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Mepitel® film versus standard care for the prevention of skin toxicity in breast cancer patients treated with adjuvant radiotherapy: A randomized controlled trial

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ABSTRACT

Background & purpose: Radiotherapy plays a key role in breast cancer treatment however, radiation-induced dermatitis can impact on treatment delivery and patient quality of life.
The primary outcome was to compare Mepitel® Film versus standard treatment in preventing radiotherapy skin toxicity onset.
Methods: A multicentre randomised controlled phase III study compared standard treatment (aqueous-urea cream − Excipial U hydrolotion applied at the beginning of radiotherapy and antiseptic cream − Flammazine or Ialugen Plus applied at the onset of moist desquamation) versus Mepitel® Film in patients with breast cancer undergoing post-operative radiotherapy. The primary outcome was the proportion of moist desquamation (RTOG score ≥ 2) in the experimental and control groups.
Results: During the study (2016–2020), 161 patients were randomized, 154 (95.7 %) were evaluable. Skin toxicity Radiation Therapy Oncology Group (RTOG) score ≥ 2 was observed in 9.5 % and 13.9 % of experimental and control groups respectively (Relative Risk = 0.68, 95 %CI 0.28–1.66; p = 0.393). RTOG scores > 0 were 90.5 % and 94.9 % in experimental and control groups respectively (Relative Risk = 0.95, 95 %CI 0.87–1.04; p = 0.294).
Multivariable analysis, controlled for age, diabetes, BMI and smoking exposure, showed a risk reduction of RTOG > 0 of 38 % (HR = 0.62 95 %CI 0.49–0.96, p = 0.028), and a risk reduction of RTOG > 1 of 33 % (HR = 0.67 95 %CI 0.26–1.76, p = 0.420) in the experimental group.
The median time to recovery from RTOG grade > 0 toxicity was 17 and 32 days for experimental and control groups, respectively (p = 0.027). At multivariable analysis, time to recovery was 38 % faster in the experimental group (HR = 1.38 95 %CI (0.99–1.93) p = 0.059).
Conclusions: Although the study did not demonstrate a statistically significant reduction in RTOG > 2 skin toxicity, there was evidence of a reduction in the rate of skin toxicity and an improvement in time to recovery. The device was well tolerated by patients.

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Introduction

Approximately 2.3 million women were diagnosed with breast cancer in 2022 [1], with radiotherapy being part of treatment in 50–60 % of patients [2,3]. Up to 95 % of patients undergoing radiotherapy experience radiation-induced dermatitis (RID), or radiation-induced skin injury [4]. Common skin reactions include erythema, dry desquamation, moist desquamation and rarely ulceration [5], which may impact on the patients' quality of life and, in severe cases, lead to treatment delays or dose reductions [6].

A variety of factors can affect the incidence and severity of reactions such as individual, disease-related, or treatment-related factors [7], however clinical trials have been performed evaluating treatments for prevention and management of RID, attempting to limit its incidence and severity [8]. Despite this, there are no consensus recommendations for the prevention or management of RID. This is due to a lack of evidence supporting the use of particular products [7], or recommendations that are conditional with low certainty of evidence (topical steroids or semi-permeable dressings in addition to standard skin care regimes to minimize RID) [9].

One approach to RID prevention is the use of a barrier films, which promote healing, reduce infection risk and are transparent, allow skin site monitoring without dressing removal [10]. The barrier film used in our study was a flexible, breathable and transparent polyurethane film contact dressing. Indications for use include a wide range of superficial wounds such as grade I/II pressure ulcers, superficial burns and superficial skin wounds. The device can also be used to prevent wounds, protecting fragile and sensitive skin.

An intra-patient randomized controlled trial reported on the same transparent polyurethane film use in 78 patients acting as their own controls with film application to the entire lateral or medial part of the irradiated breast or chest wall compared with aqueous cream application to the control area. The transparent polyurethane film was applied pre-radiotherapy and maintained during treatment and successive weeks. Overall skin reaction severity was reduced by 92 %, and moist desquamation prevented [11]. Positive results were also described by Møller et al. [12] in 101 patients receiving radiotherapy for breast cancer, randomised to have the transparent polyurethane film applied to the lateral or medial part of the chest. In areas where the skin was covered by film, patients reported statistical significant lower levels of pain, itching, burning and oedema, and had significantly lower severity of RID at the end of radiotherapy compared with standard care. More recently in a feasibility and efficacy study including 29 patients, the transparent polyurethane film was applied to the full treatment field prior to radiotherapy and remained in situ for 2 weeks after treatment completion. While the frequency of grade 2 RID was lower with the transparent polyurethane film versus standard care, two patients did develop moist desquamation (10.7 %) [13].

