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Original Article

Photobiomodulation therapy for the prevention of acute radiation dermatitis in head and neck cancer patients (DERMISHEAD trial)

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ABSTRACT

Background and purpose: The purpose of this study was to investigate the effectiveness of photobiomodulation therapy (PBMT) for the prevention of acute radiation dermatitis (ARD) in head and neck cancer (HNC) patients.
Materials and methods: A randomised, placebo-controlled trial (RCT) with 46 HNC patients who underwent radiotherapy (RT) with or without concomitant chemotherapy was set up (DERMISHEAD trial). Patients were randomised to receive PBM or placebo treatments from the first day of RT (2×/week) alongside the institutional skincare. The severity of skin reactions was assessed by the National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.03 (NCI-CTCAE v4.03) and the Radiotherapy-Induced Skin Reaction Assessment Scale (RISRAS). Quality of life (QoL) was evaluated using the Skindex-16 questionnaire.
Results: PBMT significantly reduced NCI-CTCAE grade 2–3 ARD with 49% at the end of RT.
Conclusion: The results of the first RCT in HNC patients showed that PBMT is an effective method to prevent the development of severe ARD. These results support the implementation of PBM in the clinical oncology – radiotherapy practice.

Head and neck cell cancer (HNC) is the sixth most common cancer type worldwide with 710 235 new cases in 2018 [1]. Head and neck cancers cover a heterogeneous group of tumours arising from the pharynx, larynx, sinuses, salivary glands, and oral cavity. The optimal management of HNC requires a multidisciplinary approach. Radiotherapy (RT) plays a vital role in managing HNC next to surgery, chemotherapy, targeted therapy and/or immunotherapy [2].

One of RT's most common side effects is acute radiodermatitis (ARD), an inflammatory skin reaction. Almost all HNC patients will develop some degree of ARD during RT, ranging from mild erythema or dry desquamation to, in some cases, moist desquamation [3]. ARD results from RT damage to the stem cells' mitotic ability within the basal layer of the epidermis, leading to a disruption in the skin's self-renewing property. The degree to which skin reactions develop depends on the survival of actively proliferating basal cells in the epidermis. In the first instance, erythema develops caused by increased vascular permeability and vasodilation. This is followed by an inflammatory response leading to a secondary erythematous reaction. The skin will compensate for the RT damage by increasing its mitotic rate in the basal epidermal cell layer. When new cells' turnover is faster than the old cells' shedding, a thickened, dry, scaly skin will develop (i.e., dry desquamation). Finally, moist desquamation arises if all the stem cells in the basal layer are destroyed [4].

The risk of severe ARD (i.e., moist desquamation) depends mainly on RT parameters (e.g., dose per fraction, total dose, the volume of the irradiated area, fractionation regimen). Also, chemotherapy or targeted therapy with RT makes the skin cells more susceptible to DNA damage, leading to more severe skin reactions. Furthermore, patient-related risk factors (e.g., genetics, skin type, comorbidities, obesity, nutritional and smoking status) play a role in ARD [5].

Acute RT-induced skin reactions are associated with itching, discomfort, burning sensation, and pain, affecting the patient's quality of life (QoL) [6]. In rare cases of extreme ARD, the treatment

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protocol needs to be delayed or even interrupted, compromising treatment outcome [7].

Concerning the prevention and management of ARD, there is still no general standardised protocol due to the low availability of evidence-based research. There are a wide variety of topical and oral agents but the scientific efficacy is still missing [8]. The most recent guidelines on the prevention and management of ARD were published in 2013 by the expert panel of the Multinational Association for Supportive Care in Cancer (MASCC) [9]. Therefore, it is necessary to continuously evaluate new potential prevention and management options for ARD to improve the supportive care of HNC patients [10,11].

