A novel, multi-active emollient for the prevention of acute radiation dermatitis in breast cancer patients: a randomized clinical trial

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TITLE PAGE

Title

A novel, multi-active emollient for the prevention of acute radiation dermatitis in breast cancer patients: A Randomized Clinical Trial

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Authors contribution

Conceptualization: J.R., J.M.; Methodology: J.R., J.M.; Formal analysis: J.R.; Investigation: J.R., L.V.B., S.H., M.C., J.L., L.T., M.L., E.V., J.M.; Writing – original draft: J.R.; Writing – review and editing: J.R., M.C., J.L., M.L., L.T., L.V.B., S.H., J.M., E.V., L.N., A.M., L. V. D. B., P. B., PH. B., A. S. V. D. V., K.V, E.V.;

Availability of data and material (data transparency)

Not applicable

Code availability

Not applicable

Declarations

Conflicts of interest

The authors declare that they have no conflict of interest.

Ethics approval

The ethical committees of the Jessa Hospital and the University of Hasselt approved the trial (B2432021000014).

Consent to participate

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

Consent for publication

Not applicable.

ABSTRACT

Purpose

To investigate the efficacy of a novel, multi-active emollient in preventing and managing acute radiation dermatitis (ARD) in breast cancer patients undergoing moderate hypofractionated (HF) radiotherapy (RT) compared to standard of care.

Methods

A monocentric, open-label, randomized clinical trial (RCT) with breast cancer patients receiving moderate HF (dose: 40.05-55.86Gy, fractions:15-21) was conducted between January 2022 and May 2023. The experimental group received the novel emollient, while the control group received the standard skin care. Patients applied the skin care products twice daily during the complete RT course. The primary outcome was the severity of ARD at the final RT session measured by the modified Radiation Therapy Oncology Group (RTOG) criteria. Secondary outcomes included patient symptoms, quality of life (QoL), and treatment satisfaction.

Results

A total of 100 patients with 50 patients per group were enrolled. In the control group, 50% of the patients developed RTOG grade 1 ARD and 48% grade 2 or higher, while in the experimental group, the severity of ARD was significantly lower with 82% grade 1 and 16% grade 2 ARD ($P = .013$, χ^2-test). The frequency and severity of xerosis were significantly lower in the experimental compared to the control group (Ps $\leq .036$, Mann Whiney U-test). The impact of ARD on the QoL was low, and treatment satisfaction was high in both groups, with no significant difference.

Conclusion

This RCT shows that the novel, multi-active emollient significantly reduced the ARD RTOG grade. Research in a more diverse patient population is warranted.

Trial registration number

ClinicalTrials.gov:NCT04929808(11/06/2021)

Keywords

Acute radiation dermatitis; Emollients; Radiodermatitis; Radiotherapy; Skin care; Skin toxicity

MANUSCRIPT

Introduction

Radiotherapy (RT) remains vital in managing cancer, with worldwide around 10 million people needing it in 2020 [1, 2]. Acute radiation dermatitis (ARD), an inflammatory skin reaction, is a common side effect in patients undergoing RT, developing between two to four weeks after starting RT [3, 4]. RT affects the skin barrier function resulting in a low hydration level and a high level of transepidermal water loss, related to xerosis [5-7]. An impaired barrier function makes it easier for pruritogens to enter the skin and activate epidermal nerve fibers, causing pruritus [8, 9]. The severity of ARD depends on patient- and treatment-related factors [3, 4]. ARD can impact the patients' daily activities leading to a diminished quality of life (QoL) [10, 11]. Therefore, a proper skin care protocol should be available for all RT patients [12].

Multiple guidelines on ARD prevention and management are available from specialized organizations. To prevent skin dehydration, patients are instructed to use a topical emollient daily [13-17]. Based on the United States Cutaneous Oncodermatology Management (USCOM) algorithm, a topical skincare product for ARD should be moisturizing, free of allergens and scents, and have a physiological pH level [18, 19]. To date, no general recommendation of a specific topical agent for ARD is available due to the wide variety of studied products and the need for more scientific evidence [18, 19]. Considering the Multinational Association of Supportive Care in Cancer (MASCC) clinical practice guidelines published in 2023, the most promising interventions for ARD prevention and management were Mepitel® film, mometasone furoate, betamethasone, photobiomodulation, oral enzymes, and olive oil [17].

A novel, multi-active emollient has been developed for this trial [19, 20]. One of the components is calendula officinalis, which is a garden plant with large orange flowers. The raw extract of the flowers and leaves has a high level of carotenoids, flavonoids, and essential oils with demonstrated anti-inflammatory, antioxidant, antibacterial, and analgesic effects [21]. Another component with antioxidant and anti-inflammatory properties is olive oil [22]. The most important anti-dehydration ingredients of the emollient are Aquaxyl™ and hyaluronic acid. Aquaxyl™ stimulates collagen production, helps the skin absorb and retain moisture, and enhances the skin barrier function [23]. On the other hand, hyaluronic acid maintains tissue hydration but also plays a role in cell proliferation, differentiation, and the inflammatory response [24].

The aim of this project was to evaluate the effectiveness of the multi-active emollient on the management of ARD in comparison with the current standard of care in breast cancer patients. We hypothesized that the patients applying the novel, multi-active emollient presented a significantly lower degree of ARD than those applying the standard institutional skin care at the final RT session.

