

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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154	Abstract	<p>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.</p> <p>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/cm², spot size 19.6 cm², fluence 4 J/cm²) 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).</p> <p>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, <i>p</i> = 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 (<i>ps</i> < 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, <i>p</i> = 0.017).</p> <p>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.</p>	
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Electronic supplementary material

ESM 1
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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/cm², spot size 19.6 cm², fluence 4 J/cm²) 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 Breast cancer · Photobiomodulation therapy · Radiotherapy · Skin toxicity · Radiation dermatitis · Objective skin evaluation

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).

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00520-018-4487-4>) contains supplementary material, which is available to authorized users.

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Q3 33

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. 85
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Material and methods 87

Study design and setting 88

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). 89
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Study population 102

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. 103
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Randomization and blinding 117

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. 118
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128	Interventions	
129	Radiotherapy	
130	The Eclipse™ treatment planning system was used to plan	synchronously with coincident propagation axes (average
131	the RT sessions (version 11.0, Varian Medical System,	radiant power 3.3 W). The energy density (fluence) was
132	Palo Alto, CA). The standard RT regimen consisted of	set at 4 J/cm ² based on earlier recommendations and on
133	25 daily fractions (2 Gy/fraction, 5 fractions/week) to	our clinical experience [13, 16]. During the PBMT ses-
134	the whole breast followed by boost of 8 fractions (2 Gy/	sions, the whole irradiated area was treated (whole breast,
135	fraction, 5 fractions/week) to the tumor bed during a pe-	inframammary fold, and axilla). The complete list of
136	riod of 6 to 7 weeks (total RT dose of 66 Gy). The whole	PBMT parameters can be found in Table 1. The PBMT
137	breast was irradiated with two tangential photon (half)	parameters were selected based on the successful results
138	beams set up isocentrically using a 6-MV or a 6 + 15-	of our previous trial (DERMIS trial) [14] and on the
139	MV linear accelerator (Clinac® DHX, Varian Medical	guidelines of Zecha et al. [17].
140	Systems, Palo Alto, CA) and the tumor region with a	During the sham treatments of the control group, the PBM
141	two-field conformal photon (4–15 MV) or a one-field	device did not emit light but made the same sound as an active
142	vertical electron (6–15 MeV) beam. A selected ¹ group	device. All patients, independently of their treatment group,
143	of patients were irradiated using the deep inspiration	wore safety glasses and eye shields to avoid any perceived risk
144	breath-hold (DIBH) in order to reduce the mean heart	of eye damage and to blind them during the PBM or sham
145	dose (MHD).	sessions.
146	Topical skin care treatment	
147	Each patient was individually advised to follow the gen-	Outcome measures
148	eral skin care guidelines (e.g., wear loose fit clothing,	
149	gentle washing with or without mild soap, patting dry	Patient data
150	with a soft towel instead of rubbing). Further, the patients	
151	were instructed to apply a topical, hydroactive colloid gel	Clinical information regarding the patient's personal and
152	(Flamigel®, Flen Pharma, Kontich, Belgium) on the irra-	disease- and treatment-related characteristics was collected
153	diated zone (3×/day), starting at the first day of RT. Foam,	via patient questionnaires and the patient's medical charts.
154	absorbent, self-adhesive silicone dressings (Mepilex®,	RTOG grading
155	Mölnlycke Health Care, Gothenburg, Sweden) were used	
156	in the case of painful skin reactions and/or moist	Clinically, the severity of ARD was evaluated by the criteria of
157	desquamation.	the Radiation Therapy Oncology Group/European
158	PBMT	Organization for Research and Treatment of Cancer
159	PBMT was applied from the first until the last day of RT	(RTOG/EORTC [5]). Two experienced RT nurses performed
160	(2×/week, 14 sessions) by a trained operator using the	this in a blinded manner.
161	class IV MLS® M6 laser (ASA Srl, Vicenza, Italy), as	Objective skin measurements
162	described previously [14]. This device is commercially	
163	available, built in compliance with EC/EU rules, received	In order to assess the impact of RT on the skin barrier
164	FDA approval, and is CE certified. It consists of two laser	function, the transepidermal water loss (TEWL) and the
165	diodes with different wavelengths (808–905 nm), peak	skin hydration level were determined. TEWL was mea-
166	powers (1.1–25 W), and emission modes (continuous	sured by the Tewameter® TM300 (Courage-Khazaka,
167	and pulsed). Both diodes work simultaneously and	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 mea-
		sured 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 mea-
		sure the pigmentation of the skin (e.g., melanin and ery-
		thema) as previously described by Clarys et al. [21].
		All four measurements (e.g., TEWL, hydration, erythe-
		ma, 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).