Photobiomodulation therapy (PBMT) implies the application of visible or (near)-infrared light produced by laser diodes or light-emitting diodes (LEDs) to stimulate wound healing, reduce inflammation, and diminish pain [12,13]. Our research group's recent narrative review showed that based on nine clinical trials, PBMT could effectively reduce the incidence of severe ARD, decrease the accompanying pain, and improve the patients' QoL [14]. Up to now, there was only one non-blinded randomised controlled trial (RCT) with HNC patients, demonstrating beneficial results [15].

This multicentric, placebo-controlled RCT aimed to evaluate the efficacy of PBMT in the prevention of ARD in HNC patients. Secondarily, the patients' QoL was assessed.

Materials and methods

Study design and setting

This multicentric, prospective, placebo-controlled RCT compared PBMT and standard skin care in HNC patients undergoing RT. The patients were treated at the RT department of Jessa Hospital (Hasselt, BE) or Ziekenhuis Oost-Limburg (Genk, BE) between January 2016 and January 2020. Both hospitals are embedded in the Limburg Oncology Centre (LOC), which is a non-profit organisation that manages and operates the RT services of the two distinct hospitals. The study was approved by the ethics committees of the Jessa Hospital, Ziekenhuis Oost-Limburg, and the University of Hasselt (B243201526141) and was conducted according to the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (NCT02738268).

Study population

Patients were eligible for enrolment in the study if they received primary radiotherapy with or without concomitant chemotherapy (Cisplatinum or Carboplatinum) or postoperative radio(chemo)therapy for a tumour of the head and neck. They were only eligible if they were treated with bilateral elective neck RT with a minimal total dose of 50 Gy EQD2 to both sides of the neck. Exclusion criteria were previous irradiation in the head-neck area, metastatic disease, the use of targeted-therapy, and pre-existing skin conditions or open wounds in the treatment area. Additionally, patients with medical, psychological, or social conditions that would interfere with the participation in the study or evaluation of the results were also excluded. All participants had to sign the written informed consent before the start of the study.

Randomisation and blinding

Eligible patients were stratified based on their treatment regime (i.e., RT alone or with chemotherapy), followed by a random allocation (1:1) of the patients to the PBM or control group. Patients were allocated based on a block randomisation process, with a block size of 4 using a computer-generated random number list. Only the device operator knew the allocation of the patients in the groups. All patients were blinded during the treatment sessions by using eye shields.

Table 1
Photobiomodulation parameters.

	PBM parameters		
Device information	Manufacturer	ASA srl	
	Model Identifier	MLS® laser M6	
	Year Produced	2012	
	Number of Emitters	1	
	Emitter Type	IR laser diodes	
	Beam Delivery System	Handpiece	
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 (1–2000 Hz)	
	Pulse on duration	100 ns single pulse width	
	Duty cycle	50%	
	Aperture diameter	2 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	3.14 cm^2	
	Irradiance at target	0.168 W/cm^2	
	Radiant exposure (fluence)	4 J/cm^2	
	Number of points irradiated	Head and bilateral neck region	
	Exposure duration	±300–600 s	
	Application technique	5 cm above skin with manual device	
	Timing	After the RT session	
	Frequency of treatment sessions	Biweekly from the first until the last day of RT over a period of 7 weeks (14 sessions in total)	

Interventions

Radiotherapy

The RT plan was prepared using a 3D-planning system (Eclipse™, version 11.0, Varian Medical System, Palo Alto, CA) [16]. All patients received intensity modulated RT (IMRT) by means of volumetric modulated arc therapy (VMAT) (RapidArc®, Varian Medical System, Palo Alto, CA) consisting of two arcs delivering 6 MV photons. All participants received a simultaneous integrated boost (SIB-IMRT) on the tumour site and/or on positive nodes. When RT was applied postoperatively a dose of 30 × 2 Gy was delivered to the boost region and 30 × 1.8 Gy to the bilateral elective nodes. In case of extracapsular spread or a positive surgical margin a dose of 33 × 2 Gy was applied to the boost region and 33 × 1.65 Gy to the bilateral elective node regions. In a curative setting, a dose of 35 × 2 Gy was applied to the boost region and 35 × 1.55 Gy to the bilateral elective nodes.