Materials and methods

Study design and setting

A monocentric, prospective, interventional, open-label, randomized clinical trial (RCT) evaluated a novel, multi-active emollient for preventing and managing ARD in breast cancer patients undergoing a moderate hypofractionated (HF) RT regimen. Eligible patients were recruited at the Department of Radiotherapy – Limburg Oncology Center at the Jessa Hospital (Hasselt, Belgium) between January 2022 and May 2023. The ethical committees of the Jessa Hospital and the University of Hasselt approved the trial (B2432021000014). The trial was set up according to the Declaration of Helsinki and registered at ClinicalTrials.gov (NCT04929808). This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline [25].

Patient selection

Patients diagnosed with breast cancer who were scheduled to receive moderate HF RT after lumpectomy or mastectomy, with or without systemic therapies, were recruited. Exclusion criteria included previous irradiation to the breast or chest wall, immunotherapy, metastatic disease, and pre-existing skin conditions (e.g., eczema, psoriasis, atopic dermatitis,) in the irradiated area. Patients with a medical, psychological, or other condition that was unstable or could affect the safety of the patient and their compliance in the study as judged by the investigator were excluded (e.g., mental issues, substance abuse,). Patients provided written informed consent before enrollment in the trial.

Randomization

Before randomization, patients were stratified based on their type of surgery (lumpectomy or mastectomy) and planning target volume (PTV): small (<450 cc), medium (450–800 cc), or large breasts (>800 cc). All recruited patients were randomly allocated (1:1) to the experimental or control group. Patients were allocated based on a variable block randomization process, with a block size of 2, 4, or 6, via an online software tool, CastorEDC. Researchers could not influence the randomization process.

Interventions

Radiotherapy protocol

An intensity modulation-capable linear accelerator (Varian Medical Systems, Palo Alto, SU) applying 6 MV photon beams was used for all patients. The set dose on the PTV was 40.05 Gy in 15 fractions or 42.56 Gy in 16 fractions on the whole breast or chest wall +/- regional lymph nodes if deemed necessary. When a boost was indicated, patients received a dose of 13.3 -13.35 Gy in 5 fractions on the tumor bed. If the boost volume was superficial, a single field of electrons was used, and otherwise photons using a partial VMAT arc were applied to the tumor bed. Anisotropic clinical target volume (CTV)-to-PTV margins of 10 mm in the craniocaudal and 7 mm in all other directions were applied for the breast volume. An isotropic margin of 7 mm was applied for the boost volume and lymph nodes. An in-house developed hybrid technique was used for treatment planning: min. 80% of the prescribed dose was delivered to the breast or chest wall using standard tangential beams and a multi-leaf collimator. Without nodal involvement, the residual 20% dose was delivered using static intensity modulated radiation therapy (IMRT) beams. In the case of positive nodes, patients were treated using the same base technique but three partial volumetric modulated arcs (VMAT) for the remaining 20% of the dose. Fluence extrapolation was conducted to guarantee the robustness of the treatment in all cases. Patients were lying on a dedicated breast board (ORFIT industries, Antwerp, Belgium) in a supine position with their arms supported above their heads. Online image guidance using cone beam computed tomography (CBCT) was used to ensure proper patient positioning daily. Patients with left-sided breast cancer were instructed to perform deep inspiration breath-hold (DIBH) during positioning and treatment. No boluses were used during RT.

Skincare protocol

All patients were instructed to follow the general institutional skincare guidelines (e.g., mild washing with or without a pH-neutral soap, patting dry with a soft towel, wearing no tight clothing and a non-wired bra or no bra, using no perfumed antiperspirants and perfume in the irradiated area, preventing exposure to extreme temperatures, swimming, sunbathing and application of wound plasters in the irradiated area were prohibited) during the complete course of RT. When patients experienced a painful skin reaction or moist desquamation, they could receive a foam, absorbent, self-adhesive silicone dressing (Mepilex®, Mölnlycke Health Care, Gothenburg, Sweden) to apply to the irradiated area [26]. Patients received oral and written instructions regarding the skin care protocol before start of RT.

The control group received a topical, hydroactive colloid gel (Flamigel®, Flen Pharma, Kontich, Belgium). It contains hydrocolloid, arginine, purified water, macrogol, Branch Chained Fatty Acid (BCFA), methyl-p-hydroxybenzoate (E218), propyl-p-hydroxybenzoate (E216), and disodium ethylenediaminetetraacetic acid (EDTA). The experimental group received the novel, multi-active emollient. It is a hydrating, soothing, and anti-oxidative cream containing calendula officinalis flower extract (0.5%), sodium hyaluronate, soluble collagen, xylitylglucoside, anhydroxylitol, xylitol, shea

butter oleyl esters, polyglyceryl-3 rice branate, hydrogenated ethylhexyl olivate, hydrogenated olive oil unsaponifiables, tocopherol, dimethicone, caprylic/capric triglyceride, cetylalcohol, carbomer, natrium phytate, glycerin, xanthan gum, caprylyl glycol, glycine soja oil, sodium benzoate, alcohol, and aqua.

Patients applied the experimental or control emollient twice daily during RT. In case of a painful or itchy inflammatory skin reaction, the physician could prescribe a topical corticosteroid cream, an antihistaminic, or a combination.

