard care associated PBMT protocol #3. The patients and machine operators wore glasses and PBMT application time varied according to the treated area. RD was evaluated by 4 nurses and one LT operator following the RTOG criteria. The findings suggest that PBMT may be used to treat acute RD. In the second analysis, Skindex 16 showed there was no statistical difference in quality of life between patients. The RISRAS's objective score showed a more pronounced increase in RD in the control group than in the experimental group and the RISRAS's subjective score decreased in the experimental group. The classification of the care protocol as pleasant, soothing and overall satisfaction was significantly better in the experimental group ($p = 0.001$). All patients developed RD (93.7%) and skin toxicity was equivalent between the groups before starting PBMT treatment at session 20 ($p= 0.59$).

Strouthos et al. [22] also used RT boost dose electron beam. Included patients were receiving RT after breast conservation surgery and some were on concurrent hormone therapy or immunotherapy. The patients received palmitoylethanolamide cream for dry peeling and phenol-methanal-urea-polycondensate cream in RD grade 2 as institutional skin care. The experimental group received PBMT protocol #4 twice a week at the most sensitive sites of the skin receiving radiation. Weekly photographs were taken of the irradiated area and at the end of the treatment and the degree of RD was evaluated by two radiation blind oncologists. No patient in the experimental group had to discontinue treatment. The pain was evaluated weekly using a scale that subjectively records the patient's pain intensity from 0-10, and in the PBMT group, the pain score was significantly lower compared to the control group ($p = 0.003$).

Two publications [23, 24] have complementary analyzes of the TRANSDERMIS study. The patients underwent RT plus boost with photon or electron beam and all had undergone lumpectomy. Mastectomized patients or those receiving concomitant chemotherapy were excluded from the study. Institutional skin care standards were the

same as in the DERMIS pilot study conducted in Censabella et al. [21], and in these study patients in the experimental group received PBMT protocol # 5 and treatment time varied according to sensitivity area that was receiving RT. The study was blinded and only the laser operator knew the patients' allocation. Patients in the experimental and control group wore goggles during PBMT. Two nurses assessed RD degree According to RTOG on the first day of RT, at 40 Gy and the end of RT. The subjective RISRAS score decreased in the experimental group, while it remained constant in the control group during RT and the objective score had a more pronounced increase in the control group. Overall, there was a decrease in the total Skindex-16 score in the experimental group compared to the control group [23]. The efficacy evaluation of wet peeling prevention was based on erythema, hydration level, and transepidermal water loss tests. Baseline erythema and melanin index were significantly higher in the control group ($p = 0.016$; $p = 0.019$). Skin hydration level was significantly lower at the 40 Gy RT dose in the PBMT group ($p = 0.036$) but both groups had similar skin moisture index at the end of RT and the final TEWL index, which evaluates the transepidermal loss. TEWL index was significantly lower in the PBMT group compared with the control group ($p = 0.05$) [24].

Zhang et al. [25] is the only study that evaluates the use of PBMT in patients with head and neck cancer undergoing RT. The study does not describe who analyzed the degree of RD in the patients but mentions that the RTOG scale was used for this purpose and the 0-10 skin pain rating scale. All patients received institutional skin care, including gentle wound cleaning with 0.9% saline-soaked cotton and sterile gauze to dry the area. Patients in the experimental group received PBMT protocol #6 associated with the institution's usual care. The degree of RD in the experimental group was lower than in the control group ($p <0.05$). The experimental group was mainly composed of grade 0–2 RD, including 18 cases (60.00%) of grade 0–1 and 12 cases (40.00%) of grade 2. The control group was mainly composed of grade 2–3 RD, including 19 cases of grade 2 (63.33%), 9 cases of grade 3 (30.00%) and only 2 cases of grade 0–1 (6.67%). The pain score of the experimental group was significantly lower than the control group ($p <0.05$).

Synthesis of results

One random effect meta-analysis including 270 participants from four comparative studies [19, 20, 22-24] suggested that the risk of developing grade 1 RD was 1.55 higher for people receiving PBMT in comparison of control group. There was

significant statistical difference between them (RR 1.55, 95 % CI 1.14 to 2.10) (Figure 3).