214 measurements per quadrant (see Online Resource 1). The objective measurements were described as percentages in 219
 215 average values of these measurements were taken as a order to calculate deviations from pre-treatment baseline 220
 216 value for the whole breast. The measurements were carried values, also termed as indexes. Therefore, the following 221
 217 out after a 30-min acclimatization period at room temperature formula was used: 222
 218 (20–22 °C) and 40–60% humidity. The final

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

Q4 t1.1 **Table 1** Photobiomodulation parameters

t1.2 PBMT parameters			
t1.3	Device information	Manufacturer	ASA Srl
t1.4		Model identifier	MLS® laser M6
t1.5		Year produced	2012
t1.6		Number of emitters	3
t1.7		Emitter type	IR laser diodes
t1.8		Spatial distribution of emitters	Three emitters spaced 2 cm apart in a triangle pattern
t1.9		Beam delivery system	Scanning head (five pre-settled directions)
t1.10	Irradiation parameters	Laser diode 1	Laser diode 2
t1.11		Center wavelength	808 nm 905 nm
t1.12		Number of emitters	1 2
t1.13		Spectral bandwidth	± 5 nm ± 5 nm
t1.14		Operating mode	Continuous pulsed wave mode
t1.15		Peak radiant power	1.1 W 25 W
t1.16		Average radiant power	3.3 W
t1.17		Maximum frequency (frequency range)	90 kHz (1–2000 Hz)
t1.18		- Pulse on duration - Duty cycle	- 100-ns single pulse width - 50%
t1.19		Aperture diameter	5 cm
t1.20		Irradiance at aperture	0.168 W/cm ²
t1.21		Beam divergence at 60%	42.8 mrad 59.2 mrad
t1.22		Beam profile	Two laser beams work simultaneously and synchronously with coincident propagation axes
t1.23	Treatment parameters	Beam spot size at target area	19.625 cm ²
t1.24		Irradiance at target	0.168 W/cm ²
t1.25		Radiant exposure (fluence)	4 J/cm ²
t1.26		Number of points irradiated	-Breast: Whole breast, inframammary fold and/or axilla, depending on the location of radiodermatitis
t1.27		Exposure duration	- Whole breast: ± 420–720 s - Inframammary fold: ± 103 s - Axilla: ± 68 s
t1.28		Application technique	5 cm above the skin
t1.29		Timing	After the RT session
t1.30		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

231 **Measurement collection schedule**

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

235 **Statistical analysis**

236 Differences in patient- and therapy-related characteristics be-
 237 tween both groups were analyzed by means of chi-square tests
 238 (χ^2), Fisher's exact tests, Student's *t* tests, or Mann-Whitney
 239 *U* tests, as appropriate. RTOG scores were analyzed by means
 240 of χ^2 or Fisher's exact tests, as appropriate. The objective skin
 241 measurements at each time point were analyzed by Mann-
 242 Whitney *U* tests. Longitudinal analysis of the biophysical skin
 243 measurements was performed by mixed analyses of variance
 244 (ANOVAs) with time (between the RT dose of 40 Gy and
 245 66 Gy) as within-subject factor and group (control vs.
 246 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 signifi-
 cance 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 regi-
 men 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