Outcomes

Experienced and nonblinded researchers (JR, EV, ML, LT) evaluated the patients' skin reactions using the modified version of the Radiation Therapy Oncology Group (RTOG) criteria at the first and the last RT session as the primary outcome (Figure 2). Each patient received an overall maximum score for their ARD on the complete irradiated area. In the modified version of the RTOG criteria grade 2 is split into grade 2A (tender or bright erythema +/- dry desquamation) and 2B (patchy moist desquamation, moderate oedema) [27]. As secondary outcomes, patient skin symptoms, QoL and, patient satisfaction were evaluated. The researchers evaluated the severity of pruritus based on the National Cancer Institute-Common Terminology Criteria for Adverse Events version 5 (NCI-CTCAE v5) at the first and final RT session [28]. The patients were asked to evaluate the intensity and frequency of five common symptoms of ARD: pruritus, xerosis, erythema, burning, and pain on an 11-point Numerical Rating Scale (NRS, 0 = no symptom present/no burden, 10 = worst symptom/high burden) at the first RT session, weekly, and at the final RT session. Patients' QoL was evaluated using the Skindex-29 questionnaire at the first and final RT session. It has three scales addressing emotions (10 items), symptoms (7 items), and functioning (12 items). Each item is scored on a five-point Likert scale, followed by a transfer to a linear scale (never=0, rarely=25, sometimes=50, often=75 and always =100). The overall and domain scores are the mean of all the responses and the responses per domain, respectively. A higher score is correlated with a poorer QoL. A score of 25 or higher implies a mild impact of the skin reactions on the QoL. A score of 32 or higher indicates a moderate impact, and a score of 44 or higher indicates a severe impact on patients' QoL [29-31]. Patients' general satisfaction with the skin care was rated on a five-point Likert scale (0, totally not satisfied/totally no recommendation – 5, very satisfied/very high recommendation) at the final RT session. Patients' adherence to the skin care protocol was questioned personally by the researcher and via an online questionnaire at the final RT session. The patient's personal, disease- and treatment-related characteristics were collected via patient questionnaires and medical charts.

Statistical analysis

As no preliminary data on using this novel topical agent for ARD existed, the researchers opted for a clinically relevant benefit considering an absolute reduction of the incidence of RTOG grades ≥2 of 25% due to the novel emollient. A sample size of 100 patients can detect such a difference with 80% power (using a two-tailed t-test with a significance level of 0.05). As appropriate, differences in patient-, disease-, and treatment-related characteristics were analyzed using unpaired student t-test, Mann-Whitney U-test, Fisher exact test, or Chi-Square (χ^2) test. The Wilcoxon Signed Rank and Friedman test analyzed within-group comparisons of continuous data. Bonferroni correction was used to counter the multiple testing. Between-group comparison of continuous data was analyzed by Mann-Whitney U-test and categorical data by χ^2 test or Fisher exact test, as appropriate. The effect of the novel emolient and the RTOG grade in relation to other potential confounding factors (e.g., PTV, chemotherapy, RT regimen, use of boost, smoking, endocrine therapy) was investigated by a multivariable linear regression analysis. The level of statistical significance for all analyses was set, assuming a significance level of 5% ($p < .05$, two-tailed). All the analyses were performed using SPSS 28.0 (IBM, Chicago, IL).

Results

Patient characteristics

Between January 2022 and May 2023, 221 breast cancer patients who were planned to undergo RT at the Limburg Oncology Center - Jessa Hospital (Hasselt, Belgium) were screened for eligibility. Eventually, 104 patients were randomized into the control or experimental group. In each group, two patients were lost for follow-up due to withdrawn consent before the start of the trial, resulting in a total of 100 patients for final analysis with 50 patients per group (Figure 1). The median age was 58 years (range 32-83), and the median BMI was 24.58 (range 18.83- 38.97). 42% of the control and 44% of the experimental patients received chemotherapy before RT. 82% of the control and 78% of the experimental patients underwent a lumpectomy. The most frequently used RT fractionation schedule was 16x 2.66 Gy + 5x 2.66 Gy, administered to 64% of the patients in each group. All patients, irrespective the study group, adhered the provided skin care protocol. An additional antihistaminic was used by 10% of the control and 6% of the experimental patients. 60% of the control and 52% of the experimental patients applied a foam silicone dressing on the irradiated area in addition to the standard skin care protocol. When patients presented a severe inflammatory itch, the physician prescribed 5 out of 50 control patients a corticosteroid cream and 3 out of 50 experimental patients. The corticosteroid cream was only applied on the inflamed area. On the other skin regions, the control or experimental emollient was applied. The measured patient-, disease-, and treatment-related characteristics were similar among the groups (Table 1-2).

