



Original Article

A single-blind, randomised controlled trial of StrataXRT[®] – A silicone-based film-forming gel dressing for prophylaxis and management of radiation dermatitis in patients with head and neck cancer



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ABSTRACT

Aim: Investigate the effects of StrataXRT[®] versus 10% Glycerine (Sorbolene cream) for preventing and managing radiation dermatitis in patients with head and neck cancer receiving radical radiotherapy (≥ 50 Gy) with or without chemotherapy or biotherapy.

Methods: A single-blind, randomised controlled, superiority trial was conducted. Patients either received StrataXRT[®] or Sorbolene (usual care). Skin toxicity, pain, itching and skin-related quality of life scores were collected from baseline, and up to four weeks post-treatment.

Results: A total of 197 patients were randomised into the study. Skin toxicity was dependent on the treatment group with StrataXRT[®] patients experiencing lower mean skin toxicity at the end of the radiation treatment ($P = 0.002$). At the end of treatment, the StrataXRT[®] arm had a lower percentage of grade 2 (80%) and grade 3 (28%) skin toxicity compared to the sorbolene arm (91% and 45% respectively). After adjustment for Cetuximab, the StrataXRT[®] arm had a 12% lower risk of experiencing grade 2 skin toxicity (RRR = 0.876, 95% CI: 0.778–0.987, $P = 0.031$); and a 36% lower risk of experiencing grade 3 skin toxicity (RRR = 0.648, 95% CI: 0.442–0.947, $P = 0.025$). Cox regression analysis showed that patients receiving StrataXRT[®] had a 41.0% and 49.4% reduced risks of developing grade 2 and 3 skin toxicity respectively throughout treatment compared to the Sorbolene arm. There were no differences between groups in patient-reported outcomes. No treatment interruptions and study product related adverse events were reported in either arm.

Conclusion: StrataXRT[®] is effective for preventing, and delaying the development of grade 2 and 3 skin toxicity.

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Radiation dermatitis (RD) remains one of the most common side effects affecting patients receiving radiotherapy [1,2]. Numerous prophylactic and management interventions are available for RD including; (i) topical preparations (steroidal and non-steroidal), (ii) dressings, (iii) systemic treatments (amifostine, oral hydrolytic enzymes, pentoxifylline, and zinc supplements), and (iv) hygiene practice recommendations [3–5]. Systematic reviews on prevention and management of RD found no evidence indicating a difference between topical pharmacological treatment and non-pharmacological topical treatment in patients undergoing

radiotherapy, except for corticosteroids [2,3,5,6]. However, corticosteroids can cause thinning of the skin which can potentially cause skin dehydration [7].

In recent years, silicone-based products have become increasingly used for RD. Such products act as a barrier by reducing mechanical friction [8], and transepidermal water loss (TEWL) [9], which have been shown to be associated with the severity of RD. In vitro studies have suggested that silicone has a regulatory effect on inflammatory growth factors responsible for fibrosis and acute wound healing [10,11]. The key players involved in this process are also inflammatory markers involved in acute inflammation secondary to ionizing radiation including IL-1, IL-6, TNF-alpha and TGF-Beta, which can be expressed within hours after receiving the first radiation fraction [12–14]. In terms of

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reducing mechanical friction, the stratum corneum whilst biologically dead plays an important role in maintaining barrier function through corneodesmosome adhesions as well as regulating growth factor signalling and influencing the acid gradient of the epidermis [15,16]. Desquamation and drying of the stratum corneum secondary to ionizing radiation is highly correlated with an increase in TEWL [9].