The use of the transparent polyurethane film in RID prevention for patients undergoing radiotherapy for head and neck cancers has also shown decreased skin reaction severity of around 30 %, although these studies highlighted issues with patient adherence and discomfort in relation to the site of film application [14,15,16].

Despite these interesting results, summarising evidence to support the use of this transparent polyurethane film is challenging, impaired by differences in skin toxicity assessments, assessment blinding in randomised studies, and confounding variables. Further rigorous research is required to contribute to the knowledge base regarding the use of this transparent polyurethane film in RID prevention.

The preventive/curative treatment of radiation-induced erythema in our hospitals involves the use of acqueous-urea cream (Excipial U hydrolotion) applied from the first session of radiation therapy.

This study aimed to compare efficacy and patient comfort of the transparent polyurethane film vs standard treatment in women treated with adjuvant radiotherapy after breast surgery.

The primary outcome was prevention of the onset of radiotherapy skin toxicity $\geq$ grade 2, (according to the Radiation Therapy Oncology Group (RTOG) score [17] (Suppl 1a & 1b). The secondary outcomes were: time to onset of skin toxicity, time to healing, severity of acute and late skin toxicity, patient satisfaction and comfort. The results of the study, if positive, may lead to a possible re-evaluation of treatment protocol currently in use.

Materials and methods

Study design

An open randomised controlled phase III trial, planned enrolment of 164 Caucasian patients with breast cancer undergoing post-operative radiotherapy, assigned in a 1:1 ratio to one of two treatment groups. We used a block randomization list managed by the Clinical Trial Unit, external to clinical areas. One group of patients received the Mepitel® transparent polyurethane film dressing (experimental group) and one group received standard treatment currently in used in Swiss radiotherapy departments (control group), as per Scientific Association of Swiss Radiation Oncologist (SASRO) guidelines [18].

The study was registered in Clinicaltrials.gov (NCT02741258) and approved by the Ethics Committee of Canton Ticino (CE TI 2902) and Swissmedic (2015-MD-0017).

Study setting

Multicentre trial involved two Swiss hospitals.

Participant inclusion / exclusion criteria

Eligible patients included women affected by breast cancer and treated with conservative surgery for whom whole breast post-operative radiotherapy was planned, who provided written informed consent. Only patients with bra cup size 1 (2.5 cm) and 2 (5 cm) [19]; median volume 253 cm^3 (117—485), were eligible in order to completely cover the skin with only one transparent polyurethane film.

Patients were excluded if they had known contraindications to the correct placement of the transparent polyurethane film, had undergone previous radiotherapy treatments or reconstruction on the ipsilateral breast, were participating in other research protocols, or were receiving concomitant therapy with antiblastic chemotherapy.

Patients who were eligible and consented to participate in the study were assigned to one of the two groups. Participation in the study did not change the treatment prescribed for each patient.

All patients were treated with conservative surgery and sentinel node biopsy/axillary sampling. We prescribed whole breast RT +/- boost on the surgical bed, the total dose ranged between 40 Gy if hypofractionated and 50 Gy if standard schedule, the boost dose was 10.5 Gy if hypofractionated and 16 Gy if standard schedule. Several trials [20,21,22,23,24] have compared mild hypofractionated and conventional schedules showing similar acute and late radiation dermatitis ≥ 2.

A recent *meta*-analysis [25] confirmed that telangectasia, hyperpigmentation, breast induration or fibrosis, breast shrinkage, breast oedema and breast pain were not statistically different between the two schedules. This strengthens that mild hypofractionation has improved safety profile, cosmesis, and quality of life compared with conventional one, while maintaining equivalent oncological outcomes. Patients were treated with Three-Dimensional Conformal, Intensity Modulated, or Volumetric Modulated Arc Therapy. The different techniques were compared and the best in terms of dose homogeneity to the Planning Target Volume and lower dose to the organs at risk was selected for each patient. Portal vision or cone beam CT were performed for the first 3 treatments and then weekly.