Figure 1 Consolidated Standards of Reporting Trials Diagram

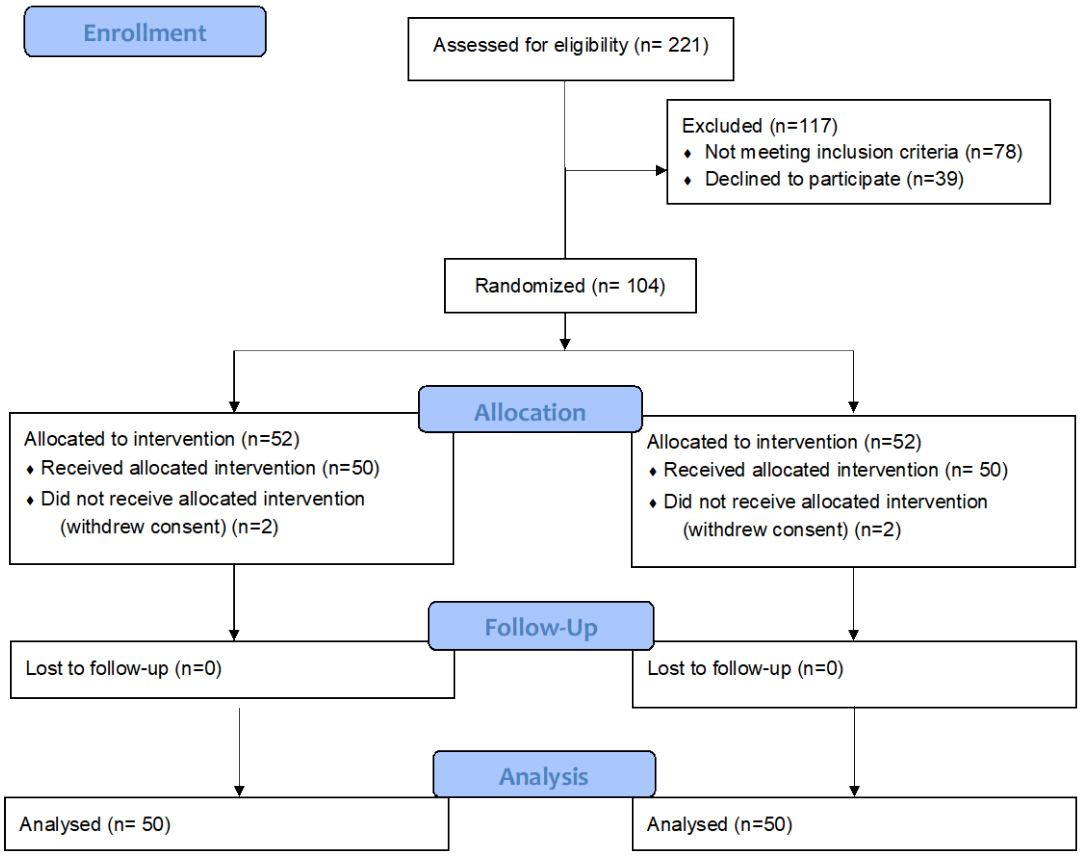


Table 1 Demographic Characteristics of Patients at Baseline

	Control group (n=50)	Experimental group (n=50)	
Patient-related	Mean (SD)	Mean (SD)	p[a]
Age (years)	58.12 (11.01)	60.18 (10.38)	0.34
Body Mass Index (BMI)	25.15 (3.5)	25.06 (3.91)	0.66
	N (%)	N (%)	P[b]
Breast size[c]			1
Small	5 (10)	5 (10)	
Medium	22 (44)	22 (44)	
Large	23 (46)	23 (46)	
WHO skin type classification[d]			0.87
Melano-compromised	9 (18)	10 (20.4)	
Melano-competent	37 (74)	34 (69.4)	
Melano-protected	4 (8)	5 (10.2)	
Smoking status			0.55
Current smoker	26 (52)	30 (60)	
Former smoker	7 (14)	8 (16)	
Never smoked	17 (34)	12 (24)	
Diabetes	1 (2)	5 (10)	0.20

Table 2 Disease- and Treatment-related Characteristics of Patients at Baseline

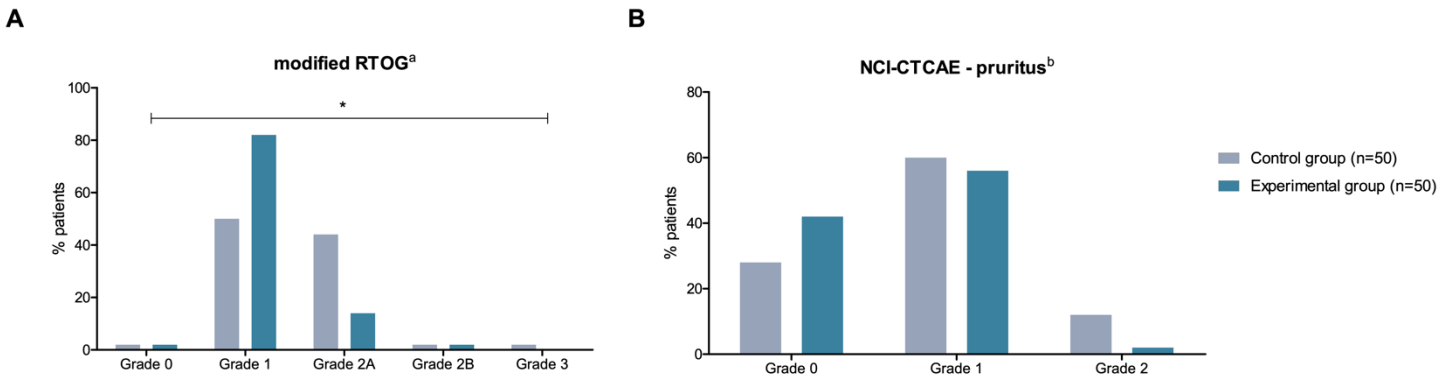
	Control group (n=50)	Experimental group (n=50)	
	N (%)	N (%)	P[a]
Disease-related			
Tumor type			
DCIS	21 (42)	20 (40)	1.00
IDC	4 (8)	6 (12)	0.74
ILC	4 (8)	7 (14)	0.53
Non specific	21 (42)	17 (34)	0.54
T-stage			0.82
x[b]	1 (2)	1 (2)	
is	2 (4)	4 (8)	
1	19 (38)	21 (42)	
2	23 (46)	18 (36)	
3	2 (4)	4 (8)	
4	3 (6)	2 (4)	
N-stage			0.46
x[c]	1 (2)	4 (8)	
0	23 (46)	22 (44)	
1	23 (46)	18 (36)	
2	2 (4)	4 (8)	
3	1 (2)	2 (4)	
M-stage			0.24
x[d]	2 (4)	4 (8)	
0	48 (96)	46 (92)	
Treatment-related			
Chemotherapy before RT	21 (42)	22 (44)	1.00
Adjuvant endocrine therapy			
Tamoxifen	22 (44)	26 (52)	0.40
Aromatase inhibitor	16 (32)	16 (32)	0.60
HER-2 inhibitor	7 (14)	6 (12)	1.00
Type of surgery			0.80
Lumpectomy	41 (82)	39 (78)	
Mastectomy	9 (18)	11 (22)	
Fractionation schedule			0.61
15x 2.67 Gy	3 (6)	5 (10)	
15x 2.67 Gy + 5x 2.67 Gy	10 (20)	6 (12)	
16x 2.66 Gy	5 (10)	7 (14)	
16x 2.66 Gy + 5x 2.66 Gy	32 (64)	32 (64)	
RT technique			0.84
VMAT	26 (52)	24 (48)	
IMRT	24 (48)	26 (52)	
RT energy level WB			1
6 Mv	45 (90)	44 (88)	
6 Mv + 15 Mv	5 (10)	6 (12)	
Boost			0.28
6Mv Photons	36 (72)	35 (70)	
6 MeV Electrons	1 (2)	2 (4)	
9 MeV Electrons	5 (10)	1 (2)	
No boost	8 (16)	12 (24)	
DIBH	35 (70)	37 (74)	0.82
Skin care - related			
Antihistaminic	5 (10)	3 (6)	0.72
Foam silicone dressing	30 (60)	26 (52)	0.55
Corticosteroid cream	5 (10)	3 (6)	0.72