Although there is early evidence suggesting the efficacy of silicone-based film dressings [17,18], these solid dressings can have some small bolus effects [17,19], do not adhere well to the skin at times [17,18], particularly in the shower or when bathing, and in males with facial hair underneath the film [18]. Recently, a silicone-based film forming gel dressing (StrataXRT® Strapharma AG, Basel, Switzerland) has become available which aims to overcome the challenges outlined above. The product is reported to have no bolus effect [20,21], have water-proof properties [21], and be conducive for areas with facial hair [21]. A non-controlled, pretest–posttest study ($n = 44$) has demonstrated the acceptability and efficacy of StrataXRT® [22]. However, to our knowledge, there is not yet any randomised controlled trials evaluating the effects of silicone-based film-forming gel products for preventing and managing RD in patients receiving radical radiation treatment. Therefore, this study aimed to investigate the effects of StrataXRT® gel versus standard care (i.e., Sorbolene) in patients with head and neck cancer receiving radical radiation therapy.

Materials and methods

In this single-blind, randomised controlled, superiority trial, patients receiving radical radiotherapy in the head and neck region at a tertiary cancer centre in Brisbane, Australia were consecutively recruited from July 2016 to December 2017. Patients aged ≥ 18 years with a definitive diagnosis of head and neck cancer receiving radiotherapy (≥ 50 Gy) either as a primary or postoperative treatment to their head and neck were eligible. Radiation treatment were either delivered using helical tomotherapy or volumetric modulated arc (VMAT), with the routine use of a 2–3 mm PTV-to-skin distance for treatment planning. Patients were excluded if they were not able to consent, had pre-existing skin rash, or had an open wound in the treatment area. Patients were also excluded if they had known allergic and other systemic skin diseases (even if not directly affecting irradiated fields), any known allergic reactions towards any ingredient of either the StrataXRT® or Sorbolene, or failed the patch test. Receiving chemotherapy or monoclonal antibodies was not an exclusion criterion. Ethical approvals were obtained prior to commencement of the study by the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/16/QRBW/153) and the Queensland University of Technology (QUT) Human Research Ethics Committee (160000418).

After consent was obtained by the research nurse, participants were randomised to either the intervention arm (StrataXRT®) or the standard care arm (Sorbolene) using a computer generated random number list prepared by an investigator with no clinical involvement in the trial. Allocation was concealed from all personnel using sealed, sequenced envelopes according to the sequence generated. Stratification by concurrent monoclonal antibody treatment was carried out. Blocked randomisation was performed using permuted block sizes of four and six.

For the StrataXRT® arm, patients were asked to start topical application of StrataXRT® on the area of skin being irradiated at the onset of radiotherapy, twice a day until the skin reaction subsided, up to 4 weeks post treatment. StrataXRT® is a silicone-based film-forming, self-drying, semi-occlusive, non-resorbable, topical gel preparation, consisting of polydimethylsiloxanes, siloxanes,

and alkylmethyl silicones. The amount of topical preparation dispensed to each patient was recorded throughout treatment. If moist desquamation occurred, treating nurses applied StrataXRT® in addition to Atrauman® Tulle Dressing 10 cm \times 20 cm [Product ID: 499536]; Hartmann, Australia dressing and a non-sterile combine roll until the wound healed. Patients were asked to continue with applying StrataXRT® onto other irradiated areas. For the standard care arm, patients were asked to start topical application of Sorbolene on the area of skin being irradiated at the onset of radiotherapy, twice a day or more as needed depending on the occurrence of RD and pain, up to 4 weeks post treatment. Sorbolene is a generic name in Australia for topical creams providing a skin barrier that is typically made up of oils, water and glycerin (10%) [23]. Patients were instructed to discontinue applying Sorbolene in the area of skin breakdown, and continue applying Sorbolene onto irradiated area that had no breakdown. The treating nurses applied Intrasite Gel [Product ID: 66027313]; Smith and Nephew, Hull, UK, Atrauman® Tulle Dressing and a non-sterile combine roll on the area of skin breakdown until the wound healed as per standard practice. All participants were given the same verbal education and written instructions on how to apply the allocated treatment (See [Supplementary Material 1](#)). General skin care advice was given to both groups of patients at the same time, as per the local guidelines.

