Prevention of Acute Radiodermatitis by Photobiomodulation: A Randomized, Placebo-Controlled Trial in Breast Cancer Patients (TRANSDERMIS Trial)

Jolien Robijns, MSc,[1*] Sandrine Censabella, PhD,[2] Stefan Claes, BSc,[3] Luc Pannekoeke, BSc,[3] Lore Bussé, MSc,[1] Dora Colson, BSc,[1] Iris Kaminski, BSc,[1] Paul Bulens, MD,[2,3] Annelies Maes, MD,[2,3] Leen Noé, MD,[2,3] Marc Brosens, MD,[2,3] An Timmermans, MD,[4] Ivo Lambrichts, MD, PhD,[1] Veerle Somers, PhD,[1] and Jeroen Mebis, MD, PhD[1,2,3]

[1]*Faculty of Medicine and Life Sciences, Hasselt University, Martelarenlaan 42, 3500 Hasselt, Belgium*
[2]*Department of Medical Oncology, Jessa Hospital, Stadsomvaart 11, 3500 Hasselt, Belgium*
[3]*Limburg Oncology Center, Jessa Hospital, Stadsomvaart 11, 3500 Hasselt, Belgium*
[4]*Department of Dermatology, Jessa Hospital, Stadsomvaart 11, 3500 Hasselt, Belgium*

Objective: Acute radiodermatitis (RD) is a distressing and painful skin reaction that occurs in 95% of the patients undergoing radiotherapy (RT). The aim of this study was to evaluate the effectiveness of photobiomodulation therapy (PBMT) in the prevention of acute RD in breast cancer (BC) patients undergoing RT.

Methods: This study was a randomized, placebo-controlled trial including 120 BC patients that underwent an identical RT regimen post-lumpectomy. Patients were randomly assigned to the laser therapy (LT) or placebo group, with 60 patients in each group. Laser or placebo treatments were applied 2 days a week, immediately after the RT session, starting at the first day of RT. PBMT was delivered using a class IV MLS® M6 laser that combines two synchronized laser diodes in the infrared range (808–905 nm) with a fixed energy density (4 J/cm^2). Skin reactions were scored based on the criteria of the Radiation Therapy Oncology Group (RTOG) and the Radiation-Induced Skin Reaction Assessment Scale (RISRAS). The patients completed the Skindex-16 questionnaire to evaluate their quality of life. All the measurements were collected at the first day, at a RT dose of 40 Gray (Gy), and at the end of RT (total dose 66 Gy).

Results: At a RT dose of 40 Gy, there was no significant difference between the groups in the distribution of RTOG grades. However, at the end of RT the severity of the skin reactions significantly differed between the two groups ($P = 0.004$), with a larger percentage of patients experiencing RTOG grade 2 or higher (e.g., moist desquamation) in the placebo group (30% vs. 6.7%, for the placebo and laser group, resp.). The objective RISRAS score confirmed these results. In addition, the Skindex-16 and RISRAS subjective score demonstrated that the patients' quality of life was significantly better in the LT than in the control group.

Conclusions: The results of this trial show that PBMT is an effective tool to prevent the development of grade 2 acute RD or higher in BC patients. In addition, it also reduces the patients' symptoms related to RD. Lasers Surg. Med. 9999:1–9, 2018. © 2018 Wiley Periodicals, Inc.

Key words: breast cancer; low-level laser therapy; photobiomodulation therapy; radiotherapy; radiodermatitis

INTRODUCTION

About 90% of the breast cancer (BC) patients undergo radiotherapy (RT) during their cancer treatment [1]. In approximately 95% of the patients, RT can lead to acute skin reactions, also known as radiodermatitis (RD) [2]. Ionizing radiation induces an inflammatory skin reaction, followed by damage to stem cells within the basal layer of the epidermis, which leads to a disruption in the self-renewing property of the skin [3]. Acute skin reactions start approximately 2 weeks after the first RT session with erythema, which can progress into dry or eventually moist desquamation [3].

The severity of RD depends of various intrinsic (e.g., breast volume, comorbidities, genetic susceptibility) and extrinsic (e.g., RT dose, fractionation regimen, use of radio sensitizers) factors [4].

RD is a distressing and painful side effect. It affects the patients' quality of life, as they have to cope with problems during their daily life (e.g., washing practices, getting

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Authors institutional affiliations: Radiotherapy department of the Limburg Oncology Center—Jessa Hospital, Stadsomvaart 11, 3500 Hasselt, Belgium.