Primary Efficacy Outcome

Most patients presented an RTOG grade 1 at the final RT session, with 50% of the control and 82% of the experimental patients. The RTOG grade 2 (A/B) rate was 46 % (44%/2%) in the control and 16% (14%/2%) in the experimental group. One patient (2%) developed a grade 3 skin reaction in the control group, while no grade 3 was present in the experimental group. One patient in each group presented no ARD (2%/group) at the final RT session. Overall, ARD was significantly more severe in the control compared to the experimental group, with an absolute reduction of RTOG grades ≥2 of 32% between the control and experimental group (χ^2 test, p= .013; Figure 2A).

The novel emollient was associated with a lower RTOG grade (estimated β= -0.282 [95% CI, −0.566 to −0.119]; P = .003), when adjusted for ARD risk factors including the PTV (estimated β= 0.208 [95% CI, 0.021 to 0.362]; p = .028), and Tamoxifen use (estimated β= 0.208 [95% CI, 0.001 to 0.024]; p = .028). No other significant confounding factors were identified.

Figure 2 Severity of acute radiodermatitis



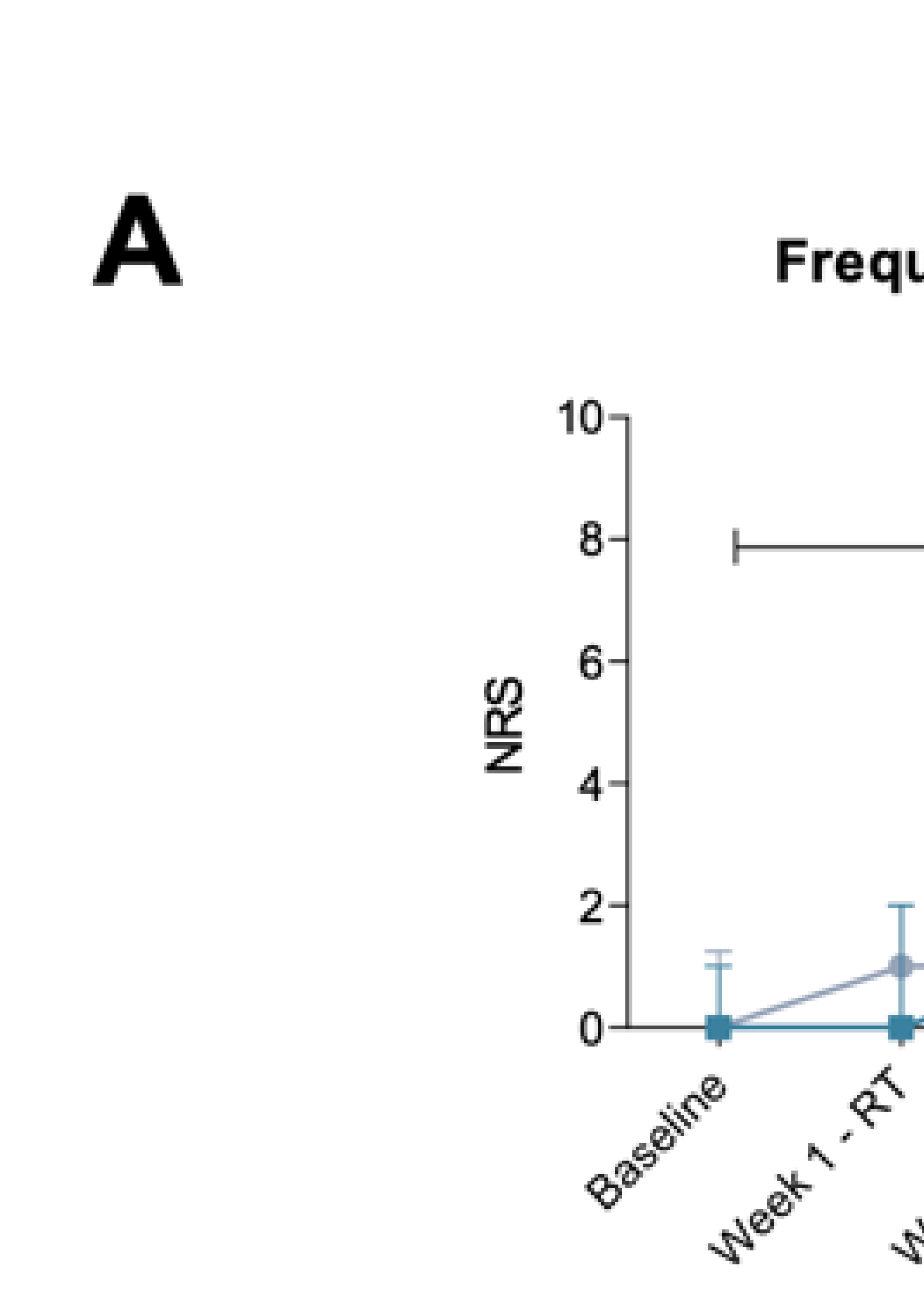
Secondary Efficacy Outcomes

Based on the NCI-CTCAE v5.0 grading scale scored by the researchers, a local or mild pruritus (grade 1) was present in 60 % of the control and 56% of the experimental patients at the last RT session. Widespread and intermittent pruritus (grade 2) was detected in 12% of the control and 2% of the experimental patients. No significant difference between the groups for the severity of pruritus was shown (χ^2-test, p= .066; Figure 2B).

The patients' subjective evaluation of ARD revealed a significant difference over time for all the symptoms' frequency and severity (pruritus, xerosis, erythema, burning, pain) within the groups (Friedman-test, Ps< .001). Post-hoc analysis showed a significant aggravation of the frequency and severity of skin symptoms between baseline and the final RT session in each group (Wilcoxon Signed Rank test, Ps< .001). Between the groups, a significant