Patients in both arms completed a range of questionnaires by interview every week from the start of radiotherapy treatment until four weeks after the completion of radiotherapy in addition to collecting data on radiation dermatitis symptoms and side effects. A sample size of 93 patients in each arm was needed to detect a 20% difference in Common Terminology Criteria for Adverse Events (CTCAE – Version 4) skin toxicity score at the end of treatment, using a 2-sided significance level of 0.05 and a power of 80%.

Primary outcomes

Severity of skin toxicity

The CTCAE – Version 4.0 was used to assess severity of RD [24]. Weekly assessments were undertaken by an experienced radiation oncology nurse (with 20 years of clinical experience in radiation oncology) who was blinded to the allocation (by inspecting de-identified photographs of the irradiated sites) and had no involvement in the clinical care of the patient. This assessor was instructed prior to the beginning of the study to score the worst toxicity present within the treatment field. The timepoints for assessments were weekly during radiation treatment and up to four weeks post radiation treatment.

Secondary outcomes

All secondary outcomes were assessed weekly from the beginning of radiation treatment up to four weeks post radiation treatment.

Skin-related quality of life

Skindex-16, a 16-item self-administered survey instrument developed by Chren and her research team in 2001, was used to measure the effects of skin condition on quality of life [25,26]. Skindex-16 comprises three scales to assess patient emotion, symptoms and functioning. Item responses are standardized from 0 (no effect) to 100 (maximal effect). The scale demonstrated good reliability at 72 h ($r = 0.68$ – 0.90) and internal consistency (Cronbach's Alpha = 0.76 – 0.86) [26–28]. This tool has been increas-

ing used in patients with skin toxicities caused by anti-cancer treatment [26–28].

Modified brief pain Inventory and itching

This study used three measures from the Brief Pain Inventory (BPI), those of the average, best, and worst pain, and pain relief scores from the preceding seven days [29]. The participants were asked to rate their pain level at the irradiated area. The time of interest of the original BPI was modified from “the past 24 h” to “the past 7 days” for the specific purpose of this study. The BPI was selected as it is a brief and easy tool for the assessment of pain within both the clinical and research settings. It has been well validated in both chronic pain and cancer settings. The scale of 0 to 10

is simple for patients to use and is commonly used in the clinical assessment of pain. Itching was scored on a numeric analogue scale of 0–10 in the treated skin (0 = no itching at all), (10 = itching as bad as you can imagine).

Treatment interruptions and adverse events

Although RD-related treatment interruptions are expected to be rare, any interruptions caused by RD were documented throughout the study (Yes/No). This decision was determined by the treating medical officers. Any adverse events (i.e., allergic reactions from the allocated treatment) were assessed by the Research Nurse weekly and recorded on the clinical research forms. Due to the