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*Correspondence to: Jolien Robijns, MSc, Faculty of Medicine and Life Sciences, Hasselt University, Martelarenlaan 42, 3500 Hasselt, Belgium. E-mail: jolien.robijns@uhasselt.be

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dressed, household activities, hobbies) [5]. In some rare cases of severe skin reactions, the radiotherapist needs to adjust the fractionation regimen or interrupt RT, which will eventually affect the treatment outcome and patient survival [6].

Concerning the prevention and treatment of RD, the Multinational Association of Supportive Care in Cancer (MASCC) developed skin care guidelines in 2013. However, the evidence supporting the effectiveness of these preventive and/or treatment options is still weak and there is no comprehensive, evidence-based consensus [7,8].

Photobiomodulation therapy (PBMT) uses non-ionizing light sources such as laser diodes and light-emitting diodes (LEDs) in the visible and near-infrared spectrum (600–1,000 nm) [9,10]. The light is absorbed in the cells by endogenous chromophores resulting in non-thermal, photophysical, and photochemical events at various biological scales. Although the underlying mechanism of PBMT is still unclear, several studies suggest that PBMT is able to stimulate wound healing and reduce inflammation, oedema, and pain [11–15].

In the last 20 years, the use of PBMT in the supportive care of cancer patients is increasing for several cancer-therapy related side effects (e.g., oral mucositis, lymphedema, neuropathy, RD) [16]. Concerning safety issues on the use of PBMT in cancer patients, the results of *in vitro* and *in vivo* studies investigating the effect of PBMT on the proliferation rate of cancer cells are reassuring [17–21].

Schindl et al. introduced the use of PBMT for the management of acute RD in the late 1990s. In a case report study, they showed a beneficial effect of PBMT for the treatment of RT-induced skin ulcers in BC patients after a mastectomy [22–24]. Recently, our study group performed a prospective trial with 79 BC patients, in which PBMT was started once the first skin reactions already developed. The results of this study demonstrated a beneficial effect of PBMT for the management of RD [25].

The aim of the current study was to evaluate the efficacy of PBMT for the prevention of RD in BC patients undergoing RT with respect to the severity of RD. Secondly, the effect on the patient's quality of life was assessed.

MATERIALS AND METHODS

Study Design and Setting

This was a prospective, placebo-controlled, randomized controlled trial to evaluate the effectiveness of PBMT in BC patients undergoing RT. Patients were divided into two groups: a control group receiving placebo treatments and a laser therapy (LT) group receiving PBMT. This was a single centre study and all patients were treated at the RT department of the Limburg Oncology Center (Jessa Hospital, Hasselt, Belgium) between April 2015 and June 2017. Both the ethics committees of the Jessa Hospital and the University of Hasselt approved the study (B243201524443). The study was registered at ClinicalTrials.gov (NCT02443493).

Study Population

Patients were eligible for inclusion if they were diagnosed with primary BC, underwent lumpectomy, and were scheduled to undergo a RT regimen consisting of 25 fractions of 2 Gray (Gy) to the whole breast and 8 fractions (2 Gy/fraction) to the tumor region (total RT dose 66 Gy). Exclusion criteria were previous irradiation to the same breast, mastectomy, metastatic disease, concomitant chemotherapy, and infection of the to-be-irradiated zone. Patients were recruited at the RT department of the Jessa Hospital (Hasselt, Belgium) during the CT-simulation session, approximately 2 weeks before start of the RT. All participants gave written informed consent before start of the study.

Randomization

Eligible patients were stratified based on their planning target volume (PTV) into three groups: small ($<$450 cc), medium (450–800 cc), and large breasts ($>$800 cc) [26]. This was followed by a random allocation (1:1) of the patients to the LT or control group. Patients were allocated based on a block randomization process, with a block size of four by using a computer-generated random number list prepared by a researcher who was not clinically involved in this trial. Only the laser operator knew the allocation of the patients in the groups.

Interventions

Radiotherapy. RT was planned using the Eclipse™ treatment planning system (version 11.0, Varian Medical System, Palo Alto, CA). Patients received a standard RT regimen consisting of a dose of 50 Gy of 25 daily fractions (2 Gy/ fraction, 5 fractions/week) to the whole breast followed by an 8-fraction boost of 16 Gy to the tumor bed over a period of 6 to 7 weeks (total dose of 66 Gy). Patients were treated in a supine position with their arms supported above their head. Irradiation to the whole breast was delivered by applying two tangential photon (half) beams set up isocentrically using a 6 MV or a 6 + 15 MV linear accelerator (Clinac® DHX, Varian Medical Systems, Palo Alto, CA). The boost treatment was delivered through a two-field conformal photon (4–15 MV) or a one-field vertical electron (6–15 MeV) beam. Segmented fields were used where required in order to reduce hot spots. Deep Inspiration Breath-Hold (DIBH) was used for a selected group of patients in order to reduce the mean heart dose.