Institutional skin care

All patients received the institutional standard skin care, which encompassed 3×/day application of topical, hydroactive colloid gel (Flamigel®, Flen Pharma, Kontich, Belgium), from the first day of RT. In case of a painful skin reaction and/or moist desquamation, a foam, absorbent, self-adhesive silicone dressing (Mepilex®, Mölnlycke Health Care, Gothenburg, Sweden) was used. Additionally, the RT nurses advised the patient to follow the general skin care guidelines (e.g., no tie, no electric shaving, no aftershave, gentle washing with or without mild soap, patting dry with a soft towel instead of rubbing).

Photobiomodulation

PBM 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) [17]. 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 [18,19]. The complete list of PBM parameters can be found in Table 1. During the sham treatments the PBM device did not emit light. All patients, independently of their treatment group, wore safety glasses and eye shields to prevent eye damage and blind them during the PBM or sham sessions.

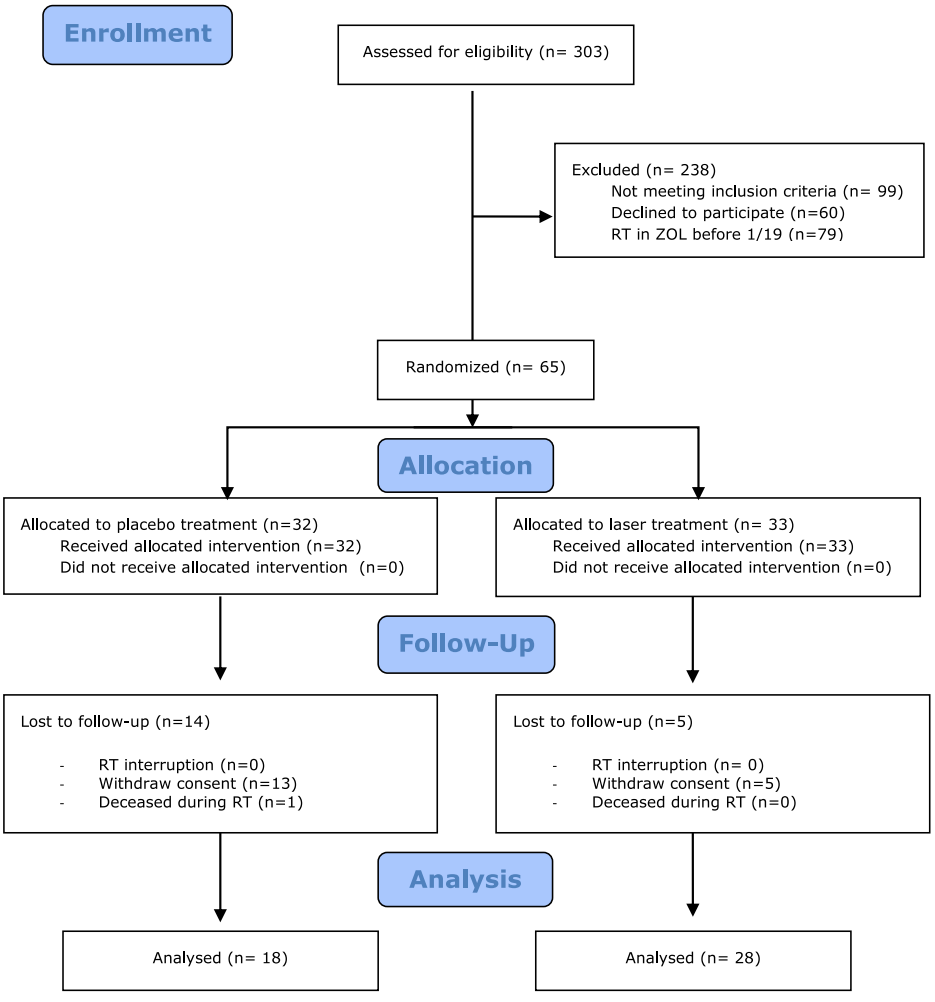

Fig. 1. CONSORT flowchart. RT, radiotherapy; ZOL, Ziekenhuis Oost-Limburg.