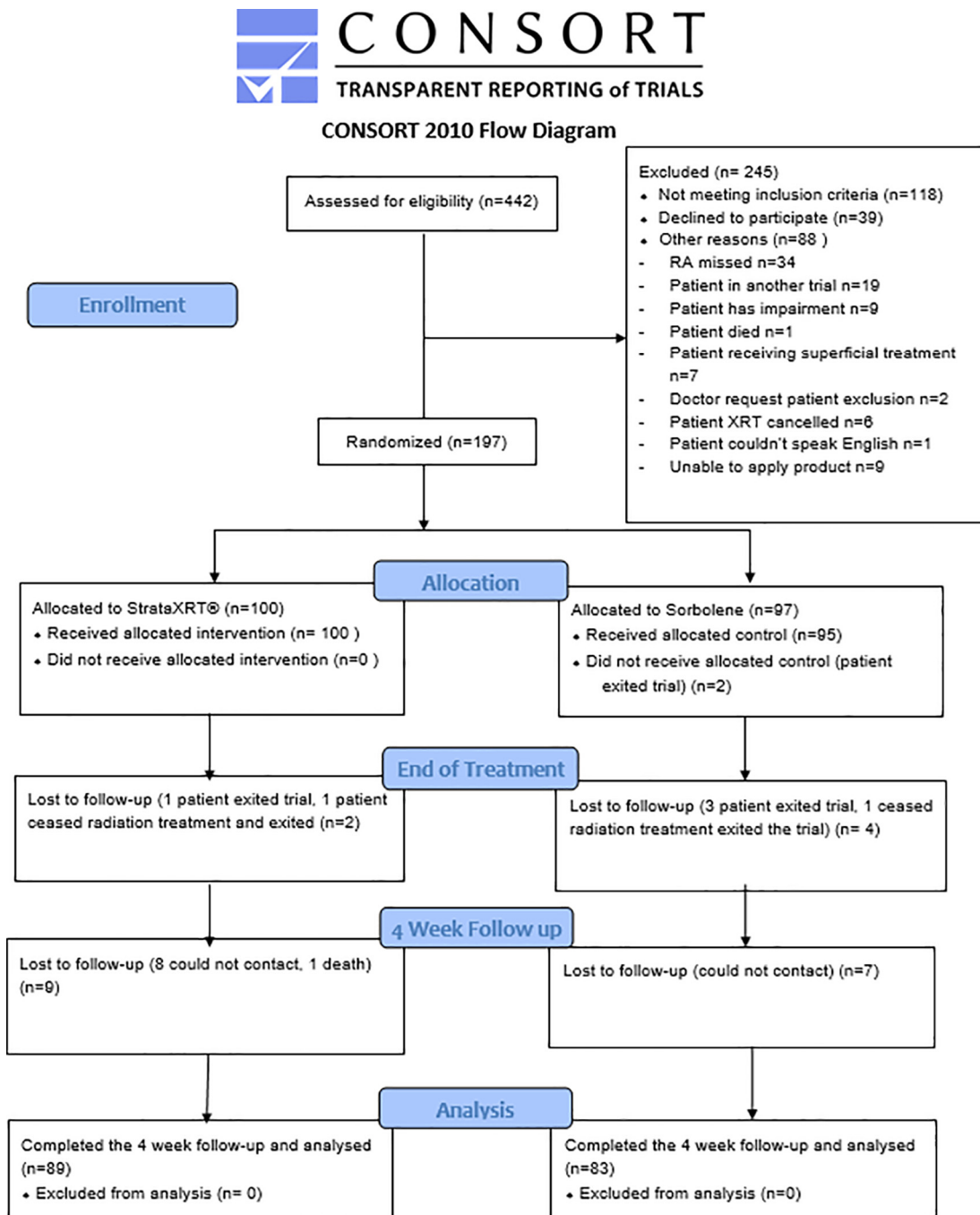


Fig. 1. CONSORT flowchart.

nature of the intervention, no serious adverse events related to the trial products were expected in this trial.

Skin dose measurement

Skin dose measurements were performed in-vivo by placing optically stimulated luminescence dosimeters (OSLDs) at the location of the maximum expected skin dose by the treating medical physicist or radiation therapist [30]. Each measurement point was determined by manually scanning through the patient plan in the relevant treatment planning system to identify the maximum skin dose. After locating this point, screenshots were taken to be referred to when placing the OSLDs on the patient. For each measurement two OSLDs were used side-by-side, and an average was taken. All measurements were performed in a single fraction within the first week of treatment. Individual dose calibration factors were determined for each OSLD multiple times over the course of the study as part of routine dosimetry quality assurance [31,32]. The uncertainty in OSLD measurements in megavoltage beams has previously been shown to be approximately $\pm 4\%$ [33].

