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Phase III randomised trial

Prophylactic use of Mepitel Film prevents radiation-induced moist desquamation in an intra-patient randomised controlled clinical trial of 78 breast cancer patients

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ABSTRACT

Purpose: Safetac-based soft silicone dressings used in a management setting decrease the severity of radiation-induced acute skin reactions but do not affect moist desquamation rates. Here we investigate the prophylactic use of another Safetac product, Mepitel Film, on moist desquamation rates.

Material and methods: A total of 80 breast cancer patients receiving radiation therapy were recruited between October 2012 and April 2013; 78 participants contributed data for analysis. Lateral and medial halves of the skin areas to be irradiated were randomised to Mepitel Film or aqueous cream; skin dose was measured using thermoluminescent dosimeters; skin reaction severity was assessed using RISRAS and RTOG scales.

Results: Overall skin reaction severity was reduced by 92% ($p < 0.0001$) in favour of Mepitel Film (RISRAS). All patients developed some form of reaction in cream-treated skin which progressed to moist desquamation in 26% of patients (RTOG grades I: 28%; IIA: 46%; IIB: 18%; III: 8%). Only 44% of patients had a skin reaction under the Film, which did not progress to moist desquamation in any of the patients (RTOG grades I: 36%; IIA: 8%).

Conclusions: Mepitel Film completely prevented moist desquamation and reduced skin reaction severity by 92% when used prophylactically in our cohort.

Moist desquamation is a clinically significant acute side effect of external beam radiation therapy particularly in breast and head & neck patients. Many studies have investigated the efficacy of topical agents on the prevention of acute radiation-induced skin reactions. A systematic review published in 2006 by the Cancer Care Ontario Supportive Care Guidelines Group concluded there was insufficient evidence to support the use of any topical agent [1]. A systematic review published in 2010 reported that topical corticosteroids and hyaluronic acid might be of some benefit [2], which was validated for corticosteroids [3], but the evidence was inconsistent for hyaluronic acid [4,5] and trolamine [6–10]. No benefit was shown for aloe vera gel [11], sucralfate cream, aqueous cream [12] or calendula cream [13]. Two barrier-forming products have been assessed to date: Cavilon and Mepilex Lite dressings. The spray-on Cavilon No-Sting barrier film significantly reduced skin toxicity, incidence of moist desquamation and pruritus in an intra-individual comparison of 61 post-mastectomy patients [14]. However, these findings were not validated in a large ($n = 333$) double-blinded multicentre follow-up RCT. This may have been due to differences in formulations and a lack of build-up of a protective layer of cream on the skin [15].

We have previously investigated the use of Safetac technology-based soft silicone dressings on the severity of acute radiation-induced skin reactions in breast cancer patients [16,17]. Like Cavilon, Safetac-based dressings provide mechanical protection from further trauma to the sub-lethally damaged basal skin layer, allowing this tissue to repair the daily damage caused by radiation therapy. Two management trials using an intra-patient controlled approach showed a significant 30–40% decrease in skin reaction severity in 24 breast cancer patients ($p < 0.001$) [16] and 74 post-mastectomy breast cancer patients ($p < 0.001$) [17]. However Mepilex Lite dressings did not affect moist desquamation rates when used to manage existing skin reactions [17]. The current trial aims to determine whether Safetac-based Mepitel Film will reduce moist desquamation rates when used prophylactically.

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Methodology

This randomised, intra-patient controlled, single centre clinical trial was approved by the University of Otago Ethics Committee in October 2012 (12/239); and is registered with the Australia New Zealand Clinical Trials Registry (ACTRN12612000949886). All participants gave written informed consent before the start of radiation therapy treatment. Based on our previous trial [17], we assumed a moist desquamation rate in our cohort of 50%. The sample size was chosen to provide a power of 80% and a p value of 0.05 to detect a reduction in moist desquamation rate from 50% (based on our previous multicentre study [17] to 25% with a drop-out rate of 10–20%.

Trial outcomes

We ascertained the effect of Mepitel Film on (1) skin reaction severity and (2) incidence of moist desquamation.

