Biophysical skin measurements to evaluate the effectiveness of photobiomodulation therapy in the prevention of acute radiation dermatitis in breast cancer patients

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Abstract

Purpose: The purpose of this study was to evaluate objectively the effectiveness of photobiomodulation therapy (PBMT) for the prevention of acute radiation dermatitis (ARD) by using biophysical skin measurements.
Methods: A randomized, placebo-controlled trial with 120 breast cancer patients who underwent an identical radiotherapy (RT) regimen post-lumpectomy was performed (TRANSDERMIS trial). Patients were randomized to receive PBM (808 nm CW/905 nm pulsed, 168 mW/cm^2, spot size 19.6 cm^2, fluence 4 J/cm^2) or placebo treatments from the first day of RT (2×/week). Biophysical skin measurements were collected to assess the skin pigmentation and barrier function. Measurements were collected at the first day of RT, a RT dose of 40 Gray (Gy), and the end of RT (66 Gy).
Results: The incidence of moist desquamation was significantly higher in the control than in the PBMT group at the end of RT (30 vs. 7%, respectively, odds ratio = 6, $p = 0.004$). The biophysical skin measures showed that the mean percentage change from the baseline transepidermal water loss (TEWL), erythema, and melanin values was significantly higher in the control than in the PBMT group at the end of RT ($ps < 0.05$). Logistic regression analysis revealed that the risk on moist desquamation was significantly increased for patients with a large (> 800 cc) breast volume (odds ratio = 4, $p = 0.017$).
Conclusions: This is the first randomized controlled trial demonstrating by objective measurements that PBMT is effective in reducing the incidence of moist desquamation in breast cancer patients undergoing RT. Additionally, a large breast volume is an important risk factor for the development of moist desquamation.

Keywords separated by ' - '	Breast cancer - Photobiomodulation therapy - Radiotherapy - Skin toxicity - Radiation dermatitis - Objective skin evaluation
Foot note information	This research was orally presented at the International Symposium of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO; June 28–30, 2018, Vienna, Austria).

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ORIGINAL ARTICLE

Biophysical skin measurements to evaluate the effectiveness of photobiomodulation therapy in the prevention of acute radiation dermatitis in breast cancer patients

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Keywords Breast cancer · Photobiomodulation therapy · Radiotherapy · Skin toxicity · Radiation dermatitis · Objective skin evaluation

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Introduction

Acute radiation dermatitis (ARD) is a severe side effect occurring in about 90–95% of the cancer patients undergoing radiotherapy (RT) [1]. This is a cutaneous reaction that is caused by direct damage of ionizing radiation, which manifests 2–4 weeks after the first RT session [2].

In normal healthy skin, the superficial cells of the epidermis (i.e., upper skin layer) are shed through normal desquamation and replaced by stem cells from the underlying basal layer. From the first RT dose, stem cells within the basal layer of the epidermis are destroyed, leading to a disruption in the self-renewing property of the skin. During RT, this process continues which will negatively affect the skin barrier function and the wound healing process. This ultimately results in changes of the skin structure and vasculature, clinically characterized by erythema, dryness, flaking skin, pruritus, folliculitis (i.e., skin rash), and hyperpigmentation. Due to the compromised skin barrier function and cutaneous immune system, the skin will become more susceptible to water loss, chemical substances, allergens, ultraviolet radiation (UV), and infections [3, 4].

Clinically, ARD is evaluated by the criteria of the Radiation Therapy Oncology Group (RTOG) into three grades: mild erythema and dry desquamation (grade 1), bright erythema and moist desquamation in skin folds (grade 2), and confluent moist desquamation (grade 3). However, this grading system lacks objectivity [5].

A variety of biophysical skin techniques are available to measure the skin pigmentation, hydration, pH, blood flow, and sebum level in order to investigate the underlying physiological mechanism of ARD [6].

Up to now, the evidence for a general consensus on the prevention and management of ARD is limited. Nevertheless, the Multinational Association of Supportive Care in Cancer (MASCC) developed skin care guidelines concerning the prevention and treatment of RD in 2013. Still, many RT centers develop their own skin care protocol [7].