difference was detected for xerosis frequency and severity at week 2, week 3, and final RT (Mann Whiney U-test, p= .021/.036, p= .01/.022, Ps< .001, resp.). At the final RT session, the control group had a median xerosis frequency and severity score of 3 (IQR: 1-5), while the experimental group had a median xerosis frequency and severity score of 1 (IQR: 0-2.25). Further, the severity score for pruritus significantly differed between the control and experimental patients at week 2 RT (Mann Whitney U-test, p= .025), with a higher score in the control compared to the experimental group (Med 1, IQR: 0-2; Med 1, IQR: 0-1, resp.). No significant difference in the frequency and severity of pruritus and xerosis on the other time points, nor erythema, burning, and pain were found between the groups (Mann Whitney U-test, Ps ≥ .064; Figure 3).

The Skindex-29 (subscales and total) scores significantly increased between baseline and at the final RT session in both groups (Wilcoxon Signed Rank test, Ps<.001). The median total Skindex-29 score at baseline was 8 (IQR: 2-15.5) and at final RT 19 (IQR: 12-36.5) in the control group. In the experimental group, the median baseline score was 6 (IQR: 2-18), and at the final RT session, 17 (IQR: 10-33.5). No significant difference was detected between the groups for all the subscales scores nor the total Skindex-29 score at all time points (Mann Whitney U test, Ps≥ .25; Figure 4).

Overall, 81.6% of the control and 80% of the experimental patients were satisfied to highly satisfied with the received skin care regimen. 83.7% of the control and 78% of the experimental patients would recommend it to other RT patients. No significant difference between the groups regarding patient satisfaction and recommendation were detected (χ^2-test, p= .052, =.072, resp.). No side effects of the novel emollient were described.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Frequ
10
8
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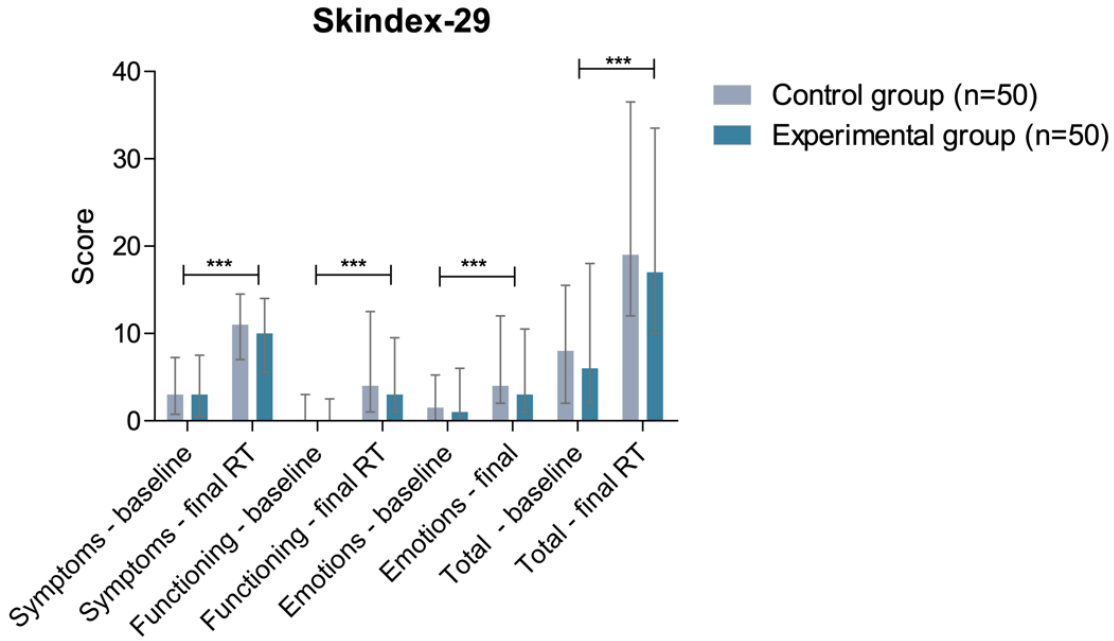
NRS
Baseline
Week 1 - RT