Topical skin care treatment. Each patient received the institutional standard skin care. This included the application of a topical, hydroactive colloid gel (Flamigel®, Flen Pharma, Kontich, Belgium) on the irradiated zone (3×/day), starting at the first day of RT. Patients that developed painful skin reactions and/or moist desquamation, received a foam, absorbent, self-adhesive silicone dressing on the irradiated zone (Mepilex®, Mölnlycke Health Care, Gothenburg, Sweden).

PBMT. Patients in the LT group received 14 sessions of PBMT (2×/week), starting at the first day of RT. PBMT was provided by a trained operator using a class IV MLS®

M6 laser (ASA Srl, Vicenza, Italy). This laser device is commercially available and built in compliance with EC/EU rules, which received FDA approval and is CE certified. The device combines two laser diodes of two different wavelengths, peak power, and emission mode. The first one is a laser diode emitting at 905 (± 5) nm in pulsed mode (peak radiant power 25W, duty cycle of 50 % independently of the repetition rate). The second one emits in continuous mode at 808 (± 5) nm (peak radiant power 1.1 W). The two laser beams work simultaneously and synchronously with coincident propagation axes (average radiant power 3.3 W, aperture diameter 5 cm, beam spot size at target 19.625 cm^2, power density at target 0.168 W/cm^2). The energy density (fluence) was set at 4 J/cm^2 based on earlier recommendations [27]. The treatment time varied according to the to-be-treated surface area in order to keep this fluence constant (for a spot size of 19,625 cm^2 a radiation exposure time of 467,27 seconds was necessary). More specific PBMT parameters can be found in Table 1.

Patients in the control group received sham treatments in which the laser device was switched off, but still made the same sound as an active laser. Patients in both groups wore safety glasses and eye shields to prevent eye damage and to blind them during the laser or sham sessions.

Outcome Measures

Skin reaction evaluation. The primary outcome measure was the degree of RD at the end of RT. The criteria of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC [28]) and the Radiation-Induced Skin Reaction Assessment Scale (RISRAS [29]) were used to

TABLE 1. Photobiomodulation Parameters

PBMT parameters			
Device information	Manufacturer	ASA srl	
	Model identifier	MLS® laser M6	
	Year produced	2012	
	Number of emitters	3	
	Emitter type	IR laser diodes	
	Spatial distribution of emitters	Three emitters spaced 2 cm apart in a triangle pattern	
	Beam delivery system	Scanning head (five pre-settled directions)	
Irradiation parameters		**Laser diode 1**	**Laser diode 2**
	Center wavelength	808 nm	905 nm
	Spectral bandwidth	±5 nm	±5 nm
	Operating mode	Continuous pulsed wave mode	
	Peak radiant power	1.1 W	25 W
	Average radiant power	3.3 W	
	Maximum frequency (frequency range)	90 kHz (1–2,000 Hz)	
	- Pulse on duration	- 100-ns single pulse width	
	- Duty cycle	- 50%	
	Aperture diameter	5 cm	
	Irradiance at aperture	0.168 W/cm^2	
	Beam divergence at 60%	42.8 mrad	59.2 mrad
	Beam profile	Two laser beams work simultaneously and synchronously with coincident propagation axes	
Treatment parameters	Beam spot size at target area	19.625 cm^2	
	Irradiance at target	0.168 W/cm^2	
	Radiant exposure (fluence)	4 J/cm^2	
	Number of points irradiated	-Breast: Whole breast, inframammary fold and/or axilla, depending on the location of radiodermatitis.	
	Exposure duration	- Whole breast: ±420–720 s - Inframammary fold: ±103 s - Axilla: ±68 s	
	Application technique	5 cm above the skin	
	Timing	After the RT session	
	Number and frequency of treatment sessions	14 sessions in total, delivered biweekly from the first until the last day of RT over a period of 7 weeks	

IR, infrared; MLS, Multiwave Locked System; PBMT, photobiomodulation therapy; RD, radiodermatitis; RT, radiotherapy.

evaluate the skin reactions by two experienced RT nurses. The RISRAS consists of a health professional score (0–24) based on the outward signs of the skin reaction and a patient score (0–12) based on the patients' personal experience of the skin reactions (pain, burning sensation, itchiness, and quality of life). Both subscale scores were summed up to become a total score (a higher score indicated a greater skin toxicity).