Photobiomodulation therapy (PBMT) is the application of visible and/or (near-) infrared light at a low power on tissue to stimulate the wound healing process and reduce inflammation and pain [8]. There is evidence that PBMT could be used as a new preventive and therapeutic tool in the management of ARD [9–12]. Recently, our research group performed two clinical trials in which we demonstrated that PBMT is able to prevent the development of ARD grade 2 or higher in breast cancer patients by clinically evaluating the skin reactions by the RTOG grading [13, 14].

In this project, we evaluated the effectiveness of PBMT in the prevention of ARD in breast patients by objectively assessing the skin hydration, transepidermal water loss (TEWL), and pigmentation.

Material and methods

Study design and setting

This was a secondary analysis of the TRANSDERMIS trial, a monocentric, prospective, placebo-controlled, randomized controlled trial (RCT) [14], to evaluate objectively the effectiveness of PBMT in breast cancer patients undergoing RT. Female patients with unilateral breast cancer who were treated at the RT Department of the Limburg Oncology Centre (Jessa Hospital, Hasselt, Belgium) were screened on eligibility between April 2015 and June 2017. The study was approved by the ethics committees of the Jessa Hospital and the University of Hasselt (B243201524443) and was conducted according to the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (NCT02443493).

Study population

To be eligible for the study, patients needed to fulfill the following criteria: female, diagnosed with primary unilateral breast cancer, underwent lumpectomy, scheduled to undergo a RT regimen consisting of 25 fractions of 2 Gray (Gy) to the whole breast and 8 fractions of 2 Gy to the tumor region (total RT dose 66 Gy). Patients were excluded when they met the following criteria: irradiation to the same breast in the past, hypofractionated RT, mastectomy, metastatic disease, concomitant chemotherapy, and infection of the to-be-irradiated zone. Eligible patients were recruited during the CT simulation session, approximately 2 weeks before the start of the RT. Written informed consent of all patients was collected before study participation.

Randomization and blinding

The planning target volume (PTV) of the eligible patients was used to stratify them into three groups: small (< 450 cc), medium (450–800 cc), and large breasts (> 800 cc) [15]. Patients were randomly assigned to the control or PBMT group in a 1:1 ratio based on a computer-generated random number list, which was held by a researcher who was not involved in the clinical part of the study. Allocation was concealed to the PBM operator until the first treatment session. Both the participating patient and the outcome assessor were blinded until the last treatment session.

Interventions

Radiotherapy

The Eclipse™ treatment planning system was used to plan the RT sessions (version 11.0, Varian Medical System, Palo Alto, CA). The standard RT regimen consisted of 25 daily fractions (2 Gy/fraction, 5 fractions/week) to the whole breast followed by boost of 8 fractions (2 Gy/fraction, 5 fractions/week) to the tumor bed during a period of 6 to 7 weeks (total RT dose of 66 Gy). The whole breast was irradiated with 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) and the tumor region with a two-field conformal photon (4–15 MV) or a one-field vertical electron (6–15 MeV) beam. A selected[1] group of patients were irradiated using the deep inspiration breath-hold (DIBH) in order to reduce the mean heart dose (MHD).

Topical skin care treatment

Each patient was individually advised to follow the general skin care guidelines (e.g., wear loose fit clothing, gentle washing with or without mild soap, patting dry with a soft towel instead of rubbing). Further, the patients were instructed to apply a topical, hydroactive colloid gel (Flamigel®, Flen Pharma, Kontich, Belgium) on the irradiated zone (3×/day), starting at the first day of RT. Foam, absorbent, self-adhesive silicone dressings (Mepilex®, Mölnlycke Health Care, Gothenburg, Sweden) were used in the case of painful skin reactions and/or moist desquamation.

PBMT

PBMT was applied from the first until the last day of RT (2×/week, 14 sessions) by a trained operator using the class IV MLS® M6 laser (ASA Srl, Vicenza, Italy), as described previously [14]. This device is commercially available, built in compliance with EC/EU rules, received FDA approval, and is CE certified. It consists of two laser diodes with different wavelengths (808–905 nm), peak powers (1.1–25 W), and emission modes (continuous and pulsed). Both diodes work simultaneously and synchronously with coincident propagation axes (average radiant power 3.3 W). The energy density (fluence) was set at 4 J/cm^2 based on earlier recommendations and on our clinical experience [13, 16]. During the PBMT sessions, the whole irradiated area was treated (whole breast, inframammary fold, and axilla). The complete list of PBMT parameters can be found in Table 1. The PBMT parameters were selected based on the successful results of our previous trial (DERMIS trial) [14] and on the guidelines of Zecha et al. [17].