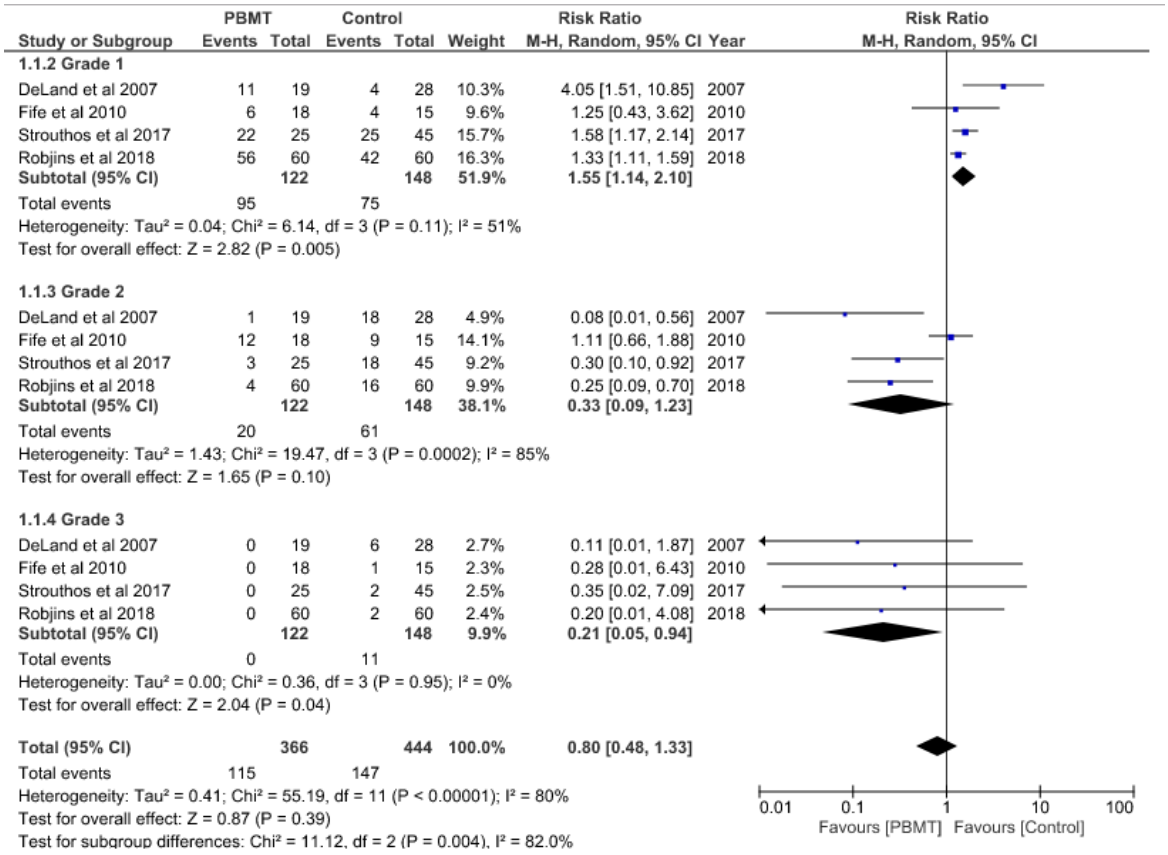

Fig. 3 Forest plot of photobiomodulation therapy vs. controls according to the degree of radiation dermatitis

Regarding the analysis for grade 2 and 3, the risk for developing RD was higher in the control group. In the analysis of RD grade 2 development the results were not statistically significant (RR 0.33, 95% CI 0.09 to 1.23) and for RD grade 3 the data were statistically significant (RR 0.21, 95% CI 0.05 to 0.94) (Figure 3).

The pain was evaluated in 3 studies [20, 22, 25]. Two studies was performed in breast cancer patients [20, 22] and only one study was performed in head and neck cancer patients [25]. Only Fife et al. [20] no demonstrated statistically significant result for pain

reduction. However no it is possible realized correlation between the studies that presenting positive results because they are different populations.