Intervention

Experimental intervention

The transparent polyurethane film was applied by dedicated nurses under the supervision of a radiation oncologist. In our study we used the largest size device (15x20cm) (Fig. 1). After randomization, patients in the experimental group had the transparent polyurethane film applied immediately before CT planning to avoid changes in breast profile with and without the device and to ascertain any intolerance before starting RT treatment (Fig. 1). Device corners were highlighted with a marker and photographed to allow the correct positioning of subsequent devices. We decided to apply only one device for an adequate reproducibility of the breast profile during radiotherapy. The device was changed nearly every week during radiotherapy and removed at the end of treatment if toxicity < 1 (RTOG scale) or in two weeks time if toxicity $>$ grade 1.

Control intervention

Patients in the control group received the standard topical treatments according to the SASRO guidelines [18] at the onset of any skin toxicity from radiotherapy. Aqueous-urea cream (Excipial U hydrolotion) was applied at the beginning of radiotherapy and antiseptic cream (Flammazine or Ialugen Plus) was applied at the onset of moist desquamation. Prescribed creams were applied autonomously by patients, after dedicated training.

Outcomes

The primary outcome was the proportion of moist desquamation (RTOG score ≥ 2) in the experimental and control groups.

The secondary outcomes were:

1a. Time to onset of erythema (RTOG score > 0), defined as the number of days between first irradiation and the onset of grade 1 toxicity.

1b. Time to onset of moist desquamation (RTOG score ≥ 2), defined as the number of days between the first irradiation and the onset of grade 2 toxicity.

2. Time to healing, defined as the number of days between the onset of grade > 0 toxicity and healing. We defined healing as no change over baseline, except mild hyperpigmentation or dryness.

3. Proportions of chronic skin toxicity grades (RTOG/EORTC: 0, 1, 2, 3, 4) in the experimental group and control group: first detection within six months after the end of RT and then during every follow up visit.

4. Patients satisfaction scores regarding the topical treatment received (by visual analogue scale – VAS and final questionnaire) and problems reported (open-ended question).

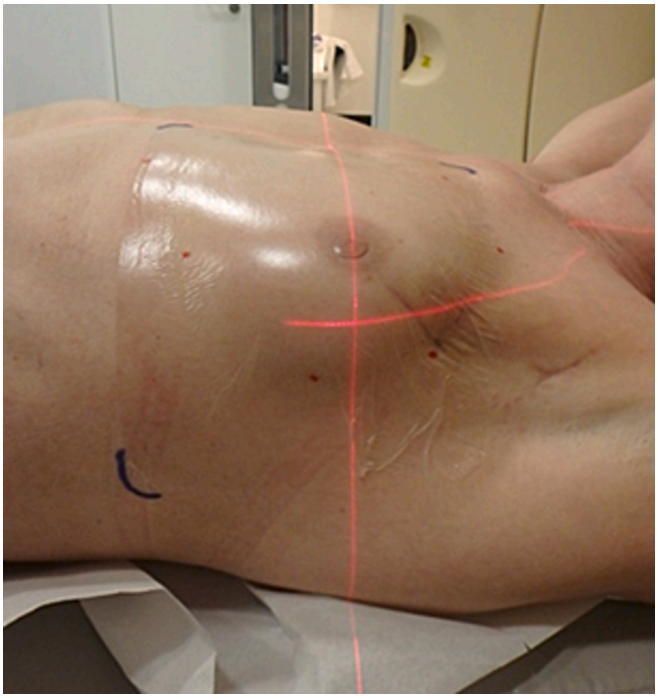

Fig. 1. Application of the transparent polyurethane film prior to CT planning.

Study procedures

All consecutive patients were screened in the outpatient clinic where eligibility criteria were checked, demographic and anamnestic data were collected and physical examination of the breast skin was performed. All patients were checked bi-weekly during the treatment and for 4 weeks after its completion (weekly). The presence of acute adverse radiotherapy reactions were classified according to the RTOG scale, ranging from 0 (no reaction) to 4 (ulceration, haemorrhage, necrosis) (Suppl 1a & 1b). The assessment of irradiated skin toxicity was repeated again during follow-up at 6 and 12 months. The radiation oncologist assessed reactions (unblinded assessment) and the status of irradiated skin was documented through photographs. All patients in both groups applied moisturizing lotion at least once a day after the end of radiotherapy. Patients in both groups were asked to fill in a questionnaire four weeks after the end of radiotherapy, indicating problems experienced and overall satisfaction with the treatment (Yes / Yes in part / No).