Outcome measures

Patient data

Patient's personal, disease- and treatment-related characteristics were collected via patient questionnaires and the patient's medical charts to rule out possible risk factors.

Skin toxicity grading

Two different grading systems were used to score the severity of the skin reactions. The NCI-CTCAE v4.03 is the most commonly used grading system for ARD in head and neck cancer patients [20]. Besides, the Radiation-Induced Skin Reaction Assessment Scale (RISRAS) was used, which encompasses a researcher ("objective") and a patient ("subjective") score [21,22]. Two experienced RT nurses evaluated the skin toxicity in a blinded manner. All the previously described measurements were collected on three time points: on the first day of RT, at an RT dose of 40 Gy, and on the last day of RT (60–70 Gy).

Quality of life

The patient's QoL was assessed by using the Skindex-16 [23]. This is a validated, 16-item self-assessment questionnaire that measures the extent to which the patients' lives are 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 QoL. QoL measures were collected at RT dose of 40 Gy and at the end of RT.

Sample size calculation

The incidence of skin toxicity of grade $\geq$2 observed during head and neck irradiation in combination with standard skin care was estimated to be 70% based on previous literature [24,25]. The objective of this study is to demonstrate a 35 % decrease in the incidence of CTCAE grade 2–3 skin reactions in the PBM treated group. To detect this difference with a power of 80% using a two-sided test at significance level 0.05, it is necessary to recruit 62 patients.

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,

Table 2
Baseline demographic patient characteristics.

	Control group (n = 18) Mean ± SD		PBM group (n = 28) Mean ± SD		p[a]
Age (years)	65.06 (10.37)		64.06 (11.78)		0.97
Body Mass Index (BMI)	25.61 (3.58)		25.79 (5.68)		0.18
	n	%	n	%	P[b]
Gender					0.69
Male	16	88.9	23	82.1	
Female	2	11.1	5	17.9	
WHO skin type classification[c]					0.39
Melano-compromised	0	0	3	10.7	
Melano-competent	15	83.3	20	71.4	
Melano-protected	2	11.1	3	10.7	
Missing	1	5.6	2	7.2	
Smoking status					0.14
Never smoked	1	5.6	7	25	
Former smoker	13	72.2	18	64.3	
Current smoker	4	22.2	2	7.2	
Missing	0	0	1	3.5	
Pack years					0.27
0	1	0	7	25	
<30	4	22.2	7	25	
30–39 years	4	22.2	7	25	
40–49 years	5	27.8	4	14.3	
> 50 years	4	27.8	2	7.2	
Missing	0	0	1	3.5	
Number of cigarettes					0.23
0	1	5.6	7	25	
<10	1	5.6	5	17.9	
10–19	5	27.7	6	21.4	
20–29	8	44.3	7	25	
30–39	1	5.6	0	0	
>40	1	5.6	2	7.2	
Missing	1	5.6	1	3.5	
Alcohol consumption (drinks/week)					0.29
0–1	3	17.6	12	42.9	
3-Jan	5	29.4	5	17.9	
10-Mar	5	29.4	7	25	
20-Oct	4	23.5	3	10.7	
>20	1	5.6	0	0	
Missing	0	0	1	3.5	

BMI, Body Mass Index; PBM, photobiomodulation; SD, standard deviation; WHO, World Health Organisation.
[a] Student *t*-test or Mann–Whitney *U* -test, as appropriate (two-tailed).
[b] Chi-square tests, or Fisher's exact tests, as appropriate (two-tailed).
[c] WHO skin type classification is based on Fitzpatrick's phototype scale: melano-compromised (Fitzpatrick's skin type I–II), melano-competent (skin type III–IV), and melano-protected (skin type V–VI).

as appropriate. NCI-CTCAE scores were analysed using χ^2 or Fisher's exact tests, as appropriate. The differences in RISRAS and Skindex-16 scores between groups were analysed with the Mann–Whitney *U* test. The level of statistical significance for all analyses was set assuming a significance level of 5% ($P < 0.05$, two-tailed). SPSS 26.0 (IBM, Chicago, IL) was used for all analyses.