Quality of life. The quality of life of the patients was assessed by using the Skindex-16 [30]. This is a validated, 16-item self-assessment questionnaire that measures to what extent the patients' life is affected by their skin condition. Each item on the scale is rated from 0 (Never Bothered) to 6 (Always Bothered). The Skindex-16 is divided in three subscales: symptoms, emotions and functioning. The total score is the average of the three subscales scores (range:0–100) and a higher score is correlated with a lower quality of life.

Measurement collection schedule. All the previously described measurements were collected on three time points: at the first day, at a RT dose of 40 Gy, and at the last day of RT (66 Gy).

Sample Size

Based on preliminary data, a decrease of the incidence of moist desquamation (RTOG grade 2 or higher) of 17.5% in the LT group was expected. Therefore, a sample size of 60 patients in each group was needed to detect such a difference with a two-sided t-test with a power of 80% and a significance level of 0.05.

Statistical Analysis

Differences in patient- and therapy-related characteristics between both groups were analysed by means of chi-square tests (χ^2), Fisher's exact tests, Student t-tests, or Mann–Whitney U-tests, as appropriate. Ordinal data (RTOG) were analysed by means of χ^2 or Fisher's exact tests. Continuous data (RISRAS and Skindex-16) were analysed by mixed analyses of variance (ANOVAs) with time (between the RT dose of 40 Gy and 66 Gy) as within-subject factor and groups (control vs. LT group) as between-subject factor. The level of statistical significance for all analyses was set assuming a significance level of 5% ($P < 0.05$, two-tailed). SPSS 24.0 (IBM, Chicago, IL) was used for all analyses.

RESULTS

Patient Characteristics

Between April 2015 and June 2017, a total of 754 patients were screened on eligibility, 139 of them were randomized into the placebo or LT group. During follow-up, 19 patients (10 and 9 in the control and LT group, resp.)

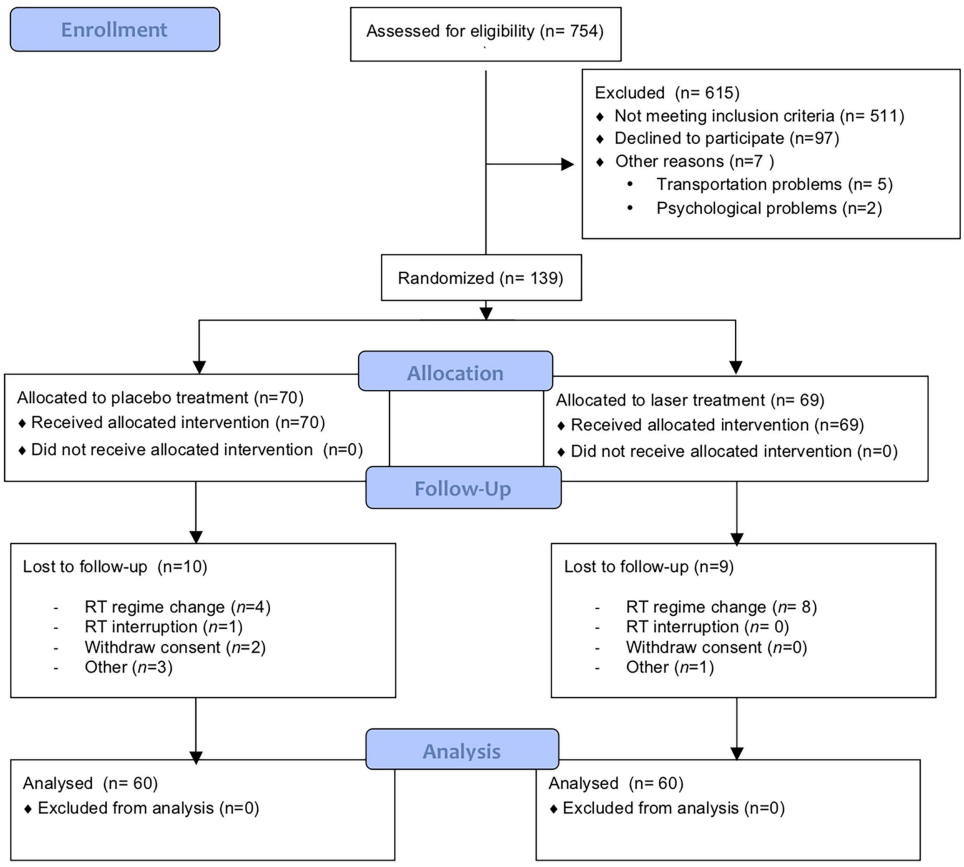

Fig. 1. CONSORT flow chart showing the patient flow through the trial.