Sample size and statistical analysis

The sample size was calculated on the basis of the main parameter studied. According to preliminary results from the study by Herst et al., [11] we expected a proportion of moist desquamation (RTOG ≥ 2) in the control group of approximately 20 %, and in the experimental group (transparent polyurethane film) of approximately 5 %. Assuming an allocation ratio of subjects to the two groups of 1, for the study to have a power of 80 % and a type error probability (α) of 0.05, we therefore calculated to include a total of 164 subjects (82 in each group). The sample size was calculated using G*Power 3.1.5. Analyses were performed for the intended population to be treated (ITT population) which included all patients who were enrolled, and by protocol (PP population) which included all patients who completed the study. The two endpoints were then compared with each other to check for differences.

The planned duration was initially estimated at 3 years, including the 12-month follow-up period. During the study, due to recruitment difficulties and with the approval of the relevant Ethics Committees, it was decided to make the study multicentre, involving another radiotherapy centre at the Hirslanden Clinic in Zurich. The recruitment at the Zurich site began in June 2017 and 63 patients were recruited (58 evaluated).

Patient, disease and outcome characteristics of interest were presented in tabular form on the total number of patients analysed and by treatment group, using summary statistics chosen according to the type of data (absolute and relative frequencies for categorical data, median, mean and relative dispersion measures for continuous data).

Efficacy analysis was performed using χ^2 test for primary outcome comparison and Kaplan-Meier curves for the secondary outcomes.

For analysis of time to onset of erythema (RTOG score > 0) and time to onset of moist desquamation (RTOG score ≥ 2), the start of observation coincided with the randomisation date, and the final observation date was the date at which the event of interest was found, or the last available date in the case of censoring. For analysis of proportions of chronic skin toxicity, the start of observation coincided with the date of RTOG > 0, and the final observation date was the date of recovery (event of interest), or the last available date in the case of censoring. For patients without RTOG > 0, the time to recovery was set $= 0$. The statistical test for comparison was the log-rank, while the semi-parametric Cox

model was used for multivariate analysis. The estimate of the effect was expressed in terms of the Hazard Ratio (Haz. exp/Haz. ctr) with the corresponding 95 % confidence intervals. Check for proportional hazard assumption was made by means of graphical methods (plotting log(−log (survival) versus log(time)) and analytic methods (Including Time Dependent Covariates in the Cox Model).

Results

The first patient was enrolled on 26/01/2016, and the last on 30/12/2020. The flow of participants through each stage of the trial is described in Supplementary 2. 161 patients were recruited of which 154 (95.7 %) were evaluable and a good balance of the distribution of characteristics in the two treatment groups was observed (Table 1).

Patients aged > 65 years were 38.3 %, smokers 28.6 % (of whom ex-smokers 16.9 %), diabetics 4.5 %, with BMI > 30 6.5 %. The median number of radiotherapy sessions was 15 (range 3–33), while the median dose was 50 Gy (range 14–66).

The treatment was completed by 137 patients (89.0 %) and adherence to the prescribed treatment was observed in 128 patients (83.1 %). Breast median volume was 253 cm^3, with minimum and maximum volumes 117 cm^3 and 485 cm^3 respectively. The median Planning Target Volume was 391 cm^3, with minimum and maximum volumes 226 cm^3 and 660 cm^3 respectively.

Primary outcome

RTOG ≥ 2 was observed in 9.5 % of the experimental group and in 13.9 % of the control group (Relative Risk = 0.68 95 %CI 0.28–1.66; p = 0.393). Of note, no RTOG grade 4 was detected in the experimental group (Table 2).

Secondary outcomes

Patients with acute toxicity RTOG score ≥ 1 were 90.5 % in the experimental group and 94.9 % in the control group (Relative Risk = 0.95 95 %CI 0.87–1.04; p = 0.294).