Participants

All women and men receiving radiation therapy for breast cancer at Dunedin Hospital were screened for recruitment between October 2012 and April 2013. Specific exclusion criteria were: previous radiation therapy to the ipsilateral chest wall, metastatic disease, breast reconstruction, impaired mobility and a Karnofski performance status score of less than 70. After completion of treatment, participants had to be able to return to the department weekly for follow-up assessments for up to 4 weeks.

Randomisation

At the start of radiation treatment, the breast or chest wall was divided into medial and lateral halves for randomisation to either Mepitel Film or aqueous cream. Randomisation was based on pre-prepared computer-generated randomisation charts and conducted (via randomisation fax) by the Principal Investigator (PMH), who had no patient involvement.

Blinding

Because the Film was in situ for days at a time; neither the research radiation therapist nor the patients were blinded to which skin area had been randomised to Film and which to cream.

Radiation therapy treatment

Patients were treated supine with their arms supported above their head. Radiation therapy to the breast or the chest wall included conventional and hypo-fractionation regimens using 6 MV or a combination of 6 and 18 MV tangential photon beams. Segmented fields were used to reduce areas of high dose. A small number of mastectomy patients had daily bolus (5 mm) applied to the chest wall (or scar). Supraclavicular and axillary lymph nodes were treated with anterior (or near anterior) and posterior photon beams when required (see Table 1 for differences in treatment regimens).

Application of film and aqueous cream

Patients doubled as their own controls to eliminate confounding patient- and treatment-related factors. Mepitel Film was applied at the start of radiation treatment by the research radiation therapist on either the entire lateral or the entire medial part of the breast or chest wall to be irradiated whilst aqueous cream was applied twice daily to the control area by the patients. It was important that the Film was not stretched during application; neither was it to overlap other pieces of Film. Gentle digital pressure was used to ease the Film neatly into all skin folds. Patients were supine for Film application not only to maximise patient comfort but also to replicate treatment position. This ensured that breast shape was as consistent as possible. If small areas of Film curled, these were carefully removed with scissors leaving the rest of the dressing in place. Film was replaced by the RRT when it curled up too much (every 1 or 2 weeks). Mepitel Film was generously donated by Molnlycke Healthcare LTD; aqueous cream was obtained from AFT pharmaceuticals (Auckland, NZ) and contained 9 g emulsifying wax, 10 g white soft paraffin, 6 g, liquid paraffin, 1 g phenoxyethanol in boiled and cooled purified water to 100 g.

Table 1
Patient demographics.

	Breast (%)	Chest wall (%)	Combined (%)
Total enrolled	46	34	80
Total completed	44 (56.4)	34 (43.6)	78 (100)
Randomisation (medial)	22 (50.0)	16 (47.1)	38 (48.7)
Sex (F)	44 (100)	32 (94.1)	76 (97.4)
Average age (y) (range)	61.2 (30–88)	58.4 (34–93)	59.9 (30–94)
BMI (Ave ± SD)	27.1 ± 6.3	27.1 ± 5.6	27.1 ± 6.0
Ethnicity			
NZ European	39 (88.6)	33 (97.1)	72 (92.3)
NZ Maori	1 (2.3)	0 (0)	1 (1.3)
Pacific Islander	2 (4.5)	0 (0)	2 (2.6)
Asian	0 (0)	1 (2.9)	1 (1.3)
Hispanic	1 (2.3)	0 (0)	1 (1.3)
Turk	1 (2.3)	0 (0)	1 (1.3)
Disease stage			
DCIS	6 (13.6)	0 (0)	6 (7.7)
I	22 (50.0)	2 (5.9)	24 (30.8)
II	13 (29.5)	18 (52.9)	31 (39.7)
III	1 (2.3)	12 (35.3)	13 (16.7)
Recurrence	0 (0)	1 (2.9)	1 (1.3)
Missing data	2 (4.5)	1 (2.9)	3 (3.8)
Radiation therapy			
50 Gy/25[#]	18 (40.9)	19 (55.9)	37 (47.4)
40 Gy/15[#]	26 (59.1)	10 (29.4)	36 (46.2)
45 Gy/20[#]	0 (0)	1 (2.9)	1 (1.3)
46 Gy/20[#]	0 (0)	2 (5.9)	2 (2.6)
50.4 Gy/25[#]	0 (0)	1 (2.9)	1 (1.3)
54 Gy/27[#]	0 (0)	1 (2.9)	1 (1.3)
Boost			
None	23 (52.3)	27 (79.4)	50 (64.1)
10 Gy/5[#]	5 (11.4)	3 (8.8)	8 (10.3)
9 Gy/3[#]	15 (34.1)	4 (11.8)	19 (24.4)
12 Gy/6[#]	1 (2.3)	0 (0)	1 (1.3)
Bolus			
0.5 mm	0 (0)	6[*] (17.6)	6 (7.7)
None	44 (100)	28 (82.4)	72 (92.3)
Chemotherapy			
None	7 (15.9)	26 (76.5)	33 (42.3)
Pre-RT	37 (84.1)	8 (23.5)	45 (57.7)
Fitzpatrick skin type			
I	3 (6.8)	2 (5.9)	5 (6.4)
II	10 (22.7)	7 (20.6)	17 (21.8)
III	20 (45.5)	17 (50.0)	37 (47.4)
IV	10 (22.7)	8 (23.5)	18 (23.1)
V	1 (2.3)	0 (0)	1 (1.3)
VI	0 (0)	0 (0)	0 (0)
Smoker			
Yes	4 (9.1)	4 (11.8)	8 (10.3)
No	40 (90.9)	30 (88.2)	70 (89.7)