During the sham treatments of the control group, the PBM device did not emit light but made the same sound as an active device. All patients, independently of their treatment group, wore safety glasses and eye shields to avoid any perceived risk of eye damage and to blind them during the PBM or sham sessions.

Outcome measures

Patient data

Clinical information regarding the patient's personal and disease- and treatment-related characteristics was collected via patient questionnaires and the patient's medical charts.

RTOG grading

Clinically, the severity of ARD was evaluated by the criteria of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC [5]). Two experienced RT nurses performed this in a blinded manner.

Objective skin measurements

In order to assess the impact of RT on the skin barrier function, the transepidermal water loss (TEWL) and the skin hydration level were determined. TEWL was measured by the Tewameter® TM300 (Courage-Khazaka, Cologne, Germany), according to the guidelines published both by the standardization group of the European Contact Dermatitis Society [18] and by the European group on Efficacy Measurements of Cosmetics and Other topical products [19]. The skin hydration was measured with the Corneometer® (Courage-Khazaka, Cologne, Germany) according to Heinrich et al. [20]. A reflectance spectrophotometer, Mexameter® MX18 (Courage-Khazaka, Cologne, Germany), was used to measure the pigmentation of the skin (e.g., melanin and erythema) as previously described by Clarys et al. [21].

All four measurements (e.g., TEWL, hydration, erythema, and melanin) were taken at the four quadrants of each breast (irradiated and non-irradiated), with three

[1] DIBH was used when the patients matched the following criteria: bilateral breast cancer; left-sided breast cancer and lymph node metastases under the age of 70 years; left-sided breast cancer and lymph node metastases above the age of 70 years and undergoing chemotherapy; left-sided breast cancer 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).

measurements per quadrant (see Online Resource 1). The average values of these measurements were taken as a value for the whole breast. The measurements were carried out after a 30-min acclimatization period at room temperature (20–22 °C) and 40–60% humidity. The final objective measurements were described as percentages in order to calculate deviations from pre-treatment baseline values, also termed as indexes. Therefore, the following formula was used:

$$\left[\left(\frac{\text{Obj.measure irradiated breast at indicated time}/\text{Obj.measure control breast at indicated time}}{\text{Obj.measure irradiated breast at baseline}/\text{Obj.measure control breast at baseline}}\right)-1\right]\times 100\%$$

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	
	Number of emitters	1	2	
	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 (1–2000 Hz)	
	- Pulse on duration - Duty cycle		- 100-ns single pulse width - 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

Measurement collection schedule

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

Statistical analysis

Differences in patient- and therapy-related characteristics between both groups were analyzed by means of chi-square tests (χ^2), Fisher's exact tests, Student's *t* tests, or Mann-Whitney *U* tests, as appropriate. RTOG scores were analyzed by means of χ^2 or Fisher's exact tests, as appropriate. The objective skin measurements at each time point were analyzed by Mann-Whitney *U* tests. Longitudinal analysis of the biophysical skin measurements was performed by mixed analyses of variance (ANOVAs) with time (between the RT dose of 40 Gy and 66 Gy) as within-subject factor and group (control vs. PBMT group) as between-subject factor. To determine the risk on moist desquamation, univariate logistic regressions with, as predictor variables, treatment group and breast size (based on the PTV) were performed. 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

A total of 139 patients were randomized into the placebo or PBMT group between April 2015 and June 2017. During the course of RT, 2 patients of the control group withdrew their consent. Further 17 patients were excluded due to a RT regimen change or a RT interruption (5 and 8 in the control and PBMT, resp.). For the final analysis data of 120 patients, 60 patients in each group were used (Fig. 1). Both groups were