The median time to RTOG > 0 was 21 days from the beginning of RT in the control group and 26 days in the experimental group. Risk reduction was 29 % (HR = 0.71 95 %CI (0.51–0.99), p = 0.035) (Fig. 2). The multivariable analysis, controlled for the factors age, diabetes, BMI and smoking exposure, showed a 38 % reduction in the risk of RTOG > 0 (HR = 0.62 95 %CI (0.49–0.96), p = 0.028. Not all patients returned to RTOG = 0 due to the ongoing presence of mild hyperpigmentation or dryness at 168 days after the end of radiotherapy.

Table 1
Summary – Evaluable Patients.

	Treatment Group					
	CTR arm		EXP arm		TOTAL	
	N	%	N	%	N	%
Age > 65 years						
No	52	65.8 %	43	57.3 %	95	61.7 %
Yes	27	34.2 %	32	42.7 %	59	38.3 %
Smoking habits						
A Never smoker	57	72.2 %	53	70.7 %	110	71.4 %
B Previous smoker	14	17.7 %	12	16.0 %	26	16.9 %
C Current smoker	8	10.1 %	10	13.3 %	18	11.7 %
Diabetes						
No	74	93.7 %	73	97.3 %	144	93.5 %
Yes	5	6.3 %	2	2.7 %	7	4.5 %
BMI > 30						
No	73	92.4 %	71	94.7 %	144	93.5 %
Yes	6	7.6 %	4	5.3 %	10	6.5 %
TOTAL	**79**	**100.0 %**	**75**	**100.0 %**	**154**	**100.0 %**

BMI – Body Mass Index, CTR – control, EXP – experimental.

Less than 50 % of patients experienced RTOG > 1. The risk reduction was 35 % (HR = 0.65 95 %CI (0.25–1.68), p = 0.368) (Fig. 3). The multivariable analysis showed a risk reduction of RTOG > 1 of 37 % (HR = 0.67 95 %CI (0.26–1.76), p = 0.420.

The median time to recovery from RTOG grade > 0 toxicity was 17 and 32 days for experimental and control groups, respectively (p = 0.027) (Fig. 4). At the multivariable analysis the time to recovery was 38 % faster in the experimental group (HR = 1.38 95 %CI (0.99–1.93) p = 0.059).

Of 159 questionnaires, we received 139 (87.4 %) suitable for analysis. Erythema/dermatitis was reported in 27.3 % of the experimental group versus 54.8 % in the control group. Patients' perceptions of erythema/dermatitis was lower than that recorded by doctors/nurses (90.5 % versus 94.9 %). Regarding patient satisfaction with treatment (responding 'Yes' or 'Yes in part'), there were no substantial differences observed between the two groups (experimental group 84.8 % versus control group 87.8 %). No patient experienced intolerance or allergy to the device before or during treatment.

Discussion

The transparent polyurethane film used in this study, has been compared to unscented moisturising cream for preventing grade 2–3 breast skin toxicity, as RID is a side effect that frequently arises during radiotherapy in breast cancer patients. Severe acute radiation dermatitis with desquamation can occur and patients can suffer from pain and discomfort and, can have long-term adverse effects including fibrosis and telangiectasia.

We evaluated this device because it has been shown to reduce radiation dermatitis but it is not widely used in clinical practice and not considered as standard treatment in national and international guidelines. The Multinational Association of Supportive Care in Cancer (MASCC) clinical practice guidelines, recommended six interventions for preventing acute radiation dermatitis. Only photobiomodulation therapy and this transparent polyurethane film reached > 75 % experts panel consensus (respectively 79 % and 76 %) for their use in the prevention of dermatitis in breast cancer patients [26].

In several trials the transparent polyurethane film decreases the severity of acute radiation-induced skin reactions and is superior to Biafine cream in reducing the severity of acute radiation-induced skin reactions and moist desquamation incidence in head and neck cancer patients [14,16,27]. Yee et al. showed a reduction in moist desquamation in breast cancer patients with the use of the transparent polyurethane film during radiation therapy and a group from New Zealand reported similar experiences [11,13]. A recently published randomized multicenter trial [28] confirmed a significant decrease of Grade 2–3 radiation dermatitis in patients treated with the transparent polyurethane film compared to standard care. The results of this trial are particularly interesting because the selected patients are at high risk of radiation dermatitis: large breasts after lumpectomy or chest wall +/- lymph nodes after mastectomy.