Statistical analysis

Data for all randomised patients were analysed using intention-to-treat analysis. Survival quartiles (time to skin toxicity) were calculated using Kaplan Meier and groups were compared using log rank tests with patients followed up until four weeks post-treatment. Cox regression was used to assess the risk of patients

suffering acute skin toxicity. Hazard ratios (HR) were reported for Cox regression models and assumptions of proportional hazards were checked using log minus log plots. The means for itchiness, pain and skin toxicity were tested at the end of the treatment period using a generalized linear model with a Tweedie distribution to account for the large portion of zeros in the data. Cox and Tweedie models were adjusted for concurrent biotherapy (Cetuximab) to account for stratified randomisation. Analysis used 95% confidence intervals for all models. The balance between StrataXRT® and Sorbolene arms was described with mean and standard deviations or frequencies and percentages and tested using t-tests or chi-square test as appropriate. Variables which were out of balance were only included in the final model if they were significantly associated with the outcome and confounding the treatment group. Poisson regression model with robust error variance was used to produce relative risk estimates. Complete case analyses were undertaken due to a small amount (<5%) of missing data.

Results

A total of 197 patients were randomised and enrolled into the study. Two patients in the Sorbolene arm never commenced radiation treatment and the trial. One hundred participants were allocated to receive StrataXRT®, and 95 were allocated to receive Sorbolene. Eleven in the StrataXRT® arm and 11 in the Sorbolene did not complete follow-up assessments at 4 weeks post treatment due to *loss to follow up as they exited the trial* ($n = 4$), *ceased*

Table 1
Study characteristics ($n = 197$).

Characteristics		StrataXRT® Mean (SD) $n = 100$	Sorbolene Mean (SD) $n = 97$	P-value
Age		64.0 (11.9)	63.6 (12.8)	0.819
Body Mass Index		28.2 (6.6)	26.0 (4.7)	0.009
Total Dose		65.6 (5.3)	65.12 (6.9)	0.597
Skin Dose Verification		1.7 (0.4)	1.7 (0.4)	0.634
Number of fractions prescribed		32.9 (4.4)	32.4 (3.9)	0.391
Planning Target Volume		139.7 (118.4)	175.7 (197.9)	0.465
		N (%)	N (%)	
Head and Neck Cancer Site	Oropharynx	47 (47.0)	44 (45.4)	0.510
	Larynx	13 (13.0)	8 (8.2)	
	Hypopharynx	4 (4.0)	5 (5.2)	
	Nasopharynx	4 (4.0)	9 (9.3)	
	Skin and other	32 (4.0)	31 (32)	
Stage at baseline	<II	28 (29.8)	32 (36.8)	0.318
	III or IV	66 (70.2)	55 (63.2%)	
Gender	Male	77 (77.0)	77 (79.4)	0.686
	Female	23 (23.0)	20 (20.6)	
Smoking	No	82 (85.4)	76 (82.6)	0.599
	Yes	14 (14.6)	16 (17.4)	
Ethnicity	Caucasian	95 (95.0)	92 (94.8)	0.961
	Non-Caucasian	5 (5.0)	5 (5.2)	
Metastasis	No	92 (92.0)	88 (90.7)	0.749
	Yes	8 (8.0)	9 (9.3)	
Radiation technique	Tomotherapy	56 (56.0)	71 (73.2)	0.012
	VMAT	44 (44.0)	26 (26.8)	
Energy	6FFF	56 (56.0)	71 (73.2)	0.008
	6 MeV	44 (44.0)	24 (24.7)	
	10 MeV	0	2 (2.1)	
Re-plan during radiation treatment	No	88 (88.0)	91 (93.8)	0.217
	Yes	12 (12.0)	6 (6.2)	
Chemotherapy	No	52 (52.0)	52 (54.7)	0.702
	Yes	48 (48.0)	43 (45.3)	
Cetuximab	No	89 (89.0)	87 (89.7)	0.875
	Yes	11 (11.0)	10 (10.3)	
Surgery	No	54 (54.0)	54 (55.7)	0.886
	Yes	46 (46.0)	43 (44.3)	

Note: VMAT = Volumetric Modulated Arc Therapy.