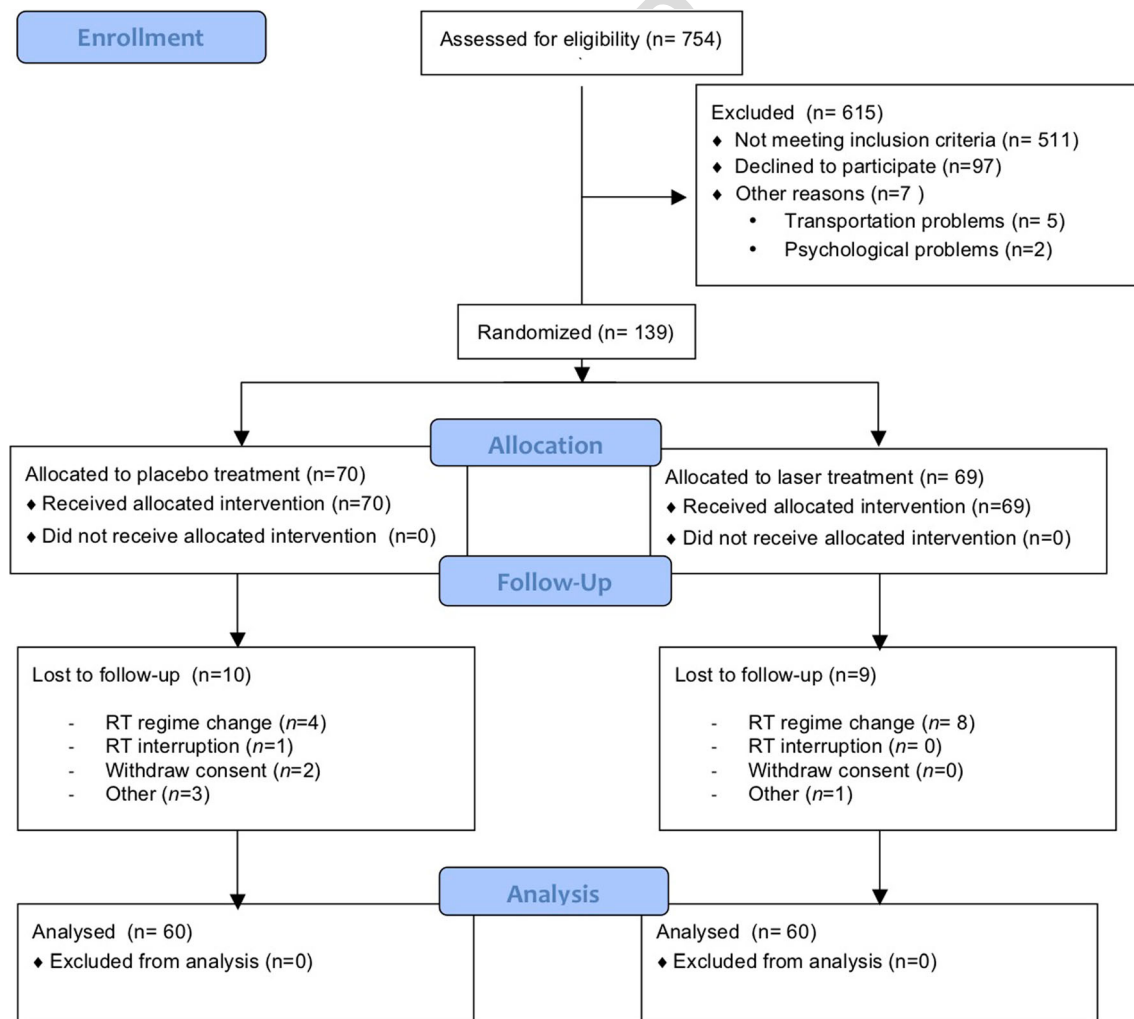


Fig. 1 CONSORT flow chart [14]

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

264 **Clinical evaluation of ARD**

265 Patients' RT-induced skin reactions were evaluated by the
 266 criteria of the RTOG, as shown in Table 3. Our results dem-
 267 onstrated that the incidence of moist desquamation (ARD
 268 grade 2 or higher) was significantly lower in the PBMT group
 269 in comparison with the control group at the end of RT ($p =$
 270 0.004). This was confirmed by the univariate logistic regres-
 271 sion analysis demonstrating that patients only receiving the
 272 standard skin care were six times more likely to develop moist
 273 desquamation in comparison with patients that also were treat-
 274 ed with PBMT ($p = 0.003$, 95% CI [OR] 1.881–19.82).
 275 Further, the risk on moist desquamation rose with an increas-
 276 ing breast volume. As such, patients with large breasts ($>$
 277 800 cc) had a four times higher risk to develop moist desqua-
 278 mation than patients with small breast volumes ($p = 0.017$,
 279 95% CI [OR] 1.290–12.936).

280 **Objective evaluation of ARD**

281 **Erythema**

282 The mixed 2×2 ANOVAs revealed a significant main
 283 time effect and group by time interaction ($ps < 0.05$) for
 284 the erythema index. However, the main group effect was

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)

not significant. As depicted in Fig. 2a, the degree of ery-
 themata in both groups increased during the course of RT.
 At the RT dose of 40 Gy, the percentage change in ery-
 themata 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 erythe-
 ma was significantly higher in the control group in com-
 parison with the PBMT group ($p = 0.016$).