A significant reduction of pain, sensitivity and oedema in breast cancer patients with the use of the transparent polyurethane film has also been reported with most patients declaring preferred preference for the Film as a standard offer during radiation therapy [12]. Our study however, did not demonstrate a statistically significant reduction of incidence of RTOG > 2 skin toxicity.

In our trial the transparent polyurethane film was applied before simulation computed tomography for avoiding changes of the breast profile. This permitted evaluation of allergies, intolerances or patient discomfort to the device before beginning radiotherapy, normally scheduled 1 week after the simulation. The device was applied for another 2 weeks after the end of radiotherapy, while in the control arm the patients continued to apply the prescribed creams. The transparent polyurethane film can be used prophylactically on small sized breasts because it is thin, transparent, stays on during showering, can remain in

Table 2
Maximum RTOG score observed – evaluable patients.

	Treatment Group						TOTAL		
	CTR arm			EXP arm					
	N	% including missing	% excluding missing	N	% including missing	% excluding missing	N	% including missing	% excluding missing
Max RTOG grade within 6 months									
0	4	5.1 %	5.1 %	7	9.3 %	9.5 %	11	7.1 %	7.2 %
1	64	81.0 %	81.0 %	60	80.0 %	81.1 %	124	80.5 %	81.0 %
2	8	10.1 %	10.1 %	6	8.0 %	8.1 %	14	9.1 %	9.2 %
3	2	2.5 %	2.5 %	1	1.3 %	1.4 %	3	1.9 %	2.0 %
4	1	1.3 %	1.3 %	.	.	.	1	0.6 %	0.7 %
.*	.	.	.	1	1.3 %	0.0 %	1	0.6 %	0.0 %
Max RTOG grade after 6 months									
0	51	64.6 %	82.3 %	57	76.0 %	91.9 %	108	70.1 %	87.1 %
1	11	13.9 %	17.7 %	5	6.7 %	8.1 %	16	10.4 %	12.9 %
.*	17	21.5 %	0.0 %	13	17.3 %	0.0 %	30	19.5 %	0.0 %
Max RTOG	4	5.1 %	5.1 %	7	9.3 %	9.3 %	11	7.1 %	7.1 %
0									
1	64	81.0 %	81.0 %	61	81.3 %	81.3 %	125	81.2 %	81.2 %
2	8	10.1 %	10.1 %	6	8.0 %	8.0 %	14	9.1 %	9.1 %
3	2	2.5 %	2.5 %	1	1.3 %	1.3 %	3	1.9 %	1.9 %
4	1	1.3 %	1.3 %	.	.	.	1	0.6 %	0.6 %
TOTAL	**79**	**100.0 %**	**100.0 %**	**75**	**100.0 %**	**100.0 %**	**154**	**100.0 %**	**100.0 %**

* missing data.