were lost due to different reasons of which change of RT regimen change was the most frequent one (63%). Eventually a total of 120 patients, 60 patients in each group, were included in the present analysis, as shown in the patient flow chart (Fig. 1). Patient- and treatment-related characteristics are shown in Tables 2 and 3 and supplementary Table S1. Statistical analysis revealed that there were no significant differences between the two groups with respect to any of these characteristics. Therefore, both groups were perfectly comparable with respect to extrinsic and intrinsic risk factors for RD.

Skin Reaction Evaluation

At a RT dose of 40 Gy, almost all patients in both groups developed some degree of RD. As such, there was no significant difference between the two groups at this time point ($P = .562$). However, as RT progressed, the degree of skin reactions worsened in the control group ($P = .008$), while in the LT group the skin reactions stabilized ($P = .204$). As such at the end of RT, there was a significant difference in degree of RD between the control and LT group ($P = .004$), with a higher percentage of patients presenting RD grade 2 or worse in the control group (30% vs. 6.7% in the control and LT group, resp.). In the control group, there were even two patients that presented the most severe form of RD (grade 3), while in the LT group no patient developed this grade (Fig. 2).

Regarding the RISRAS, the mixed 2×2 ANOVAs revealed no significant main group effect for all the scores. However, the main effect of time and the group by time interaction was significant for the all the RISRAS scores (Ps < 0.05). As shown in Figure 3, the subjective RISRAS score decreased in the LT group, while it remained constant in the control group during RT. The increase of both the objective and total score between the RT dose of 40 Gy and the end of RT was more pronounced in the control than in the LT group (Fig. 3).

Quality of Life

Figure 4 demonstrates the progression of the quality of life of the patients during RT. There was a significant main time effect for the Symptom and Emotions subscale and the total Skindex-16 scale (Ps < 0.05), but not for the Functioning subscale ($P = .704$). In addition, for all the subscales and the total scale the main group effect (Ps < 0.05) and time by group interaction were significant (Ps < 0.05). As shown in Figure 4, the Emotions and Symptoms subscale scores decreased more prominently in the LT group than in the control group. While, the functioning subscale score increased in the control group, it decreased in the LT group. In overall, there was a decrease in the total Skindex-16 score in the LT group, while it remained constant in the control group.

Comparison With the DERMIS Trial

There was no significant difference in the RTOG scores between the LT group of the TRANSDERMIS trial and the LT group of the previous reported DERMIS trial (Ps > 0.3 at a dose of 40 Gy and at the end of RT). In both groups most of the patients presented RD grade 1 at the end of RT and only a minority of patients developed grade 2 skin reactions (6.7% and 2.6% in the TRANSDERMIS and DERMIS trial, resp.) [25].

DISCUSSION

Results of this trial show that PBMT is able to prevent the development of severe acute skin reactions and it seems to provide symptomatic relief during RT.

Theses results are in line with our previous pilot trial (DERMIS trial), in which PBMT was started during RT (i.e., at fraction 20 of RT, dose of 40 Gy) [25]. This indicates that starting with PBMT at the first day of RT does not provide an advantage compared to starting with PBMT once the patient already established RTOG grade 1. However, this can mean a more practical benefit for both the patient and the laser therapist, by reducing the number of PBM sessions that are necessary to deliver a positive effect.

Other studies investigating the use of PBMT in the management of acute RD are limited. There were three studies that evaluated the use of LED-PBMT for acute RD in BC patients. The study by DeLand et al. treated 19 BC patients undergoing intensity-modulated radiation treatments (IMRT) with LED-PBMT (590 nm, standard 100-pulse, 250 milliseconds per pulse at a fluence of 0.15 J/cm^2) on a daily basis and compared the grade of RD with a retrospective control group of 28 patients. The incidence of severe skin reactions (grade 2 or higher) at the end of RT in the LED group was 5.3%. In the control group of Deland the incidence of severe skin reactions was higher than in our study (85.7% vs. 26.7%, resp.). This dissimilarity may be due to differences in standard skin care used in both studies [31]. Fife et al. compared the degree of skin reactions of a LED-PBMT treated group ($n = 18$) with a