Risk of bias across studies

The selected studies were considered relatively homogeneous because they were all comparative studies. Most studies included breast cancer patients and the RT dose between studies was similar. The type of laser used varied among studies, as well as the scales used to evaluate RD. Among the studies using the same type of laser, the application protocol differed among them, which may lead to greater methodological heterogeneity between the studies. Additionally, the institutional skin care used in the control groups varied between studies.

Quality of evidence

According to the GRADE, the quality of evidence of the primary outcomes was low to prevent RD grades 1 and 3, and very low to prevent RD grade 2 (Table 3).

Table 3. Quality of evidence of primary outcomes according to GRADE approach

Certainty assessment							Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
To prevent RD grade 1							
4	RCT	very serious [a]	serious [b]	not serious	not serious	none	⊕⊕◯◯ LOW
To prevent RD grade 2							
4	RCT	very serious [a]	very serious [c]	not serious	not serious	none	⊕◯◯◯ VERY LOW
To prevent RD grade 3							
4	RCT	very serious [a]	not serious	not serious	not serious	none	⊕⊕◯◯ LOW

CI: Confidence interval, **RCT:** randomized clinical trials

Explanations

a. Two studies presented a high risk of bias in the random sequence generation and in allocation concealment. One study had a high risk of bias in domain blinding of participants and personnel and blinding of outcome assessment.

b. Presence of statistical heterogeneity ($I^2 = 51\%$).

c. Presence of statistical heterogeneity ($I^2 = 85\%$).

Discussion

To the best of our knowledge, this is the first systematic review that evaluates the use of PBMT to prevent or to treat RD in cancer patients undergoing RT.

PBMT uses non-ionizing light sources near the visible or infrared spectrum (600-1000 nm), which by means of the stimulated emission physical phenomenon creates a beam capable of penetrating tissues and activating cellular processes for injury prevention or treatment through modulation of inflammatory mechanisms and healing promotion [3, 26, 27]. The mechanism by which PBMT is capable of promoting therapeutic effects is not yet fully understood as well as the appropriate dose to stimulate the healing process [3, 28].

The pathophysiology of acute RD demonstrates that RT doses produce oxidative stress (OS) that compromise epidermal and dermal cell structure and DNA leading to immediate tissue damage and the recruitment of inflammatory cytokines that increase its production with each RT session [2, 7, 8]. Today, it is known that PBMT is based on photochemical absorption reactions that alter the mitochondrial pathway to produce more ATP, that will serve as an energy source to stimulate repair [3, 29]. PBMT is also capable of regulating the production of reactive oxygen species that will result in the production of various proteins that modulate cytokine levels and inflammatory mediators and assist in cell migration and proliferation [3, 28, 29]. PBMT may modulate the production of cytokines involved in RD and produce growth factors that more quickly indicate wound bed epithelialization [30]. In addition, PBMT stimulates the release of nitric oxide which consequently causes vasodilation to increase immune cell recruitment and oxygen availability at the irradiated site [30].

The studies included in this review suggest that PBMT was statistically significant in the prevention of grade 3 RD [19, 20, 22-24]. Patients that develop this grade or upper usually need to interrupt the RT for at least a week, which impact negatively the therapeutic plan. In the metanalysis, we observed that the result was favorable to control in the Grade 1 subgroup. However, this result maybe be masking by the effect of PBMT that causes redness in the skin, which is one of the signs of RD Grade 1.

The protocols of the PBMT in the included studies of this systematic review varied regarding the PBMT source, energy density, exposure duration, distance from the tissue,

frequency and duration of the application. In general, the studies included in this systematic review that presented data regarding the PBMT protocol for RD prevention used a energy density of 0.15 or 4 J/cm^2, with the exposure time ranged from 35 to 720 seconds according to the PBMT source and the irradiated points, in contact of the tissue or the 2 or 5 cm of distance, and was most often used twice a week. The power density variated of 44.6 or 168 mW/cm^2 and a wave-length of 590 to 905 depending on laser type.