[*] One patient had bolus over the scar only and one patient had bolus removed after 10 fractions.
[#] Number of fractions.

Trial endpoint: Moist desquamation

The date of onset and location of moist desquamation were recorded for each patient. Moist desquamation was treated according to standard departmental protocol (Mepilex Lite dressings).

Severity of skin reactions

Both the modified RISRAS scale [18,19] (Supplementary Fig. 1) [16,17] and the RTOG scale [20] were used. RTOG scores were reported by the research radiation therapist as follows; grade 0; no change; grade I: follicular faint or dull erythema; grade IIA: tender or bright erythema; grade IIB: patchy moist desquamation; grade III: confluent moist desquamation other than in skinfolds. For RISRAS, the research radiation therapist scored the visible extent of the skin reactions whilst the patient scored the level of pain, itchiness and burning as well as the effect on day to day life. Summation of these two scores gives the combined RISRAS score. Both research radiation therapists responsible for measuring skin reaction severity had used RISRAS in our previous two trials. Scores were determined three times weekly from start to completion of radiation treatment, then once a week for 4 weeks after completion. RISRAS scores for each area were added up and divided by the number of assessments, yielding an average RISRAS score for that area.

Dose measurements

Thermoluminescent dosimeters (TLDs) were used on all patients to calculate the skin dose received by both the Mepitel Film covered skin and the aqueous cream treated skin. For each mastectomy patient two groups of 5 TLDs (1 in the centre and 4 at the corners) were placed on a grid in the superior medial and inferior lateral aspects of the chest wall. In addition, 2 TLDs were placed in the axilla (total 12 TLDs per patient). For patients who had not had a mastectomy, 2 TLDs were placed in the axilla, 2 TLDs in the lateral Inframammary fold, 2 TLDs in the medial inframammary fold and 3 TLDs in the superior medial aspect (total 9 TLDs per patient). Measures for groups of TLDs were averaged per site (axilla and superior medial aspect for all patients, inframammary fold for breast patients and inferior lateral aspect for mastectomy patients).

Phantom studies

Percentage Depth Dose (PDD) measurements were taken at various depths when Mepitel Film was applied to the surface, thus calculating its bolus effect. A PTW RW3 Slab phantom was assembled to measure PDDs. Two slabs were bored to house an Advanced Markus chamber (PTW, Freyburg, Germany; TW34045). A source-to-surface distance (SSD) of 100 cm was maintained throughout all measurements. A 10 cm thickness of RW3 was placed below the chamber holder as backscatter material. RW3 slabs were added on top of the chamber in 1 mm increments up to 0.5 cm and then in 5 mm increments to a total of 3 cm. Measurements were taken with the Advanced Markus chamber in combination with the PTW Unidos E electrometer (PTW) for both 6× and 18× photon beams at each depth. Readings were made with and without the Mepitel Film on the surface of the phantom. Measurements were corrected for polarity perturbation. The depth of dose maximum was determined for each beam energy and used as the divisor to determine the PDD.