Results

A total of 303 HNC patients were assessed on eligibility between January 2016 and January 2020. Eventually, 65 patients were enrolled in the study and randomised into the PBM or control group. In total 19 patients were lost for follow-up with as main reason, withdrawn informed consent. The preliminary analysis was performed on 46 patients with 18 patients in the control and 28 patients in the PBM group (Fig. 1). There were no significant differences between the demographical and treatment-related data between the two groups (Tables 2 and 3).

At the RT dose of 40 Gy there was no significant difference in skin toxicity between the control and PBM group ($p = 0.57$). As demonstrated in Fig. 2(A and B), most of the patients developed a grade 1 skin reaction (70.6% vs. 84%, in the control and PBM group, resp.). Towards the end of RT, the number of severe skin reactions (grade 2–3) increased significantly ($p = 0.01$) in the control group. On the contrary, in the PBM group the development of ARD remained stable ($p = 0.21$). As such, there was a significant difference in skin toxicity between the two groups at the end of RT, with a higher percentage of patients presenting a grade 2–3 in the control group (77.8% vs. 28.6%, in the control and PBM group, resp., $p = 0.002$).

The patients in the PBM group reported lower median RISRAS scores than the control group at both RT dose 40 Gy and the end of RT. However, these findings were not statistically significant (Fig. 2C and D).

No significant differences were detected between the two groups at RT dose of 40 Gy and at the end of RT regarding the patients' QoL (Fig. 3).

Discussion

After the successful results in the management of ARD in breast cancer patients, we set up the DERMISHEAD trial to investigate if PBM could be effective in HNC patients [26,27]. To our knowledge, this is the first placebo-controlled RCT that demonstrates that PBM can effectively reduce the severity of ARD in HNC patients. In the PBM group, 29% demonstrated grade 2 ARD, while no one had ARD grade 3. On the other hand, 61% of the control patients developed grade 2 ARD, while 17% developed grade 3. Consequently, grade 2–3 ARD incidence significantly diminished, with 49% by PBM at the end of RT. The overall RISRAS score increased in both groups, though no significant group differences were detected. The patients' QoL between both groups did not significantly differ.

These results are in line with a recent narrative review on the use of PBMT for the prevention and management of ARD. Based on nine clinical trials in both breast and HNC patients, the researchers concluded that PBM can significantly reduce the severity of ARD and especially the more severe forms of ARD (grade 2–3) [14]. To date, only two clinical trials investigated the use of PBM in HNC patients. Zhang et al. performed a non-blinded RCT with 60 HNC patients. The control group ($n = 30$)

Table 3
Disease and treatment-related characteristics.