TABLE 2. Baseline Demographic Patient Characteristics

	Control group ($n = 60$)	LT group ($n = 60$)	
	Mean ± SD	Mean ± SD	P[a]
Age (years)	56.92 (10.34)	56.52 (10.54)	0.88
Body Mass Index (BMI)	25.03 (4.47)	25.27 (3.87)	0.63

BMI, Body Mass Index; LT, laser therapy; SD, standard deviation.
[a]*Wilcoxon Mann–Whitney U-test (two-tailed).*

TABLE 3. Disease and Therapy-Related Characteristics

Characteristic	Control group ($n=60$)		LT group ($n=60$)		P^a
	n	%	*n*	%	
Disease-related					
Tumour type					0.85
Ductal carcinoma *in situ*	6	10	7	11.7	
Invasive ductal adenocarcinoma	48	80	48	80	
Invasive lobular adenocarcinoma	5	8.3	5	8.3	
Missing	1	1.7	0	0	
Tumour stage					0.30
0	1	1.7	1	1.7	
I	18	30	12	40	
II	33	55	17	55	
III	6	10	2	3.3	
Missing	2	3.3	0	0	
Other cancer therapy					
Chemotherapy prior to radiotherapy	46	76.6	44	73.3	0.83
Hormone therapy	44	73.3	46	76.7	0.58
Trastuzumab	12	20.0	15	25.0	0.50
Radiotherapy-related					
Energy level					0.19
6 MV	43	71.7	50	83.3	
6 MV + 15 MV	17	28.3	10	16.7	
Boost type					0.86
Photons	31	51.7	29	48.3	
Electrons	29	48.3	31	51.7	
DIBH[b]	17	28.3	11	18.3	0.28
Number of segmented fields					0.068
0	4	6.7	5	8.3	
1	23	38.3	22	36.7	
2	18	30.0	29	48.3	
3	10	16.7	4	6.7	
4	4	6.7	0	0	
5	1	1.7	0	0	
	Mean ± SD		Mean ± SD		P[c]
Breast PTV (cm^3)[d]	796.27 ± 439,67		742.55 ± 353.92		0.67
Maximum dose (%)[e]	106.73 ± 1.08		106.79 ± 0.97		0.81

DIBH, deep inspiration breath hold; LT, laser therapy; MV, megavolt; PTV, planning target volume; SD, standard deviation.
[a]*Chi-square tests, or Fisher's exact tests, as appropriate (two-tailed).*
[b]*DIBH was used when the patients matched the following criteria: ≤70 years with left-sided breast cancer and lymph node metastases; >70 years undergoing chemotherapy; patients with left-sided BC without lymph node metastasis but with a MHD ≥35 Gy. DIBH was applied using the Varian Real-Time Position Management (RPM) Gating system (Varian Medical System, Palo Alto, CA).*
[c]*Wilcoxon Mann–Whitney U-test (two-tailed).*
[d]*Radiotherapy target volume that consists of the macroscopic primary tumour, the surrounding microscopic tumour spread and a margin to account for patient- and/or organ movement, shape changes of the tumour and daily setup variations. PTV was measured via treatment planning system by contouring manually each slice of breast tissue on planning CT.*
[e]*Maximum received irradiation dose (expressed in percentage of prescribed dose).*

placebo group ($n=15$). Patients in the PBMT group received LED-PBMT (same parameters as Deland et al.) before and after each three-dimensional conformal RT session, while the placebo group received sham LED treatments. This study showed that still 66.6% of the LED-PBMT patients developed grade 2 RD, while in the placebo group also 66.6% of the patients presented RD grade 2 or higher [32]. The contrasting results of both LED studies may be caused by a variety of factors such as the type of RT technique, non-blinded vs. blinded scoring of skin reactions, and set–up of the LED treatment. More recently, Strouthos et al. treated 25 BC patients with LED-PBMT (660–850 nm, peak radiant power 1390 mW, average power density 44.6 mW/cm^2, 250 ms per pulse at a fluence of 0.15 J/cm^2) twice weekly from the start of RT prior to their RT session and compared the skin reaction