Exit questionnaire

On completion of the trial, patients were given an exit questionnaire to comment on different aspects of participating in the trial. A total of 60 patients returned the questionnaire. Responses were subjected to a content analysis by D.B.P. and checked by P.M.H. and M.L.J. to provide a comprehensive account of the participants' experiences.

Statistical analysis

SPSS 15.0 (IBM, Chicago, IL) was used for all the statistical analyses unless otherwise noted. The statistical significance between differences in Mepitel Film and control RISRAS scores was determined by non-parametric Wilcoxon signed ranks test, as the scores were not all normally distributed (Fig. 2A–C). Averages, standard deviations and unpaired two tailed Student *t*-tests were determined for dose measurements using Excel (Microsoft v 2010; Redmond Campus, Redmond, Washington, USA). Chi-squared tests for independence (with Yates Continuity Correction) were used to determine the association between skin reaction severity/moist desquamation on one hand and Fitzpatrick skin type, smoking status, diabetes, hypertension, BMI and separation on the other hand. In all cases, $p < 0.05$ was considered statistically significant.

Results

Mepitel Film has a negligible bolus effect

The Mepilex Lite dressings used in our previous trials had a small bolus effect (0.5 mm) [16] and were removed during radiation. In the current trial Mepitel Film could be safely left on during radiation because we determined that the Film has a clinically insignificant bolus effect of 0.12 mm (Supplementary Fig. 2).

Patient demographics

Between October 2012 and April 2013 80 patients were recruited with 78 patients yielding data for analysis (Fig. 1). Of these, 76 were women and two were men; the average age of the cohort was 60 years. With respect to ethnicity, the vast majority of participants identified as European, one as Maori, two as Pacifica, one as Asian, one as Hispanic and one as Turk. Most participants presented with stage II or III disease at the time of diagnosis. Treatment- and patient-related factors such as chemotherapy before radiation, boosts, axillary node dissection, smoking status, BMI,

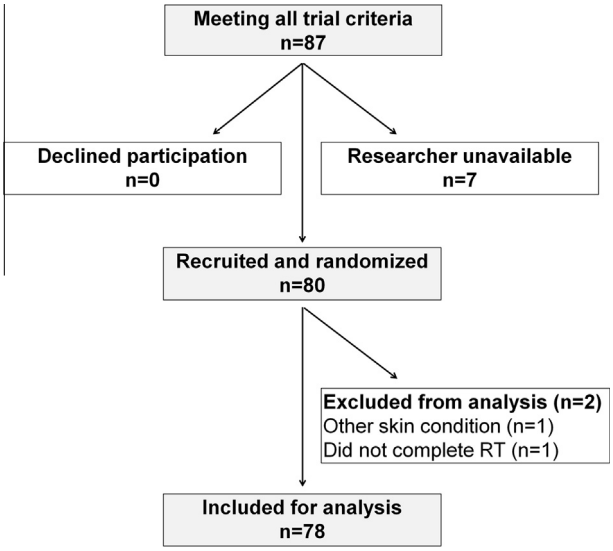

Fig. 1. Consort diagram showing flow of patients through the trial. A total of 80 patients enrolled in the trial, 78 of whom completed the trial and yielded a full data set for analysis.

breast separation, diabetes, hypertension and skin type are shown in Table 1.

Mepitel Film decreases the extent of radiation-induced skin reactions by more than 90%

Skin reaction severity was scored using the Radiation-Induced Skin Reaction Assessment Scale (RISRAS) [16,17] and RTOG [20]. RISRAS scores for the Mepitel Film areas were not normally distributed but strongly skewed towards zero (Fig. 2A–C). Mepitel Film significantly decreased the combined, researcher and patients RISRAS scores ($p < 0.0001$) by 92% (Fig. 2D) compared with aqueous cream. With respect to RTOG grades, of the 78 skin patches treated with aqueous cream, 22 (28%) developed grade I, 36 (46%) grade IIA, 14 (18%) grade IIB and 6 (8%) grade III reactions. Of the 78 skin areas treated with Mepitel Film, 44 (56%) did not develop any reactions, 28 (36%) developed grade IA and 6 (8%) developed grade IIA reactions. Photographs taken of the skin of four of the patients demonstrate the effect of Mepitel Film on their skin reactions (Fig. 3).