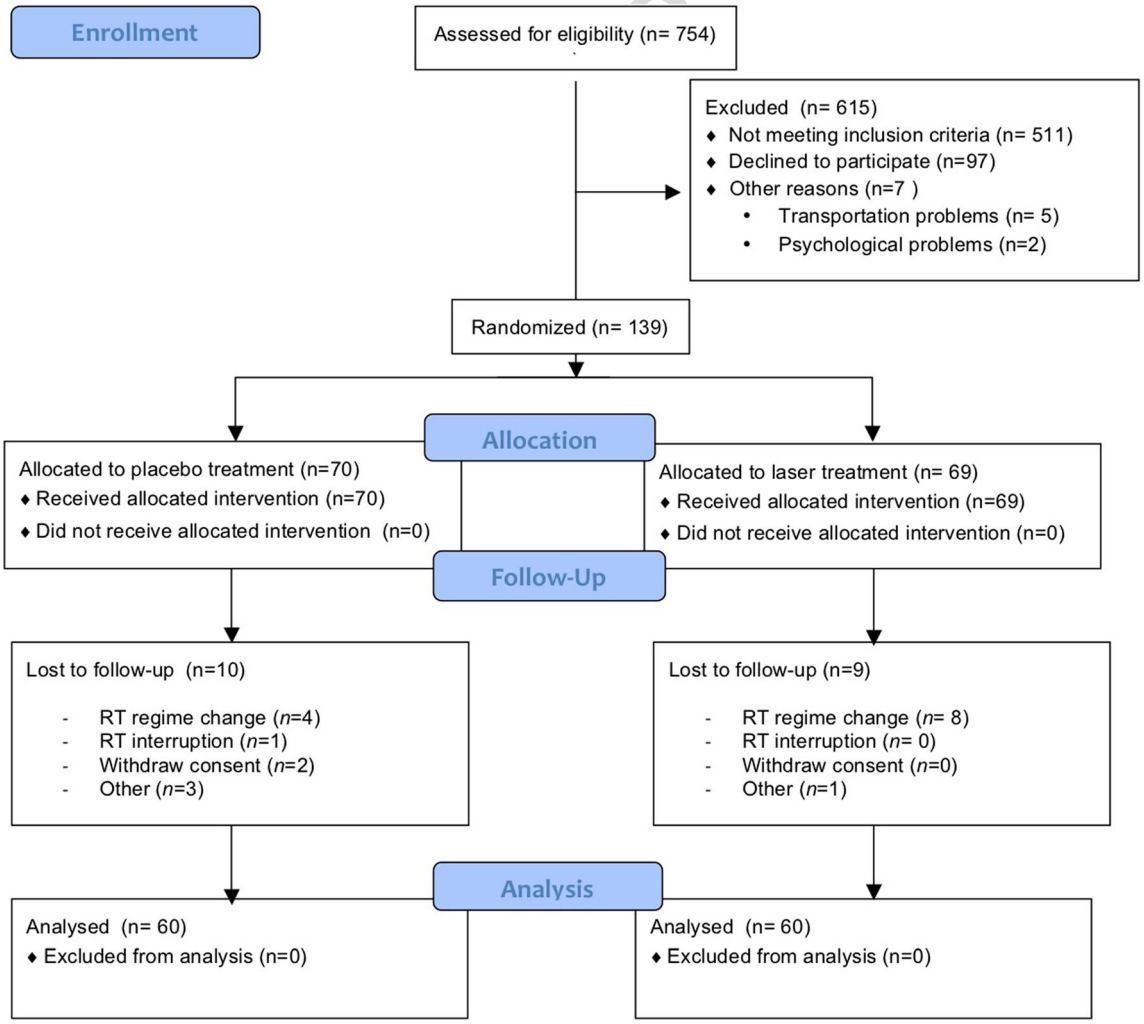

Fig. 1 CONSORT flow chart [14]

matched for all the patient- and treatment-related characteristics (Table 2).