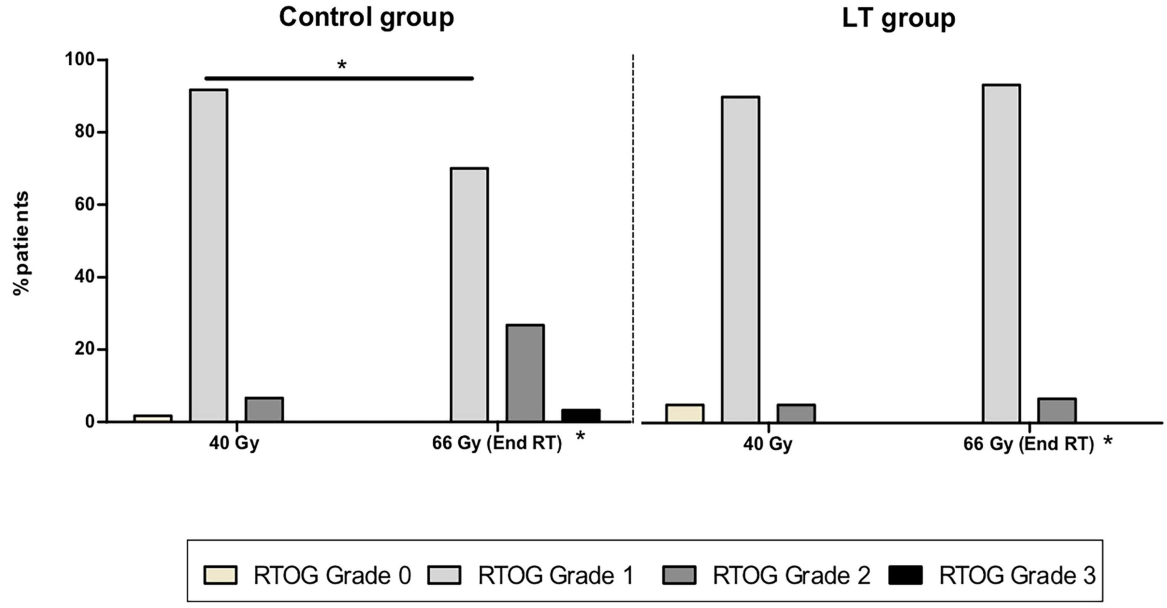

Fig. 2. Severity of acute radiodermatitis expressed in RTOG grades for the control and LT group at a RT dose of 40 Gy and at the end of RT (66 Gy). *Significant difference within the control group between the two time points and between the two groups at the end of RT ($P < 0.05$; χ^2 or Fisher's exact tests, two-tailed). *Gy, Gray; LT, laser therapy; RT, radiotherapy*; *RTOG: Radiation Therapy Oncology Group (Grade 0: no change; grade 1: follicular, dull, or faint erythema, dry desquamation; grade 2: tender or bright erythema, patchy moist desquamation; grade 3: confluent moist desquamation other than skin folds).*

results with 45 control patients that only received the standard skin care. Their results showed that in the LED-PBMT group 12% of the BC patients demonstrated grade 2 RD, while in the control group 44.4% of the patients developed RD grade 2 or higher [33]. Bay et al. performed another study concerning the use of PBMT for wound healing purposes. They exposed the left or right side of the buttock of 20 healthy volunteers to PBMT (830/590, 109 mW/cm^2, 65 J/cm^2 per treatment) or placebo (595 nm, 0.19 mW/cm^2, 0.13 J/cm^2 per treatment) during five daily sessions after ablative fractional laser-assisted photodynamic therapy (PDT), to investigate the effectiveness of PBM in the reduction of inflammatory skin reactions. Results of this study did not show any benefit of PBMT in the reduction of PDT-induced skin reactions [34].

All together, these results demonstrate that PBMT is only an effective treatment option for wound healing, when