Figure 4 Patients' quality of life


Skindex-29
Score
40
30
20
10
0
***
***
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Symptoms - baseline
Symptoms - final RT
Functioning - baseline
Functioning - final RT
Emotions - baseline
Emotions - final
Total - baseline
Total - final RT
Control group (n=50)
Experimental group (n=50)

Discussion

The novel, multi-active emollient significantly reduced the RTOG grade ≥2 skin reaction incidence compared to the control intervention by 32%. In addition, the novel topical product significantly lowered the frequency and severity of xerosis from week two to the final RT session. The skin care regimens were similar in counteracting itch. Regardless of their skincare protocol, all patients developed a certain degree of erythema, burning, and pain towards the end of RT, but no differences between the groups were detected. There was a low impact of ARD on patients' QoL. Both skin care protocols were highly appreciated and recommended by the patients.

HF RT is more convenient for the patients and the caregivers regarding time consumption and (in)direct costs [32-34]. A critical review by Kim et al. (2022) included eleven RCTs investigating HF in breast cancer patients, of which six specifically studied moderate HF [32]. No information regarding used skin care protocols for each individual trial was described in the original manuscripts. Results showed that the incidence of ARD grade 2 ranged between 3 and 36%, while the incidence of grade 3^{+} ARD ranged from 0 to 1.5% [35-40]. In our trial, the incidence of grade 2 and 3 ARD was 31% and 1%, respectively, in line with the previous studies. A systematic review and meta-analysis by Xie et al. (2021) evaluating risk factors of ARD showed a significant protective effect of HF compared to conventional RT (RR = 0.28, 95% CI = 0.19– 0.43, I^2 = 84.5%) [41]. A possible explanation for this phenomenon is that a higher total dose in the case of conventional fractionation may result in more tissue damage based on the linear quadratic model [42].

The MASCC, the Oncology Nursing Society (ONS), USCOM, the International Society of Nurses in Cancer Care (ISNCC), and the Society and College of Radiographers (SCoR) evaluated a wide variety of possible interventions to prevent and manage ARD ranging from natural and miscellaneous agents, topical non-steroidal agents, barrier films and dressings, photobiomodulation, topical corticosteroids, growth factors, oral agents, antibiotics, alternative therapies, multi-component therapies, to general skin hygiene and antiperspirants use [13-17, 19]. As the current trial investigates a moisturizing topical agent with calendula as an active ingredient, this discussion focuses on topical non-steroidal and natural agents. An expert panel of the MASCC evaluated interventions for ARD prevention and management based on evidence of existing medical literature in 2023 [13, 17]. Considering topical non-steroidal agents, no product was recommended for ARD prevention, but hydroactive colloid gel reached a near-consensus supporting recommendation [13]. A meta-analysis on topical non-steroidal products showed that only Biafine® could reduce ARD severity but not trolamine nor hyaluronic acid [43]. Regarding the natural agents, the MASCC expert panel only recommended olive oil for ARD prevention [13]. A meta-analysis on natural agents demonstrated that only oral enzymes and olive oil significantly reduced ARD severity, but not calendula [44]. The ONS (2020) recommended the use of general emollients and lotions as part of the standard skin care regimen rather than specialty non-

steroidal interventions (e.g., Vitamin D ointment, Cavilon™ barrier cream, an oil-based emulsion containing allantoin) [3, 14]. The USCOM II algorithm (2022) recommended a daily skincare routine based on avoiding exposure to irritants and sun, cleaning, and moisturizing the skin [19]. The ISNCC, in collaboration with an international and interdisciplinary group of experts in radiation oncology (2021), could not recommend any non-steroidal topical agent they investigated (e.g., doxepin, aloe vera, heparinoid) [15]. The ScoR (2020) concluded that there was no strong evidence to support or recommend any of the topical agents that they reviewed (e.g., boron gel, heparinoid, emu oil, aloe vera, an emulsion containing melatonin, olive oil-based product) [16].

Regarding calendula in ARD prevention, the MASCC meta-analysis included three trials with breast cancer patients. Only the physician-blinded study by Pommier et al. (2004, n = 254) demonstrated that calendula could significantly reduce the incidence of ARD grade 2^+ compared to trolamine (41% vs. 64%, resp., p=0.001)[45]. These results align with our study, demonstrating that 48% of the patients in control and 16% of the experimental patients developed ARD grade 2+, indicating a positive effect of calendula on ARD severity. On the other hand, Sharp et al. (2013) (n = 390) was not able to show any significant difference between the calendula and aqueous cream groups regarding RD severity, which could be due to the long evaluation interval [46]. Siddiquee et al. (2021) (n = 81) did not report any significant effect of calendula compared to sorbolene on RD grade 2+ incidence [47]. There was also a high level of bias among these three studies, the number of studies was limited, and the composition of the studied emollients differed. As such, there is a lack of consensus regarding the benefit of calendula in ARD prevention and management [13, 44]. However, the USCOM II algorithm (2022) listed calendula as a potentially valuable topical product [19].

The novel skin care product has two important anti-hydration components: AquaxylTM and hyaluronic acid. The effects of these components are clearly shown in the significantly better xerosis symptom scores. Sekiguchi *et al.* (2022) investigated the effectiveness of moisturizers for ARD prevention in breast cancer patients in a systematic review and meta-analysis. They included 6 RCTs with various topical agents (e.g., aloe vera gel, heparinoid, lipiderm, olive oil, and commercial moisturizing cream). They concluded that moisturizers might be able to reduce ARD RTOG grade 3^+ and improve patients' QoL. However, the amount of evidence was weak due to high variability in study settings and products under investigation [48].