Bensadoun and Nair [6] describe that there are an optimal dose and parameters for the use of PBMT with therapeutic effect, considering that doses higher than the ideal value may result in negative effects and lower doses may not promote therapeutic effect. Thus, it is believed that there is a bio stimulatory dose window that makes the PBMT parameters effective for the therapeutic use [5, 27]. Ideally, use the lowest dose rate that can offer therapeutic benefits.

Standardization of protocols should be performed for results to be consistent and reliable. Bensadoun et al. [5] provides a list of verification parameters that must be presented in studies for the study to be reproducible. Without standardization of beam parameters that go far beyond dose, the results cannot be replicated.

Concerning about frequency, DeLand et al. [19] and Fife et al. [20] used the GentleWaves LED PBMT and all similar application protocol parameters to prevent RD in breast cancer patients, however, the frequency of application, the distance from the tissue and the exposure duration was different. Fife et al. [20] assumed that increasing the frequency of application of PBMT, using the same light regulation parameters, could intensify the preventive effect of RD. However, their results were not statistically significant, which leads us to think that increasing the frequency of application of this type of PBMT does not produce positive results. In a review performed by Bensadoun et al. [5] the authors suggested lower doses are better than high doses of PBMT because the treatment becomes better tolerated.

Censabella et al. [21], Robjins et al. [23] and Robjins et al. [24] used the MLS® IV Laser M6 diode to manage RD in breast cancer patients. Both studies used the same PBMT protocol, differing only by the time of application, one of the studies had the start at the 20 RT session (40Gy) [21] whether the other one had the protocol initiating in the first session of RT [23, 24]. Results were statistically significant in both studies to delay

the development of degrees ≥2 of RD. The researchers recommends this type of laser may be a tool used to prevent or to treat RD in breast cancer patients.

Zhang et al. [25] was the only study that evaluated the use of PBMT to treat RD in patients with head and neck cancer and found a statistically positive result. They used red light phototherapy twice a day, but the parameters of the PBMT protocol were not described in the study, which makes it difficult to replicate the study to confirm results in other populations. Park et al. [31] performed a pilot study in patients with head and neck cancer and lymph node supraclavicular who received 60 Gy or more RT in the neck to assess the using PBMT with 60 J/cm^2 of the HEALITE II® laser in reducing the severity of RD. Their results showed that PBMT is clinically viable to be used and able to reduce the degree of RD [31]. We know that about 80-90% of head and neck cancer patients undergoing RT develop RD and approximately 25% of these patients develop severe RD [10]. Therefore, studies evaluating the potential of PBMT to prevent or treat RD in this population should also be performed.

Bensadoun et al. [6] and Zecha et al. [32] proposes PBMT protocols for the prevention and treatment of various treatment-induced toxicities speciffically for patients with head and neck cancer, including RD. The protocol suggests that for RD prophylaxis the PBMT should be daily and start with RT or when the patient has grade 1 RD. The energy density suggested for prevention is 2-3 J/cm^2. For treatment, PBMT should be applied at least 3 times a week until RD signs improve. The energy density suggested for treatment is at least 4 J / cm^2. In both cases, PBMT should be applied under the skin surface submitted of ionizing radiation at 630-680 nm wavelength and 20-150 mW / cm^2 when using red laser diodes or 20-80 mW / cm^2 when using mixed red and infrared LED.

The use of PBMT was also related to pain control [27, 28]. The analgesic effects of PBMT are associated with light absorption by nociceptors that inhibit neural fibers and slow down the transmission of pain information by blocking axonal flow by suppressing neurogenic information [6, 33]. Among the studies included in this systematic review, Fife et al. [20], Strouthos et al. [22] and Zhang et al. [25] assessed pain in the sample evaluated. Only Fife et al. [20] found no statistically significant result for pain reduction.