Characteristic	Control group ($n = 18$)		PBM group ($n = 28$)		
	n	%	*n*	%	*p*[a]
Disease-related					
Tumour site					0.13
Oropharynx	6	33.3	13	46.4	
Larynx	6	33.3	4	14.3	
Oral cavity	4	22.3	10	35.7	
Salivary gland	0	0	1	3.6	
CUP	2	11.1	0	0	
T-stage					0.66
is	2	11.1	1	3.6	
1	1	5.6	3	10.7	
2	8	44.4	11	39.3	
3	4	22.2	9	32.1	
4	3	16.7	4	14.3	
N-stage					0.42
0	5	27.7	8	28.6	
1	3	16.7	10	35.7	
2	9	50	8	28.6	
3	1	5.6	2	7.1	
Treatment-related					
Surgery	9	50	16	57.1	>0.99
Concomitant chemotherapy	6	33.3	11	39.3	0.76
RT regimen					
-Postoperative					
30 × 2 Gy boost[b] + 30 × 1.8 Gy elective neck[c] (5/wk)	6	33.3	8	28.6	0.73
-Postoperative + extracapsular spread or positive margin					
33 × 2 Gy boost[b] + 33 × 1.65 Gy elective neck[c] (5/wk)	1	5.6	3	10.7	0.54
-Curative					
35 × 2 Gy boost[b] + 35 × 1.55 Gy elective neck[c] (5/wk)	10	55.5	15	53.6	0.9
35 × 2 Gy boost[b] + 35 × 1.55 Gy elective neck[c] (6/wk)	1	5.6	2	7.1	0.84

CUP, Carcinoma of unknown primary; PBM, photobiomodulation.
[a] Chi-square tests, or Fisher's exact tests, as appropriate (two-tailed).
[b] Simultaneous integrated boost (SIB) on tumour and/or positive lymph nodes.
[c] Bilateral lymph nodes.