Mepitel Film prevents moist desquamation

Moist desquamation rates were 0% for Mepitel Film covered areas and 26% for control areas (24% in mastectomy patients and 27% in non-mastectomy patients) ($p < 0.001$). Mean time to moist desquamation in the control areas was 35 days (range 29–39 days); mean time to healing (using Mepilex Lite dressings) was 9 days (range 3–11 days).

Mepitel Film and control patches received a similar dose

As skin dose contributes significantly to skin reaction severity, we used groups of TLDs to measure the dose at various locations within the treatment field on all our patients. We compared the dose to Mepitel Film and aqueous cream covered skin at these specific locations. Table 2 summarises the dose at these locations separated into a conventional fractionation group (50–54 Gy in 25–27 fractions over 5 weeks) and a hypo-fractionation group (40–46 Gy in 15–20 fractions over 3–4 weeks). Of the 39 patients in the conventional fractionation group, 20 (41%) developed moist desquamation in the control area, whereas this only occurred in 7 out of 39 (18%) patients in the hypo-fractionation group, which was statistically significant ($p = 0.012$). There was no statistically significant difference between dose to the skin covered in Mepitel Film and the dose received in the control area.

Other Factors that may influence the severity of radiation-induced skin reactions

In order to determine the effect of a variety of patient-related factors on skin reaction severity and moist desquamation rates, we categorised combined control RISRAS scores into low (<1.5) moderate (1.5–3) and high (>3), BMI into normal/overweight (18.5–30) and obese (30 and over) and breast separation into low (<200) and high (>200). We grouped the Fitzpatrick skin types into light (types I + II), medium (types III + IV) and dark (types V + VI). We found no significant association between moist desquamation and smoking status ($p = 0.694$), skin type ($p = 0.958$), diabetes