t2.1 **Table 2** Patient and treatment characteristics

	Control group ($n = 60$)	PBMT group ($n = 60$)	p^a
t2.3 Mean age (SD), years	56.92 (10.34)	56.52 (10.54)	0.88
t2.4 Mean body mass index (SD)	25.03 (4.47)	25.27 (3.87)	0.63
t2.5 Mean breast size (SD) ^b , cc	796.27 (439.67)	742.55 (353.92)	0.67
t2.6 Breast size ^b , n (%)			0.97
t2.7 Small (< 450 cc)	11 (18.3)	12 (20)	
t2.8 Medium (450–800 cc)	26 (43.3)	26 (43.3)	
t2.9 Large (> 800 cc)	23 (38.3)	22 (36.7)	
t2.10 Prior chemo, n (%)	46 (76.6)	44 (73.3)	0.83
t2.11 RT energy level, n (%)			0.19
t2.12 6 MV	43 (71.7)	50 (83.3)	
t2.13 6 MV + 15 MV	17 (28.3)	10 (16.7)	
t2.14 Boost type, n (%)			0.86
t2.15 Photons	31 (51.7)	29 (48.3)	
t2.16 Electrons	29 (48.3)	31 (51.7)	
t2.17 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

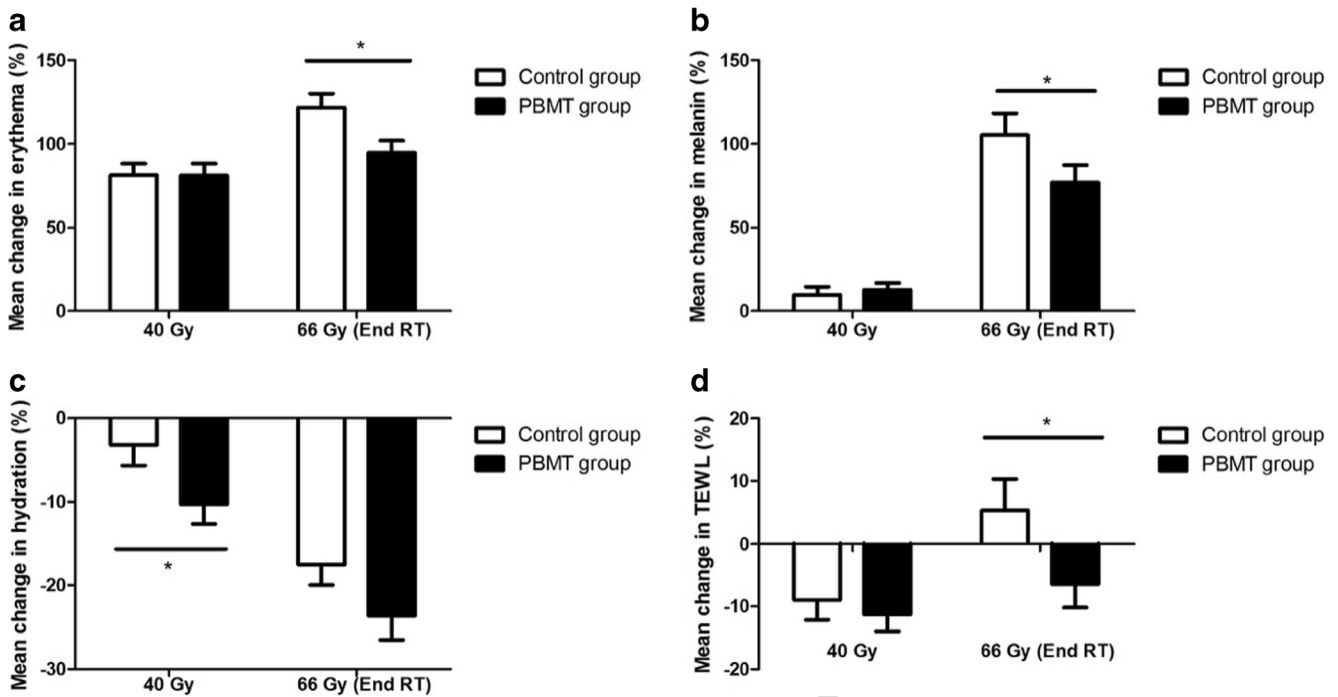


Fig. 2 Evaluation of the skin pigmentation (erythema (a) and melanin (b)) and barrier function (hydration (c) and TEWL (d)) by biophysical measurements. Data are shown as mean percentage change from baseline (\pm SEM). *Significant difference between the two groups at the indicated

time point ($p < 0.05$; Mann-Whitney U test, two-tailed). TEWL, transepidermal water loss; PBMT, photobiomodulation therapy; RT, radiotherapy

293 **Pigmentation**

294 Concerning the melanin index, there were both a signif- 317
 295 icant main time effect and group by time interaction (p_s 318
 296 < 0.05), but no significant main group effect. Figure 2b 319
 297 demonstrates that the degree of pigmentation increased 320
 298 during the progression of RT in both groups. The incre- 321
 299 ase in pigmentation started off slowly, with no signif- 322
 300 icant difference in percentage change over baseline in 323
 301 melanin between the two groups at the RT dose of 324
 302 40 Gy. Towards the end of RT, the melanin index was 325
 303 significantly higher in the control than in the PBMT 326
 304 group ($p = 0.019$).