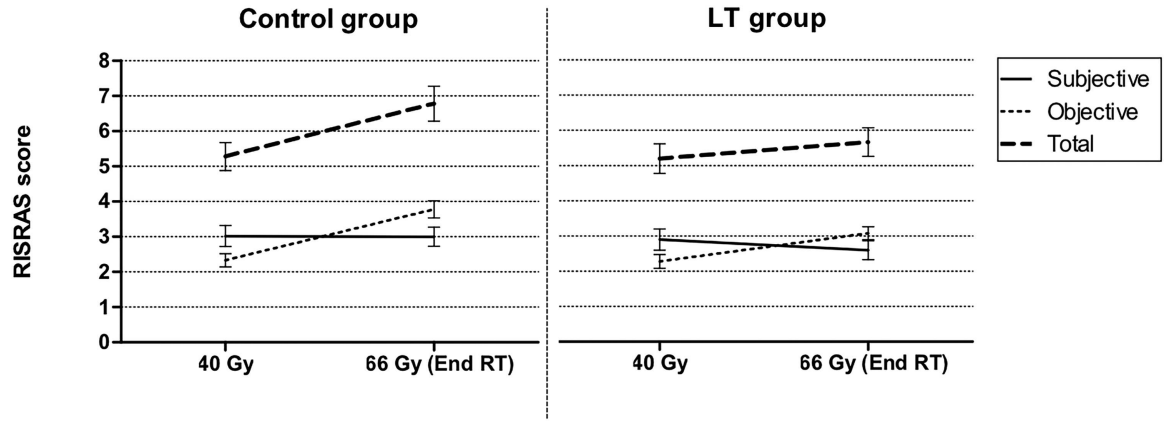

Fig. 3. Average subjective, objective and total RISRAS scores of the control and LT group at a RT dose of 40 Gy and the end of RT (66 Gy). Data are shown as means (±SEM) and higher scores indicate a more severe skin reaction. *Gy, Gray; LT, laser therapy; RISRAS: Radiotherapy-Induced Skin Reaction Assessment Scale; RT, Radiotherapy; SEM, standard error of measurement.*

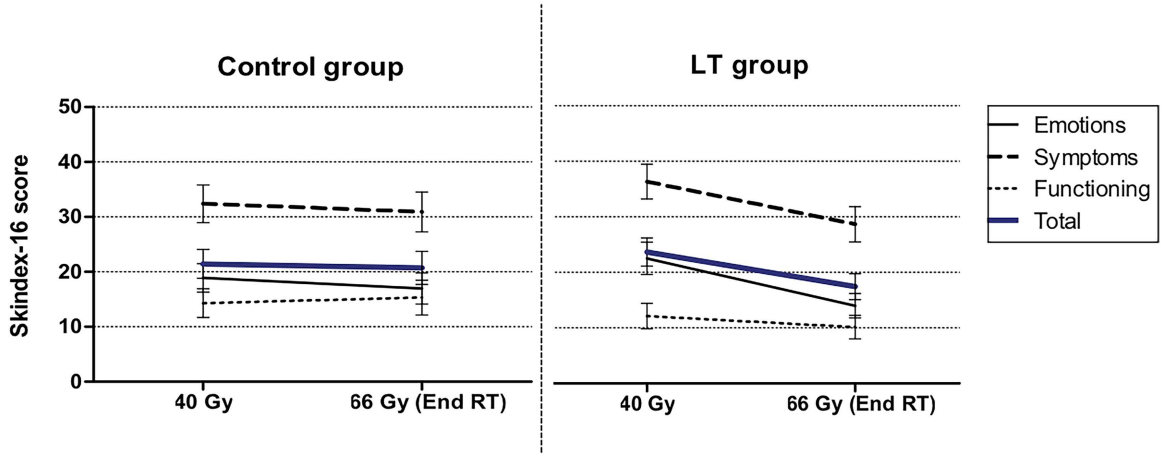

Fig. 4. Skindex-16 scores (Symptoms, Emotions, Functioning and total score) of the control and LT group at a RT dose of 40 Gy and the end of RT (66 Gy). Data are shown as means (±SEM) and higher scores indicate a diminished patients' quality of life. *Gy, Gray; LT, laser therapy; RT, Radiotherapy; SEM, standard error of measurement.*

the appropriate irradiation and treatment parameters are applied [35,36]. Not only for the treatment of acute RD, but also for chronic (i.e., late) RD (e.g., telangiectasia's, fibrosis, and ulceration/necrosis) the application of laser therapy (PBMT or pulsed dye laser, PDL) seems to be effective [23,24,37–39].

A few limitations of the present study need to be addressed. The RTOG grading system as well as the researcher component of the RISRAS scale lack objectivity. Over the past few years, a variety of objective skin measurement techniques have been reported and will increase the objectivity of the study results. Most of these techniques have been developed to measure the degree of erythema and the skin barrier function (e.g., transepidermal water loss and skin hydration measurements) [40–43]. Another important limitation might be the patient population, which was confined to breast cancer patients that underwent a lumpectomy and a standard RT regimen of 33 fractions. More clinical trials in a broader patient population with different cancer types and RT regimens need to be conducted, which will increase the generalisability of the study results. Finally, a center trial will allow us to include a larger number of participants of clinical centers at different geographic locations. This will be necessary for validation of this promising treatment technique for RD.

CONCLUSION

This was the first randomized, placebo-controlled clinical trial demonstrating that a twice-weekly treatment with PBM starting from the first day of RT in breast cancer patients can prevent the development of moist desquamation (RTOG grade 2 or higher). In addition, PBMT also seems to improve the patients' quality of life during RT. Future (multi)center trials are necessary to confirm these positive results in a larger patient population with a broader range of cancer types and at different clinical centers. This will increase the general applicability of PBMT in supportive care of cancer patients.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article.