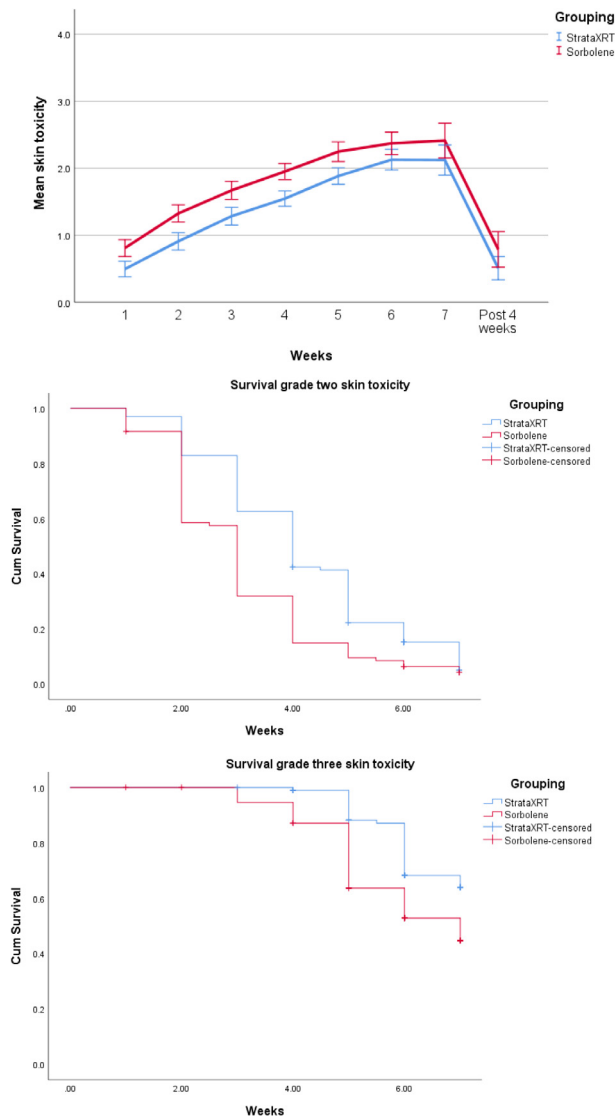


Fig. 2. Mean skin toxicity levels from week 1 to 4 weeks post treatment and cumulative survival (time to grade 2 and grade 3 skin toxicity).

radiation treatment ($n = 2$), could not be contacted ($n = 15$), or death ($n = 1$) (see Fig. 1). Participant and treatment characteristics are outlined in Table 1. Both arms had similar age distributions, with the average age of sample of 63.8 (SD = 12.3). The groups had a similar proportion of males, smokers, and Caucasians. Treatment characteristics including treatment sites, number of prescribed fractions, total dose, skin dose verification, and proportion of patients receiving concurrent chemotherapy or monoclonal antibodies were also similar between groups. A thermoplastic mask was used for all patients except for one in the Sorbolene group. The StrataXRT[®] arm were found to be slightly more overweight ($P = 0.009$) and had a lower proportion of patients receiving helical

tomotherapy ($P = 0.012$) than the Sorbolene arm. However, after adjustment body mass index and radiation technique (helical tomotherapy versus VMAT), these factors were not found to be significant predictors of outcome variables or confound the treatment effect. Therefore, BMI and radiation technique were removed from final models.

Severity of skin toxicity

Skin toxicity was found to be dependent on treatment group with patients receiving StrataXRT[®] (mean = 2.4, 95% CI: 2.2–2.6) experiencing lower mean skin toxicity at the end of radiation treatment period, compared to the Sorbolene arm (mean = 2.7, 95% CI: 2.5–3.0, $P = 0.002$) (see Fig. 2). At the end of radiation treatment, the majority of grade 3 and above RD were located in the neck and collar (18/65, 27.7%), and face, neck and collar (17/65, 26.2%) regions (Supplementary Materials, 2). At the end of treatment, the StrataXRT[®] arm had a lower percentage of grade 2 (80%) and grade 3 (28%) skin toxicity compared to the Sorbolene arm (91% and 45% respectively). After adjustment for Cetuximab, the StrataXRT[®] arm had a 12% lower risk of experiencing grade 2 skin toxicity (RRR = 0.876, 95% CI: 0.778–0.987, $P = 0.031$); and a 36% lower risk of experiencing grade 3 skin toxicity (RRR = 0.648, 95% CI: 0.442–0.947, $P = 0.025$), compared to the Sorbolene arm.