305 **Hydration**

306 The mixed 2×2 ANOVAS revealed a significant main 327
 307 time and group effect ($p_s < 0.05$), but no significant group 328
 308 by time interaction for the skin moisture level. As shown 329
 309 in Fig. 2c, during the course of RT, the skin hydration 330
 310 level decreased in both groups in comparison with the 331
 311 baseline values. The skin hydration level was significantly 332
 312 lower at the RT dose of 40 Gy in the PBMT group in 333
 313 comparison with the control group ($p = 0.036$). However, 334
 314 at the end of RT, both groups showed a comparable skin 335
 315 moisture index. 336

316 **Transepidermal water loss**

317 Regarding the TEWL, there was a significant main time and 318
 319 group effect ($p_s < 0.05$), but no significant group by time in- 320
 321 teraction. The TEWL decreased in comparison with the base- 321
 322 line value in both the control and PBMT groups at the RT dose 322
 323 of 40 Gy, to a comparable level (Fig. 2d). Towards the end of 323
 324 RT, the TEWL level increased in both groups, although the 324
 325 final TEWL index was significantly lower in the PBMT group 325
 326 in comparison with the control group ($p = 0.05$). 326

327 **Discussion**

328 Results of this trial show that PBMT is an effective tool to 327
 329 prevent the development of moist desquamation. This was 328
 330 confirmed by objectively evaluating the skin's biophysical 329
 331 condition. Our results demonstrated that PBMT was able to 330
 332 reduce the increase in the skin's pigmentation level and im- 331
 333 prove the skin barrier function. Additionally, the main risk 332
 334 factor for the development of severe ARD is the breast vol- 333
 335 ume, which implies that patients with large breasts (> 800 cc) 334
 336 have an increased risk on moist desquamation. 335

337 The erythema index progressively increased during RT in 336
 338 both treatment arms. These findings are in line with previous 337
 339 studies [22–25]. This increase in erythema is caused by the 338

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

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

364 In healthy skin, a low TEWL and a high hydration
 365 value correlate with a good barrier function [36].
 366 Ionizing radiation deregulates the cellular function and
 367 causes apoptosis of the epidermal cells, resulting into an
 368 affected skin barrier function, correlated with a high
 369 TEWL and a low skin moisture level [6, 27, 37, 38].
 370 The findings in our control group are in line with these
 371 studies. However, in the PBMT group, both the TEWL
 372 and hydration index were significantly decreased at the
 373 end of RT. The epidermal thickening effect might explain
 374 these conflicting results. This effect is characterized by
 375 epidermal hyperproliferation leading to a thickened stratum
 376 corneum (outermost layer of the epidermis) caused by
 377 repetitive exposure to external stimuli. The thickening of
 378 the stratum corneum improves the skin barrier function
 379 and thereby it is correlated with a decrease in TEWL
 380 [38, 39]. Several studies, both in vitro and in vivo, have
 381 demonstrated that PBMT can stimulate the proliferation of
 382 several types of cells, including keratinocytes. PBMT
 383 seems to be able to stimulate the epidermal thickening
 384 effect in the skin caused by RT and thereby it can improve
 385 the skin barrier function [40–43].

386 The results of the logistic regression analysis demon-
 387 strated that patients who were treated with standard skin
 388 care had a six time higher risk to develop moist desqua-
 389 mation in comparison with the patients treated with
 390 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 pub-
 lished 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 reg-
 imen. 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 reduc-
 ing the incidence of moist desquamation in breast cancer pa-
 tients. 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 pa-
 tients. 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 proce-
 dures performed in the study were in accordance with the ethical stan-
 dards 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
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Q5 439

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AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES.

- Q1. Please check if the affiliations are presented correctly.
- Q2. Please check if the article note is presented correctly.
- Q3. Please check if the section headings are assigned to appropriate levels.
- Q4. Tables 1, 2, 3, and 4 were slightly modified. Please check if data are presented correctly.
- Q5. Please supply/verify the standard abbreviation of the journal name in References Robijns and Laubach (2018) and Barolet (2018).

UNCORRECTED PROOF