This systematic review showed that the quality of evidence was poor across studies, and there was a high or medium risk of bias for most individual studies. In

addition, only two studies [21, 25] investigated the ability of PBMT to treat RD in different types of cancer, which made it difficult to correlate PBMT effectiveness for this purpose. Another limitation of this systematic review is the heterogeneity of the types of PBMT and the protocols used in studies that do not allow us to draw a recommendation on the pattern of use for PBMT. The safety assessment of PBMT in studies seeking the management of RD is still scarce. However, just as there is a need for PBMT standardization, it is also necessary that safety data be searched.

Conclusion

The PBMT showed positive results for the prevention of RD, especially for grade 3. However, there were no sufficient evidence to support the indication of PBMT for the prevention or treatment of RD, due to the methodological weaknesses of the evaluated studies and the poor quality of evidence. Thus, it is necessary that more studies be performed using laser parameters that already have a positive result in order to generate recommendations of the type of PBMT to be used.

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Appendix 1 Search strategy performed in databases CINAHL, COCHRANE CENTRAL, LILACS, LIVIVO, PUBMED, SCOPUS, WEB OF SCIENCE, GOOGLE SCHOLAR, OPEN GREY and PROQUEST on June 04th, 2019

Electronic database	Strategy	Result
CINAHL	("radiodermatitis" OR “radiation dermatitis” OR "radiation reaction" OR "acute radiation reactions" OR “radiation-induced dermatitis” OR “skin reaction” OR “skin reactions” OR “skin toxicity” OR “skin toxicities” OR “radiation toxicity” OR “tissue complications”) AND ("low-level light therapy" OR "phototherapy" OR “low-level laser therapies” OR “low intensity laser” OR “low-intensity light” OR “low-power laser” OR “photomodulation” OR “photobiomodulation” OR “light emitting diode” OR “laser biostimulation” OR “laser therapy” OR “lasertherapy” OR “photodynamic therapy”)	122
COCHRANE CENTRAL	("radiodermatitis" OR “radiation dermatitis” OR "radiation reaction" OR "acute radiation reactions" OR “radiation-induced dermatitis” OR “skin reaction” OR “skin reactions” OR “skin toxicity” OR “skin toxicities” OR “radiation toxicity” OR “tissue complications”) AND ("low-level light therapy" OR "phototherapy" OR “low-level laser therapies” OR “low intensity laser” OR “low-intensity light” OR “low-power laser” OR “photomodulation” OR “photobiomodulation” OR “light emitting diode” OR “laser biostimulation” OR “laser therapy” OR “lasertherapy” OR “photodynamic therapy”) in Trials	74
LILACS	(tw:("radiodermatitis" or "radiodermatite")) AND (tw:("phototherapy" or "Fototerapia")) AND (tw:("Low-Level Light Therapy" or "Terapia por Luz de Baja Intensidad" or "Terapia com Luz de Baixa Intensidade"))	0
LIVIVO	(“radiodermatitis”) AND ("phototherapy" OR "low-Level light therapy")	1
PUBMED	("radiodermatitis"[MeSH Terms] OR "radiodermatitis"[All Fields] OR “radiation dermatitis”[All Fields] OR "radiation reaction"[All Fields] OR "acute radiation reactions"[All Fields] OR “radiation-induced dermatitis”[All Fields] OR “skin	175