Patients receiving StrataXRT[®] had a longer period without grade 2 skin toxicity with a median survival of four weeks compared to three weeks for the Sorbolene arm. Cox regression analysis showed that patients receiving StrataXRT[®] had a 41.0% reduced risk of developing grade 2 skin toxicity throughout treatment compared to the Sorbolene arm (Table 2, Fig. 2). Patients receiving StrataXRT[®] also had a longer period without grade 3 skin toxicity with 75% of patient's surviving six weeks compared to five weeks for the Sorbolene arm. Cox regression showed that patients receiving StrataXRT[®] had a 49.4% reduced risk of developing grade 3 skin toxicity throughout treatment compared to the Sorbolene arm (Table 3, Fig. 2).

Pain, itching, skin-related quality of life, treatment interruption, and adverse events

Patients in the StrataXRT[®] arm generally reported better scores (lower pain and itching, and better quality of life) compared to the Sorbolene arm, these findings did not reach statistical significance (Table 4). Baseline scores were not found to be predictive of the end of treatment scores except for quality of life. The groups were equal at baseline and adjustment produced similar results. Therefore, baseline characteristics were not adjusted for the final models. No treatment interruptions and adverse events related to study products were reported in either arm.

Discussion

To the best of our knowledge, this RCT is the first definitive trial to yield significant, positive effects of non-steroidal topical preparation for RD in patients with head and neck cancer [6]. The results

Table 2
Survival estimates and hazard ratios for grade two skin toxicity ($n = 194$).

	Grouping	Total N	N of Events	Censored		Median survival	95% CI for Median survival		Hazard Ratio	95% CI for Hazard		P-value
				N	%		Lower Bound	Upper Bound		Lower	Upper	
Group	StrataXRT [®]	99	86	13	13.1	4.000	3.518	4.482	0.590	0.437	0.797	<0.001
	Sorbolene	95	89	6	6.3	3.000	2.816	3.184	1.000			
Cetuximab	Yes								1.090	0.669	1.777	0.728
	No								1.000			

Table 3Survival estimates and hazard ratios for grade three skin toxicity ($n = 194$).

Group	StrataXRT® Sorbolene	Total N	N of Events	Censored		75% survival	95% CI for 75% survival		Hazard Ratio	95% CI for Hazard		P-value
				N	%		Lower Bound	Upper Bound		Lower	Upper	
Cetuximab	Yes	99	31	68	68.7	6.00	5.470	6.260	0.506	0.318	0.803	0.004
	No	95	47	48	50.5	5.00	4.577	5.423	1.000	1.296	4.169	0.005

Table 4Mean itchiness, pain and skin toxicity at the end of treatment ($n = 189$).

	Arm		Mean	95% CI		P-value
				Lower	Upper	
Itching	Cetuximab	StrataXRT	2.560	1.777	3.687	0.856
		Sorbolene	2.646	1.826	3.835	
Worst pain	Cetuximab	Yes	2.280	1.233	4.216	0.419
		No	2.971	2.464	3.583	
Least pain	Cetuximab	StrataXRT	4.066	2.913	5.677	0.448
		Sorbolene	4.716	3.382	6.575	
Average pain	Cetuximab	Yes	6.248	3.773	10.348	0.011
		No	3.069	2.496	3.774	
Quality of life	Cetuximab	StrataXRT	1.180	0.703	1.981	0.991
		Sorbolene	1.184	0.714	1.962	
Quality of life	Cetuximab	Yes	1.350	0.602	3.027	0.546
		No	1.035	0.771	1.391	
Quality of life	Cetuximab	StrataXRT	0.939	0.461	1.913	0.521
		Sorbolene	1.200	0.635	2.269	
Quality of life	Cetuximab	Yes	1.292	0.451	3.697	0.494
		No	0.873	0.587	1.298	
Quality of life	Cetuximab	StrataXRT	19.321	14.628	25.521	0.333
		Sorbolene	22.464	17.112	29.490	
Quality of life	Cetuximab	Yes	25.344	16.514	38.895	0.094
		No	17.126	14.549	20.160	