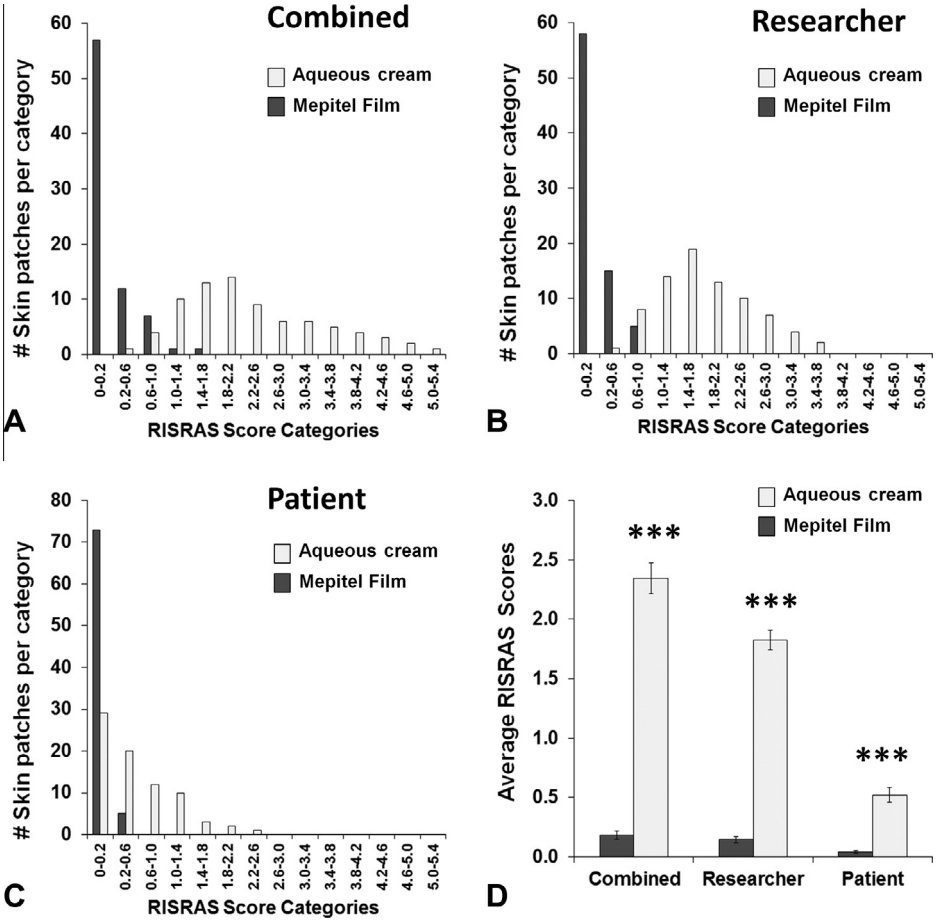

Fig. 2. Distribution of Radiation-Induced Skin Reaction Assessment Scale (RISRAS) scores. (A–C) RISRAS scores of skin patches were grouped into categories and displayed as total number of skin patches per category; (D) RISRAS scores broken down into separate components and presented as mean values ± SEM of skin patches of 78 patients (***$p < 0.0001$).

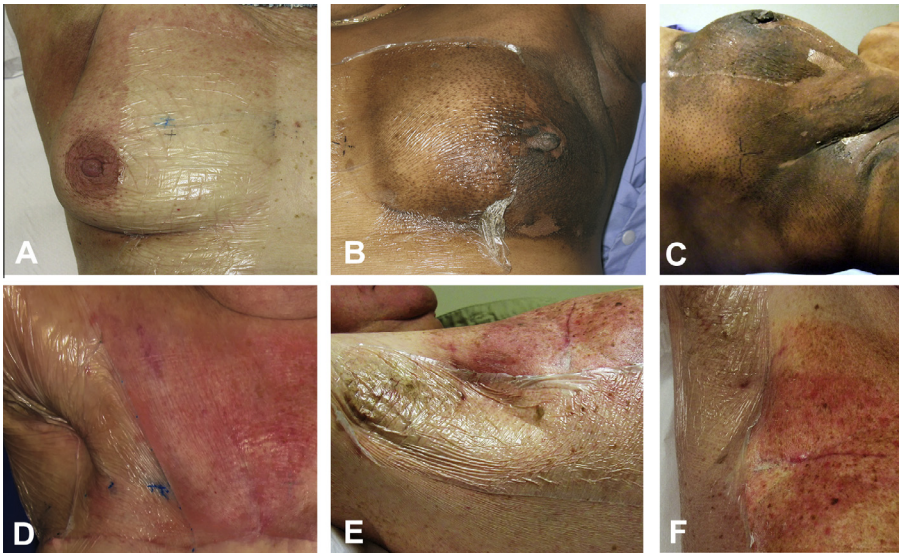

Fig. 3. Photographs of irradiated skin of four trial patients. (A) 1 week after completion of treatment; (B and C) same patient at the last fraction; (D) 1 week after completion of treatment; (E and F) same (male) patient in final week of treatment.

Table 2
Average radiation dose to different areas of the skin.

	Location			# MD*	Ave ± SD	*p* Value**
All patients	Axilla	50–54 Gy	Mepitel	0	34.878 ± 3.638	0.372
			Control	10	35.867 ± 2.795	
		40–46GY	Mepitel	0	29.388 ± 2.020	0.748
			Control	3	29.726 ± 3.809	
	Superior medial aspect	50–54 Gy	Mepitel	0	30.874 ± 3.685	0.952
			Control	4	30.753 ± 7.846	
		40–46GY	Mepitel	0	25.529 ± 3.345	0.319
			Control	2	24.440 ± 1.979	
No mastectomy	Inframammary fold	50–54 Gy	Mepitel	0	37.900 ± 4.239	0.573
			Control	5	38.863 ± 5.255	
		40–46GY	Mepitel	0	30.810 ± 2.964	0.194
			Control	2	29.424 ± 3.789	
Mastectomy	Inferior Lateral Aspect	50–54 Gy	Mepitel	0	33.970 ± 3.267	0.448
			Control	1	35.150 ± 3.537	
		40–46GY	Mepitel	0	27.433 ± 2.131	0.966
			Control	0	27.521 ± 4.484	

* Seven patients developed moist desquamation in two different locations.
** Unpaired two tailed Student *t*-test; $p < 0.05$ is statistically significant.