Clinical evaluation of ARD

Patients' RT-induced skin reactions were evaluated by the criteria of the RTOG, as shown in Table 3. Our results demonstrated that the incidence of moist desquamation (ARD grade 2 or higher) was significantly lower in the PBMT group in comparison with the control group at the end of RT ($p = 0.004$). This was confirmed by the univariate logistic regression analysis demonstrating that patients only receiving the standard skin care were six times more likely to develop moist desquamation in comparison with patients that also were treated with PBMT ($p = 0.003$, 95% CI [OR] 1.881–19.82). Further, the risk on moist desquamation rose with an increasing breast volume. As such, patients with large breasts (> 800 cc) had a four times higher risk to develop moist desquamation than patients with small breast volumes ($p = 0.017$, 95% CI [OR] 1.290–12.936).

Objective evaluation of ARD

Erythema

The mixed 2 × 2 ANOVAs revealed a significant main time effect and group by time interaction ($ps < 0.05$) for the erythema index. However, the main group effect was not significant. As depicted in Fig. 2a, the degree of erythema in both groups increased during the course of RT. At the RT dose of 40 Gy, the percentage change in erythema from baseline did not significantly differ between the control group and the PBMT group. However, at the end of RT, the percentage change from baseline in erythema was significantly higher in the control group in comparison with the PBMT group ($p = 0.016$).

Table 3 RTOG grading at a RT dose of 40 and 66 Gy (end RT)

RTOG grading	Control group ($n = 60$) *N* (%)	PBMT group ($n = 60$) *N* (%)	p[a]
40 Gray			0.562
Grade 1	1 (1.7)	3 (5)	
Grade 2	55 (91.7)	54 (90)	
Grade 3	4 (6.7)	3 (5)	
66 Gray (end RT)			0.004
Grade 1	42 (70)	56 (93.3)	
Grade 2	16 (26.7)	4 (6.7)	
Grade 3	2 (3.3)	0 (0)	

PBMT, photobiomodulation therapy; *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)

[a] Chi-square tests (two-tailed)

Table 2 Patient and treatment characteristics

	Control group ($n = 60$)	PBMT group ($n = 60$)	p[a]
Mean age (SD), years	56.92 (10.34)	56.52 (10.54)	0.88
Mean body mass index (SD)	25.03 (4.47)	25.27 (3.87)	0.63
Mean breast size (SD)[b], cc	796.27 (439.67)	742.55 (353.92)	0.67
Breast size[b], *n* (%)			0.97
Small (< 450 cc)	11 (18.3)	12 (20)	
Medium (450–800 cc)	26 (43.3)	26 (43.3)	
Large (> 800 cc)	23 (38.3)	22 (36.7)	
Prior chemo, *n* (%)	46 (76.6)	44 (73.3)	0.83
RT energy level, *n* (%)			0.19
6 MV	43 (71.7)	50 (83.3)	
6 MV + 15 MV	17 (28.3)	10 (16.7)	
Boost type, *n* (%)			0.86
Photons	31 (51.7)	29 (48.3)	
Electrons	29 (48.3)	31 (51.7)	
DIBH	17 (28.3)	11 (18.3)	0.28

DIBH, deep inspiration breath-hold; *PBMT*, photobiomodulation therapy; *RT*, radiotherapy; *SD*, standard deviation

[a] Student's *t* test, Wilcoxon-Mann-Whitney *U* test, chi-square tests, or Fisher's exact tests, as appropriate (two-tailed)

[b] Radiotherapy target volume that consists of the macroscopic primary tumor, the surrounding microscopic tumor spread and a margin to account for patient and/or organ movement, shape changes of the tumor, and daily setup variations. PTV was measured via treatment planning system by contouring manually each slice of breast tissue on planning CT