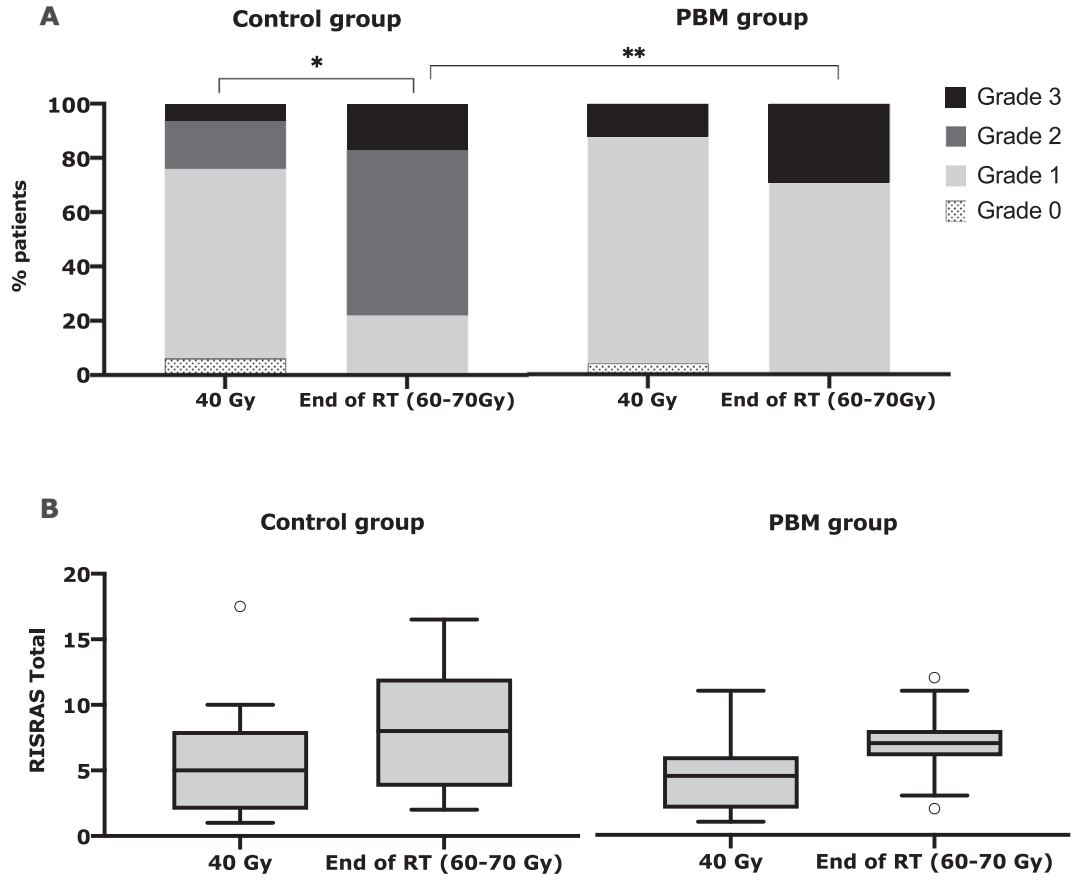

Fig. 2. Severity of the skin reactions. (A) *NCI-CTCAE v4.03:* ARD severity (grade 0–3) in control and PBM group evaluated at RT dose 40 Gy and the end of RT (60–70 Gy). *Significant difference within the control group measured by the Wilcoxon Signed-rank test ($p = 0.01$). **Significant difference between the control and PBM group at the end of RT based on χ^2 – test ($p = 0.002$). (B) *RISRAS:* Tukey boxplots of the total RISRAS-scores (sum of the patient score and investigator score) in the control and PBM group at RT dose 40 Gy and end of RT. Higher scores indicate a more severe skin reaction. For each boxplot the solid line indicates the median; the box indicates the interquartile range (IQR); the whiskers indicate the range excluding outliers; and the circles indicate outliers, points more than 1.5 IQR from the box. No significant differences were detected. *ARD, acute radiodermatitis; NCI-CTCAE, National Cancer Institute – Common Terminology Criteria for Adverse Events; PBM, photobiomodulation; RISRAS, Radiotherapy-Induced Skin Reaction Assessment Scale; RT, radiotherapy.*

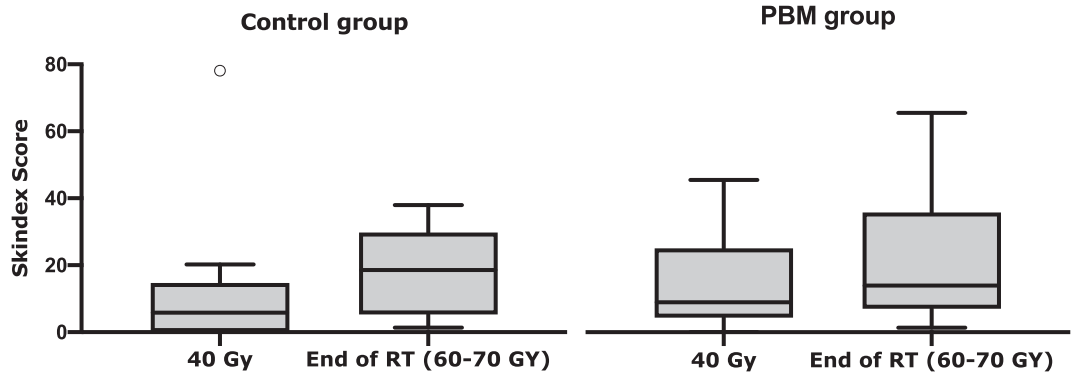

Fig. 3. Quality of life. Tukey boxplots of the total Skindex-16 scores of the control and PBM group assessed at RT dose 40 Gy and end of RT. Higher scores indicate a lower QoL. For each boxplot the solid line indicates the median; the box indicates the interquartile range (IQR); the whiskers indicate the range excluding outliers; and the circles indicate outliers, points more than 1.5 IQR from the box. No significant differences were detected. *PBM, photobiomodulation; QoL, quality of life; RT, radiotherapy.*

received the institutional standard care comprising a skin protective agent, skin self-care, and health education. Further saline cotton balls with 0.9% normal saline were used to gently clean the wound and remove necrotic tissue, followed by drying the wounds with sterile gauze. The PBM group ($n = 30$) was treated with PBM (2×/day) alongside the institutional skin care protocol. They did not mention specific PBM parameters, which makes it hard to compare it with our trial. The Radiation Therapy Oncology Group (RTOG) criteria were used for grading the skin reactions. Overall, the severity of ARD was significantly lower in the PBM group than in the control group. About 40% of the patients in the PBM group developed grade 2 skin reactions, while no one presented grade 3 ARD. In the control group, 93% of the patients presented grade 2–3 ARD, with 30% grade 3 skin