($p = 0.218$), hypertension ($p = 0.90$), BMI ($p = 0.160$) and separation ($p = 0.148$). There was also no association between combined control RISRAS scores and smoking status ($p = 0.227$), skin type ($p = 0.452$) diabetes ($p = 0.602$), hypertension ($p = 0.622$), separation ($p = 0.458$) and BMI ($p = 0.440$).

Patients' perspective

All participants scored their skin reactions based on subjective sensations as part of the RISRAS whilst 60 out of 78 participants (77%) returned exit questionnaires after trial completion in which they commented on their trial experience with particular emphasis on the advantages and disadvantages of Mepitel Film. All patients described the trial as a positive experience and almost all would take part in a similar trial again; reasons given included altruism, more frequent staff interactions and perceived superior care. The vast majority of patients ($n = 55$) preferred Film to cream with only five patients not having any preference. When asked what they liked about Mepitel Film, most patients mentioned that it was very comforting to wear and felt protective. Other positive aspects of the Film were that it made the skin less red, less itchy and less painful. Negative aspects were that it rolled up at the edges, was visible in exposed areas and caused some itching (in 3 patients).

Cost-benefit analysis

An important question when trying out new dressings is that of cost effectiveness. We spent just under NZ$60 per patient on Mepitel Film. This consisted of Mepitel Film strips (average 5 strips per patient: NZ$22.50) and radiation therapist time (5–10 min per dressing application: NZ$35 per patient). For patients who developed moist desquamation in the control areas, we used an additional 11 Mepilex Lite dressings (NZ$200 per patient).

Discussion

This is the first time that Mepitel Film has been used in the radiation therapy setting. Both Mepitel Film and Mepilex Lite are Safetac-based soft silicone dressings which adhere to healthy skin but do not stick to open wounds. Mepilex Lite dressings decrease

skin reaction severity but not moist desquamation rates; they do not stick well in the axilla or inframammary fold or when perspiring [17], they cannot be worn in the shower, have a small bolus effect (0.5 mm) [16] and need to be replaced at least twice a week [16,17]. Mepitel Film can be used prophylactically because it is thin, transparent, stays on during showering, can remain in situ for many days, has a negligible bolus effect (0.12 mm) and can be left on during radiation.

The most important finding of this trial is that Mepitel Film completely prevented moist desquamation in our patient cohort. Moist desquamation rates in the control group (26%) were lower than previously reported in the literature [14,15]. We reported a wide variation in moist desquamation rates between radiation therapy centres in New Zealand [17] and the results of this trial are consistent with the previous results in Dunedin. Patient scores for Mepitel Film were particularly low which was further substantiated by 92% of patients preferring the Film over the cream and commenting on how protective and comforting the Film felt on the skin. Mepitel Film decreased the extent of acute radiation-induced skin reactions in our patient cohort using RISRAS (by 92%) and RTOG (for control areas: grades I: 28%; IIA: 46%; IIB: 18%; III: 8%; for Mepitel Film areas: grades IA: 36%; IIA: 8%). Using Mepitel Film prophylactically is a financially viable option, particularly for centres with high moist desquamation rates.

The finding that patients receiving hypo-fractionation were less likely to develop moist desquamation than patients who received conventional fractionation (18% and 49% respectively; $p = 0.012$) was surprising as acute reactions are less sensitive to hypo-fractionation than chronic reactions; however this has been reported previously [21].

Anecdotal evidence has suggested that patient-related factors may affect skin reaction severity. Smoking has been linked to increased skin reaction severity in some [12] but not in other studies [22,23]. The widely held belief that fair skinned people develop more severe skin reactions than dark skinned people has not been validated by clinical studies [17,24,25]. Similar to our previous trial [17], we did not find any association between skin reaction severity or moist desquamation on one hand and smoking status, skin type, diabetes, hypertension, BMI or separation on the other hand.

Limitations

Because of the Film's visibility and longevity of application, we were unable to blind the trial. Using patients as their own controls circumvented possible confounding by treatment and patient related factors whilst dose measurements confirmed that dose differences between Film and control areas were similar and therefore not a confounding factor in this trial.

Conclusion

When used prophylactically, Mepitel Film prevents the occurrence of radiation-induced moist desquamation and decreases the extent of skin reaction severity by 92%.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2014.01.005.

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