In overall, the novel emollient was highly appreciated by the study population. As the emollient is hypoallergenic, it did not induce any complications such as contact allergy, as reported by earlier studies[49].

Study strengths and limitations

The trial had many strengths, such as the randomized design and the use of a comparator product, the validated questionnaires, and grading tools to evaluate skin reactions and QoL. Another strength of this study is that the skin reactions were evaluated from both the physicians' and the patients' point of view via clinician- (CROs) and patient-reported outcomes (PROs). Due to logistic reasons, it was impossible to blind the participants and the researchers and evaluate the patients weekly via CROs, which might have led to potentially biased results. However, patients did evaluate their skin symptoms via a weekly online questionnaire. The addition of biophysical outcome measures to evaluate ARD more objectively could be an added value for future research. The focus of this trial was put on breast cancer patients receiving moderate HF. However, other RT regimens (e.g., ultra-HF) and other patient populations (e.g., head and neck, skin, gynecological cancer,) are also interesting to study. As the RT-induced skin reactions can still progress up to two weeks post-RT, an extended follow-up time would have given us more insight in the development and resolution of ARD over time.

Conclusion

This prospective, monocentric, non-blinded RCT showed that the novel, multi-active emollient led to a significantly lower modified RTOG degree of ARD in breast cancer patients treated with moderate HF RT. Future research in a double-blinded RCT with a more diverse patient population and a longer follow-up time is needed.

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Table legends

Table 1 Demographic Characteristics of Patients at Baseline

Abbreviations: IQR, interquartile range; PTV, planned target volume; SD, standard deviation; WHO, World Health Organization;

[a] Unpaired 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] Small: PTV<450 cc, Medium: 450-800 cc, Large: >800 cc
[d] 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).

Table 2 Disease- and Treatment-related Characteristics of Patients at Baseline

Abbreviations: DCIS, ductal carcinoma in situ; DIBH, Deep Inspiration Breath Hold; IDC, invasive ductal adenocarcinoma; ILC, invasive lobular carcinoma; IMRT, Intensity Modulated RadioTherapy; RT, radiotherapy; VMAT, Volumetric-Modulated Arc Therapy; WB, whole breast

[a] Chi-square tests, or Fisher's exact tests, as appropriate (two-tailed)
[b] T-Stage - X: "Main tumor cannot be measured"
[c] N-stage: X: "Cancer in nearby lymph nodes cannot be measured"
[d] M-stage: 'X': "Metastasis cannot be measured"

Figure legends

Figure 1 Consolidated Standards of Reporting Trials Diagram

Figure 2 Severity of acute radiodermatitis

A) Modified RTOG: The severity of ARD evaluated by the modified version of the RTOG criteria in the control and experimental group at the final RT session. The severity of the skin reactions was significantly lower in the experimental compared to the control group (Chi-square test, p= .013). [a] *Grade 0: No visible change to the skin; Grade 1: Faint or dull erythema; Grade 2A: Tender or bright erythema; Grade 2B: Patchy moist desquamation; Grade 3: Confluent moist desquamation.*

B) NCI-CTCAE v5.0 pruritus: The severity of xerosis evaluated by the NCI-CTCAE criteria V5.0 at the final RT session. No significant difference between the groups has been detected (Chi-square test, p= .066) [b] *Grade 0: No change; Grade 1: Mild or localized; topical intervention indicated; Grade 2: Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL.*

**, P ≤ 0.05; ** P ≤ 0.01; *** P ≤ 0.001; **** P ≤ 0.0001.*

Abbreviations: ADL, Activities of Daily Living; ARD, acute radiation dermatitis; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; RTOG, Radiation Therapy Oncology Group

Figure 3 Frequency and severity of patient skin symptoms during RT

The frequency and severity of pruritus (A), erythema (B), xerosis (C), burning (D), and pain (E) were evaluated by the patient using a numerical rating scale (NRS) at baseline, weekly and at the final RT session. The frequency and severity of pruritus, erythema, xerosis, burning and pain changed significantly over time (Friedman test, Ps< .001). In addition, the frequency and severity of xerosis at week 2, week 3 and final RT significantly differed between the control and experimental group (Mann Whiney U-test, p= .021/.036, p= .01/.022, Ps< .001, resp.). The severity of pruritus was significant lower in the experimental compared to the control group at week 2 RT (Mann Whitney U-test, p= .025). The data are represented as median ± interquartile range. *, P ≤ 0.05; ** P ≤ 0.01; *** P ≤ 0.001; **** P ≤ 0.0001. *Abbreviations: NRS, numerical rating scale; RT, radiotherapy*

Figure 4 Patients' quality of life

The Skindex-29 subscale (symptoms, functioning, emotions) total scores reflect the patient's QoL at baseline and the final RT session. A higher score is correlated with a poorer QoL. A score of 25 or higher implies a mild impact of the skin reactions on the QoL. A score of 32 or higher indicates a moderate impact, and a score of 44 or higher indicates a severe impact on patients' QoL. In both groups all the subscale and the total scores significantly increased between baseline and at the final RT session (Wilcoxon Signed Rank test, Ps<.001). No significant difference was detected between the groups for all the subscales nor the total Skindex-29 scores at all time points (Mann Whitney U test, Ps ≥ .25). *, P ≤ 0.05; ** P ≤ 0.01; *** P ≤ 0.001; **** P ≤ 0.0001. *Abbreviations: RT, radiotherapy*