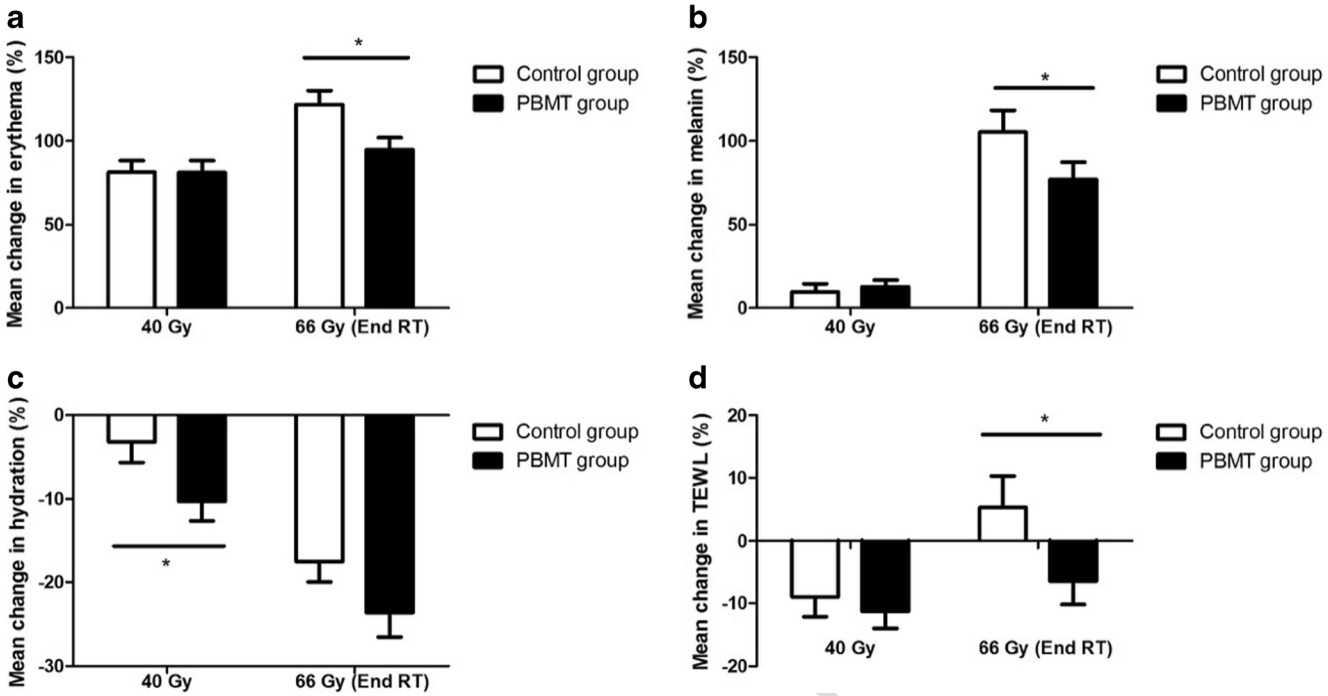

Fig. 2 Evaluation of the skin pigmentation (erythema (**a**) and melanin (**b**)) and barrier function (hydration (**c**) and TEWL (**d**)) by biophysical measurements. Data are shown as mean percentage change from baseline (± SEM). *Significant difference between the two groups at the indicated time point ($p < 0.05$; Mann-Whitney *U* test, two-tailed). *TEWL*, transepidermal water loss; *PBMT*, photobiomodulation therapy; *RT*, radiotherapy

Pigmentation

Concerning the melanin index, there were both a significant main time effect and group by time interaction ($ps < 0.05$), but no significant main group effect. Figure 2b demonstrates that the degree of pigmentation increased during the progression of RT in both groups. The increase in pigmentation started off slowly, with no significant difference in percentage change over baseline in melanin between the two groups at the RT dose of 40 Gy. Towards the end of RT, the melanin index was significantly higher in the control than in the PBMT group ($p = 0.019$).

Hydration

The mixed 2 × 2 ANOVAS revealed a significant main time and group effect ($ps < 0.05$), but no significant group by time interaction for the skin moisture level. As shown in Fig. 2c, during the course of RT, the skin hydration level decreased in both groups in comparison with the baseline values. The skin hydration level was significantly lower at the RT dose of 40 Gy in the PBMT group in comparison with the control group ($p = 0.036$). However, at the end of RT, both groups showed a comparable skin moisture index.

Transepidermal water loss

Regarding the TEWL, there was a significant main time and group effect ($ps < 0.05$), but no significant group by time interaction. The TEWL decreased in comparison with the baseline value in both the control and PBMT groups at the RT dose of 40 Gy, to a comparable level (Fig. 2d). Towards the end of RT, the TEWL level increased in both groups, although the final TEWL index was significantly lower in the PBMT group in comparison with the control group ($p = 0.05$).