Note: Higher score representing worse outcomes.

of this study suggest that StrataXRT® is superior to Sorbolene (standard care) in preventing, delaying, and reducing severity of skin toxicity. Over the past, numerous systematic reviews and clinical trials have been undertaken to investigate the best interventions for preventing and managing RD [3,5]. However, the results were mostly disappointing as common shortfalls were obvious methodological flaws and reporting of negative results, with the exception of trials that tested corticosteroids [3]. The most promising interventions are those that are supported by a novel biological rationale and an extraordinary claim of effectiveness [34]. In this case, we evaluated a silicone-based film forming gel dressing that aimed to reduce TEWL and mechanical friction, thereby preventing, delaying, and reducing grade 2 and 3 RD.

We consider these results and this proposed hypothesis a major breakthrough in the RD literature. Although there have been emerging evidence suggesting the usefulness of silicone-based film dressings [17,18], most of the products tested in the literature were solid dressings. These dressings do not adhere well to certain areas of the body or in the shower [18]. The film forming gel dressing tested in this current trial has been shown to be easy to apply, acceptable, feasible and effective for head and neck cancer patients, even in situations where body hair is present. Further, the invisible nature is likely to be appealing to patients. It was also worth noting that there were no adverse events/allergic events due to products in this study. This can be also due to the exclusion of any known allergy to the study products at enrolment.

We were not able to demonstrate any differences in patient-reported outcomes including dermatitis related quality of life and symptoms such as itching, and pain. Firstly, this trial was not powered to detect differences in secondary outcomes. Although

patients in the StrataXRT® arm generally reported better scores (lower pain and itching, and better quality of life), these findings did not reach statistical significance. Secondly, it is not uncommon for RD trials to fail to detect differences in patient-reported outcomes [2]. One possible explanation is the lack of well-validated quality of life tools for patients with RD [2,25,26]. The Skindex-16 might not have been sensitive enough to detect the treatment effects on RD. In terms of pain and itching, patients could have taken other measures of self-management strategies such as over the counter medications. Collecting data on self-management strategies was not within the scope of this trial.

There were limitations in this study. During the design phase of the study, the researchers made a decision to compare StrataXRT® with standard care (i.e. Sorbolene) which is one of the most commonly used topical preparation in preventing or managing RD. As such, we were not able to blind the patient or clinicians. We did, however blind the outcome assessor (for the primary outcome) to the treatment allocation. Therefore, we considered the single blind approach as a minor limitation as this should have no effect on the assessment of the primary outcome. Adaptive radiation therapy was provided to patients as clinically indicated, however, no ongoing skin dose measurements were taken during the course of radiation treatment. This limitation was expected to have a minimal (if any) impact on the outcome in this randomised trial. Another limitation is that this trial only focused on head and neck cancers treatment fields. While it is reasonable to postulate that the findings can serve as secondary evidence for other cancer types/treatment areas of the body, this trial should be replicated to confirm the efficacy of StrataXRT® for other cancer types or treatment fields.

Conclusions

This definitive RCT suggests that StrataXRT[®] is effective for preventing, delaying and reducing severity of RD in patients with head and neck cancer. This trial should be replicated to determine the clinical effectiveness of StrataXRT[®] for other cancer types.

Funding/Conflicts of interest

The research costs and products used in this industry sponsored trial were provided by the manufacturer (*Strat Pharma Switzerland*). None of the investigators own any shares of the products in any form. StratPharma had no involvement in the study design and conduct of the trial. However, StratPharma was given an opportunity to review the paper prior to the submission of this manuscript. There is no limitation for the investigators to publish the results in peer-reviewed journals.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2019.07.014>.

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