	reaction”[All Fields] OR “skin reactions”[All Fields] OR “skin toxicity”[All Fields] OR “skin toxicities”[All Fields] OR “radiation toxicity”[All Fields] OR “tissue complications”[All Fields]) AND (“low-level light therapy"[MeSH Terms] OR "low-level light therapy"[All Fields] OR "phototherapy"[MeSH Terms] OR "phototherapy"[All Fields] OR “low-level laser therapies”[All Fields] OR “low intensity laser”[All Fields] OR “low-intensity light”[All Fields] OR “low-power laser”[All Fields] OR “photomodulation”[All Fields] OR “photobiomodulation”[All Fields] OR “light emitting diode”[All Fields] OR “laser biostimulation”[All Fields] OR “laser therapy”[All Fields] OR “lasertherapy”[All Fields] OR “photodynamic therapy”[All fields])	
SCOPUS	TITLE-ABS-KEY ("radiodermatitis" OR "radiation dermatitis" OR "radiation reaction" OR "acute radiation reactions" OR "radiation-induced dermatitis" OR "skin reaction" OR "skin reactions" OR "skin toxicity" OR "skin toxicities" OR "radiation toxicity" OR "tissue complications") AND TITLE-ABS-KEY ("low-level light therapy" OR "phototherapy" OR "low-level laser therapies" OR "low intensity laser" OR "low-intensity light" OR "low-power laser" OR "photomodulation" OR "photobiomodulation" OR "light emitting diode" OR "laser biostimulation" OR "laser therapy" OR "lasertherapy" OR "photodynamic therapy") AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "ip"))	297
WEB OF SCIENCE	("radiodermatitis" OR “radiation dermatitis” OR "radiation reaction" OR "acute radiation reactions" OR “radiation-induced dermatitis” OR “skin reaction” OR “skin reactions” OR “skin toxicity” OR “skin toxicities” OR “radiation toxicity” OR “tissue complications”) AND ("low-level light therapy" OR "phototherapy" OR “low-level laser therapies” OR “low intensity laser” OR “low-intensity light” OR “low-power laser” OR “photomodulation” OR “photobiomodulation” OR “light emitting diode” OR “laser biostimulation” OR “laser therapy” OR “lasertherapy” OR “photodynamic therapy”)	124

GOOGLE SCHOLAR	radiodermatitis "low-Level light therapy" OR “photobiomodulation”	69
OPEN GREY	“radiodermatitis” AND ("low-Level light therapy" OR “photobiomodulation”)	0
PROQUEST	("radiodermatitis" OR “radiation dermatitis” OR "radiation reaction" OR "acute radiation reactions" OR “radiation-induced dermatitis” OR “skin reaction” OR “skin reactions” OR “skin toxicity” OR “skin toxicities” OR “radiation toxicity” OR “tissue complications”) AND ("low-level light therapy" OR "phototherapy" OR “low-level laser therapies” OR “low intensity laser” OR “low-intensity light” OR “low-power laser” OR “photomodulation” OR “photobiomodulation” OR “light emitting diode” OR “laser biostimulation” OR “laser therapy” OR “lasertherapy” OR “photodynamic therapy”)	222

Appendix 2 Excluded articles and reasons for exclusion (n=22)

Author, year	Full articles excluded with reasons
Cheng et al, 2008 [1]	7
Chi, 2017 [2]	7
ClinicalTrials.gov identifier (NCT number): NCT00573365; 2007 [3]	7
Costa et al, 2014 [4]	7
Fife et al, 2008 [5]	7
Gobbo et al, 2016 [6]	7
Gobbo et al, 2016 [7]	7
Hjmn, 2016 [8]	7
Laubach and Robijns, 2018 [9]	7
Metelitsa and Dover, 2010 [10]	7
Musabaeva, Lisin and Velikaia, 2014 [11]	9
Partl, Ottl and Kapp, 2011 [12]	7
Pletnev and Karpenko, 1985 [13]	9
Popovich, 1992 [14]	9
Popovich et al, 1991 [15]	9
Robijns et al, 2016 [16]	7
Robjins et al, 2017 [17]	7
Robjins et al, 2018 [18]	7
Robjins et al, 2019 [19]	7
Roma et al, 2013 [20]	7
Schindl, Schindl and Schindl, 1997 [21]	7
Xu, 1983 [22]	9

Reasons:

(1) Not cancer patients (n = 0);

(2) Use of ultraviolet light therapy (n = 0);

(3) Use PBMT to other skin lesions (n = 0);

(4) Chronic RD (n = 0);

(5) Data not individualized for RD (n = 0);

(6) *In vitro* or *in vivo* animal studies (n = 0);

(7) Non-comparative studies, reviews, letters, chapters, protocols, personal opinions and conference abstracts (n = 17);

(8) Studies that did not report sufficient information (n = 0);

(9) Language restrictions (studies without using alfa-roman alphabet) (n = 5).

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