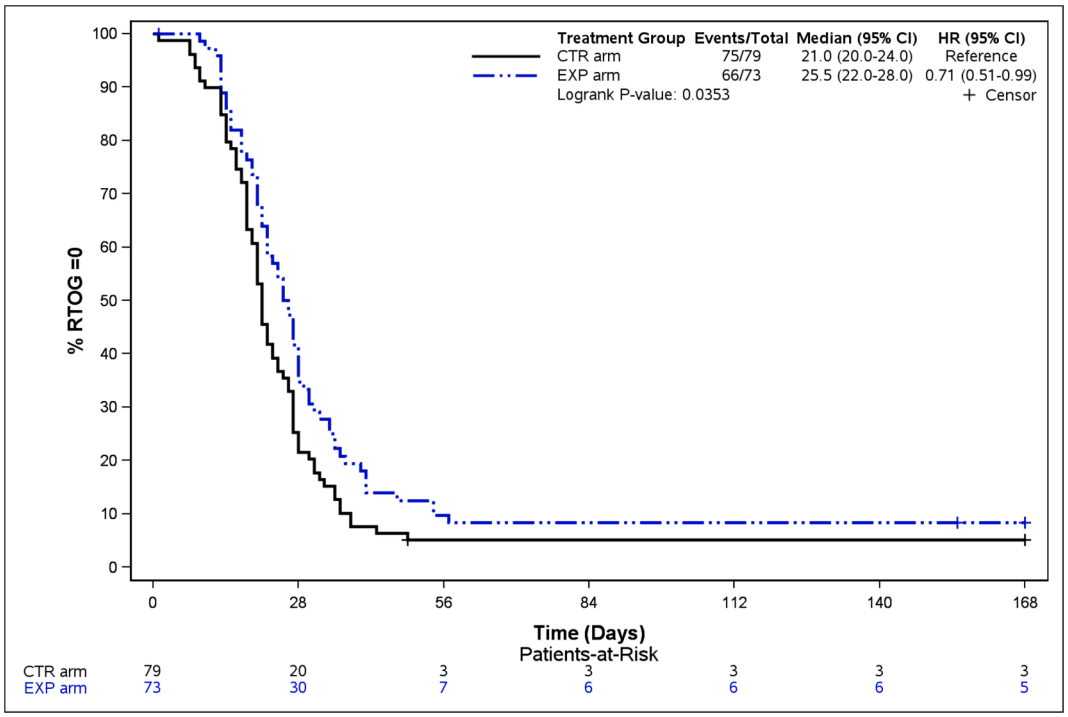

Fig. 2. Time to first event (RTOG > 0).

situ for many days and has a negligible bolus effect (0.12 mm).

There are some limitations in our study. We recruited only patients with small breasts (max cup size 2) in order to completely cover the irradiated skin with only one device. This attitude allowed optimal reproducibility of the breast profile during treatment and a perfect daily match of the irradiated volume even if the recruitment was longer than expected. We did not recruit patients with big or pendulous breasts, which often have greater skin toxicity [29]. Behroozian et al demonstrated that in these patients and in post-mastectomy patients the use of the transparent polyurethane film reduces significantly radiation dermatitis [28]. It may be interesting to evaluate the application of the transparent polyurethane film only in the areas of greatest risk, even if this could modify the breast profile every time it is changed. We have no data to suggest this policy in big breasts, but this could be investigated in future trials. While we evaluated RID toxicity using the RTOG, it is recognised that other clinician-assessed scoring criteria are available including the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [30]. Similarly, use of a validated patient reported outcome measure such as the Dermatology Life Quality Index [31] could provide greater understanding of the impact of RID for patients.

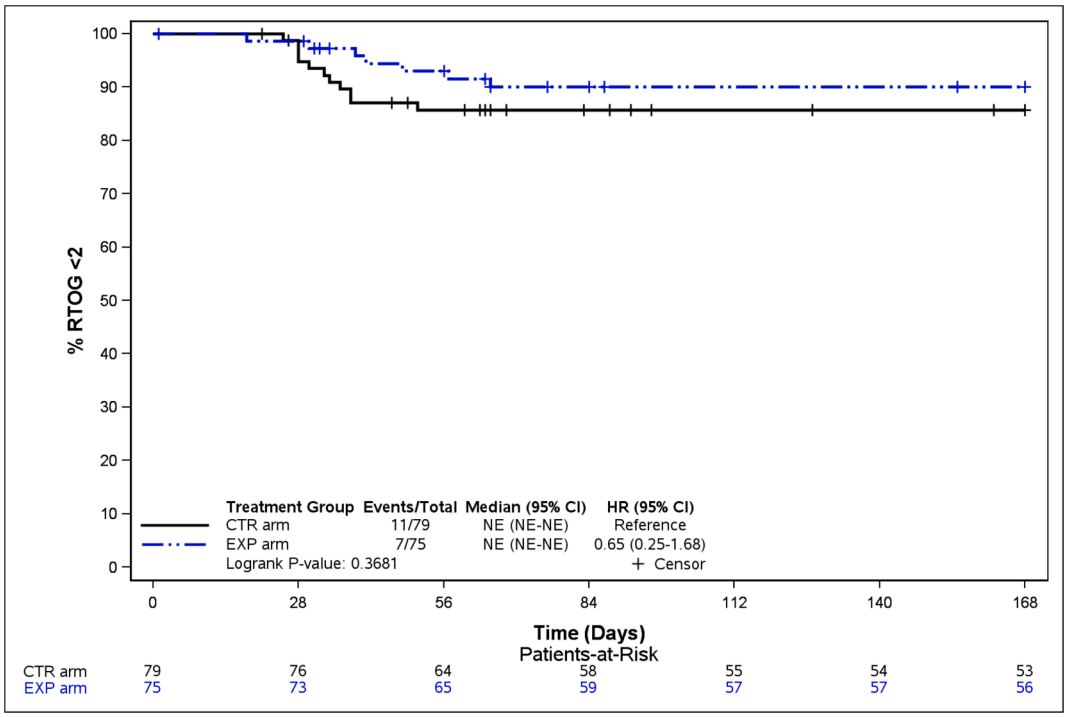

Fig. 3. Time to first event (RTOG > 1).