reactions [15]. Park et al. conducted a pilot trial with 33 HNC patients. They all received institutional skin care, which included a topical moisturiser (2×/day). In case of a painful skin reaction, a foam, absorbent, self-adhesive silicone dressing was used. Topical antibiotics were applied in case of a bacterial infection. All patients underwent PBM (3×/week, 590–830 nm, 60 J/cm^2, 100 mW/cm^2). At the end of RT, approximately 39% of the patients presented a grade 2 skin reaction, while no grade 3 ARD was present [28]. These results are in line with our trial as the DERMISHEAD trial showed that about 29% of the patients in the PBM group presented a grade 2 ARD and no grade 3 skin reactions at the end of RT.

The DERMISHEAD trial results are comparable to those of our previously published RCT in breast cancer patients (TRANDERMIS trial), as both studies demonstrate a lower incidence of moist desquamation after PBM [27]. An interesting difference between the two trials is that the percentage decrease in severe ARD was higher in the DERMISHEAD trial than the TRANSDERMIS trial (49% vs. 23%, resp.). This difference can be rationalised because in total more control HNC patients group developed grade 3 ARD than control breast cancer patients (17% vs. 5%). A possible explanation for this finding can be related to the difference in treatment parameters between the two trials.

Other clinical trials investigating the incidence of grade 2–3 ARD in HNC patients even demonstrated higher incidences [25]. For example, a study by Iacovelli et al. showed that 78% of the HNC patients presented grade 2 or higher ARD after a 7-week IMRT period with a median dose of 70 Gy. All patients received Xonrid®, a topical water-based gel, as a pre-emptive treatment for ARD [24]. In the trial by Tao et al., 73% of the HNC patients developed moist desquamation after RT (total dose 70 Gy) combined with Cetuximab. Skincare consisted of a regenerating agent, which is an alternative wound healing approach using innovative-engineered biopolymers [29]. Chan et al. demonstrated in a single-blind, randomised controlled trial comparing a silicone-based film forming gel dressing versus 10% Glycerine (Sorbolene cream), that 41% in the dressing group and 49% in the cream group developed grade 3 ARD. In a RCT by Menon et al. topical betamethasone was compared with the institutional standard skincare in 121 HNC patients. 33% versus 51% of the patients developed grade 2 ARD and 20% versus 24% grade 3 ARD in the experimental and control arm, respectively [30]. These contrasting numbers on severe ARD are due to differences in the treatment protocol (e.g., total RT dose, use of concomitant therapies, the volume of the treated area) and the standard skincare used [6].

Our RCT is not without limitations. Based on a sample size calculation, a total of 62 patients was needed to detect significant differences between the two groups. In the first instance, a total of 65 patients were randomised into the two study groups. However, 19 patients were lost to follow-up with most of the patients withdrawing their informed consent due to patient-specific reasons. Patients with HNC often have poor physical and psychosocial health even before starting their treatment trajectory. The main reason for the low adherence rates is the additional demand that study protocol put on the patient during an already burdensome period. Furthermore, other factors played a role in the attrition rate ranging from forgetting PBM sessions or the fact that patients did not experience skin problems at the start of the trial [31]. Previous clinical trials with HNC patients already described this low adherence rate [32–35]. However, our trial also has many advantages, including the randomised and multicentric design, the blinding of patients and assessor, well-defined PBM parameters, and the usage of validated grading tools and questionnaires.

Conclusion

The DERMISHEAD trial proved that PBMT significantly reduces the severity of ARD. Thereby, it improves the patients' QoL during their RT course. The trial supports the further implementation of PBM in the supportive care of cancer patients undergoing RT.

Conflict of interest

The authors declare that they have no competing interests.

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