Discussion

Results of this trial show that PBMT is an effective tool to prevent the development of moist desquamation. This was confirmed by objectively evaluating the skin's biophysical condition. Our results demonstrated that PBMT was able to reduce the increase in the skin's pigmentation level and improve the skin barrier function. Additionally, the main risk factor for the development of severe ARD is the breast volume, which implies that patients with large breasts (> 800 cc) have an increased risk on moist desquamation.

The erythema index progressively increased during RT in both treatment arms. These findings are in line with previous studies [22–25]. This increase in erythema is caused by the

RT-induced inflammatory reaction leading to vasodilation and leaking of the blood vessels [6, 26, 27]. However, the increase was significantly lower in the PBMT than in the control group at the end of RT. This proves that PBMT is able to reduce the degree of erythema. These results are consistent with earlier in vivo studies and clinical trials on various erythematous skin disorders (e.g., acne vulgaris, UV damage, laser resurfacing wounds, burn wounds) [28–31]. The anti-inflammatory effect of PBMT, correlated with a decrease in inflammatory cytokine production, might explain this observation [28, 32].

Further, our results also showed a significant increase in skin pigmentation in both groups during the course of RT. This is explained by post-inflammatory hyperpigmentation (PIH) after the RT-induced skin reaction [6, 27]. PIH is caused by the stimulation of melanocytes due to an inflammatory skin reaction leading to an increased melanin production and transport to the surrounding keratinocytes. Remarkably, our results demonstrated that at the end of RT, the increase in melanin content of the skin was significantly lower in the PBMT than in the control group. As such, PBMT was able to stabilize the hyperpigmentation reaction of the patients' skin during RT. Several in vitro studies showed that PBMT can inhibit the melanin synthesis in human melanocyte cultures [33]. Also, clinical trials demonstrated that PBMT is able to reduce hyperpigmentation in numerous skin conditions (e.g., acne vulgaris, photoaging, melasma) [34, 35].

In healthy skin, a low TEWL and a high hydration value correlate with a good barrier function [36]. Ionizing radiation deregulates the cellular function and causes apoptosis of the epidermal cells, resulting into an affected skin barrier function, correlated with a high TEWL and a low skin moisture level [6, 27, 37, 38]. The findings in our control group are in line with these studies. However, in the PBMT group, both the TEWL and hydration index were significantly decreased at the end of RT. The epidermal thickening effect might explain these conflicting results. This effect is characterized by epidermal hyperproliferation leading to a thickened stratum corneum (outermost layer of the epidermis) caused by repetitive exposure to external stimuli. The thickening of the stratum corneum improves the skin barrier function and thereby it is correlated with a decrease in TEWL [38, 39]. Several studies, both in vitro and in vivo, have demonstrated that PBMT can stimulate the proliferation of several types of cells, including keratinocytes. PBMT seems to be able to stimulate the epidermal thickening effect in the skin caused by RT and thereby it can improve the skin barrier function [40–43].

The results of the logistic regression analysis demonstrated that patients who were treated with standard skin care had a six time higher risk to develop moist desquamation in comparison with the patients treated with PBMT. This implies that the preventive application of PBMT can seriously lower the severity of the RT-induced skin reactions, as previously published by our study group [14]. Further, our results showed that patients with large breasts developed more severe skin reactions. These findings are consistent with those of earlier published studies [44, 45].

The main limitation of the study was the enrolled patient population, which was confined to breast cancer patients post-lumpectomy, who underwent a standard fractionated RT regimen. In the future, more clinical trials in a broader patient population with different cancer types and RT regimens need to be conducted, which will increase the generalizability of the study results.

Conclusion

This is the first RCT demonstrating by an objective approach that the preventive application of PBMT is effective in reducing the incidence of moist desquamation in breast cancer patients. The biophysical skin measurements showed that PBMT is able to stabilize the degree of pigmentation (both erythema and melanin) and improve the skin barrier function during the course of RT. Interestingly; patients with a large breast volume have an increased risk on moist desquamation. In conclusion, we can state that PBMT is an effective tool to prevent the development of severe ARD in breast cancer patients. Further, screening patients on breast volume before the start of RT can allow the radiotherapist to optimize the skin management during the course of RT.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval The ethics committees of the Jessa Hospital and the University of Hasselt approved the study (B243201524443). All procedures performed in the study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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