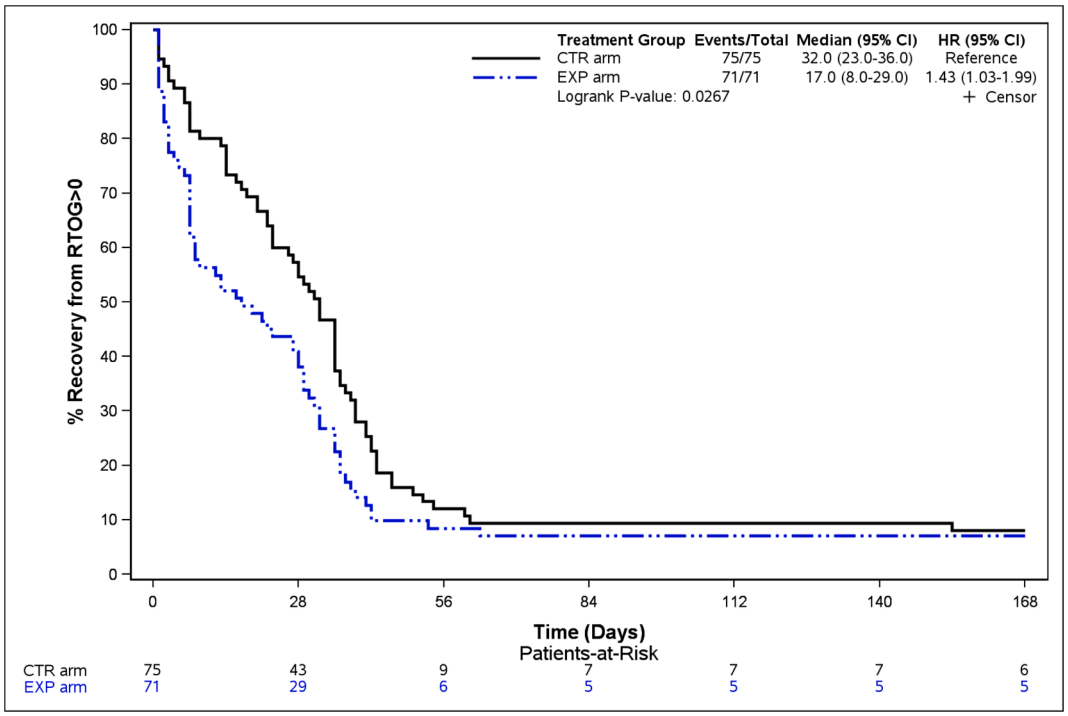

Fig. 4. Time to recovery from RTOG > 0.

Conclusions

The proportion of moist desquamation (RTOG score ≥ 2) in the experimental and control groups has not reached statistical significance even if we found an overall reduction in skin toxicity in the experimental group. In addition we registered a longer time to evidence of RTOG toxicity > 0 and a faster skin recovery time in the experimental group. The device was well tolerated by patients, as reported by questionnaires. In consideration of the positive results obtained we can confirm previous findings within the literature and recommend a more extensive use of the device.

CRediT authorship contribution statement

Dario Valcarenghi: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration,

Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Angela Tolotti:** Formal analysis, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Hansjoerg Vees:** Investigation, Visualization, Writing – review & editing. **Valter Torri:** Formal analysis, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Sarah Jayne Liptrott:** Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Giovanni Presta:** Investigation, Resources, Visualization, Writing – review & editing. **Andrea Puliatti:** Investigation, Resources, Visualization, Writing – review & editing. **Laura Moser:** Data curation, Formal analysis, Project administration, Visualization, Writing – review & editing, Writing – review & editing. **Davide Sari:** Funding acquisition, Resources, Visualization, Writing – review & editing. **Mariacarla Valli:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2025.100936.

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