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Barrier Films and Dressings for the Prevention of Acute Radiation Dermatitis: A Systematic Review and Meta-Analysis

Jolien Robijns PhD[1] (ORCID:0000-0002-6286-1581), Michele Aquilano MD[2] (ORCID: 0000-0001-9460-6406), Suvam Banerjee MBBS(C), MIPHA, AMRSPH (UK)[3] (ORCID: 0000-0002-8441-0642), Saverio Caini MD PhD[4] (ORCID: 0000-0002-2262-1102), Julie Ryan Wolf PhD MPH[5] (ORCID: 0000-0002-0592-7820), Corina van den Hurk PhD[6] (ORCID: 0000-0002-7802-1034), Mara Beveridge MD[7], Henry Lam MLS[8] (ORCID: 0000-0003-4517-5552), Pierluigi Bonomo MD[9] (ORCID: 0000-0001-8999-5208), Edward Chow MBBS[10] (ORCID: 0000-0002-3075-1898), Tara Behroozian MD (C)[11]

Affiliations

[1]Faculty of Medicine and Life Sciences, Limburg Clinical Research Center, Hasselt University, Hasselt, Belgium

[2]Department of Biomedical, Experimental, and Clinical Sciences "Mario Serio", University of Florence, Florence, Italy

[3] Burdwan Medical College and Hospital, The West Bengal University of Health Sciences, Department of Health and Family Welfare, Government of West Bengal, India

[4] Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPO), Florence, Italy

[5] Departments of Dermatology and Radiation Oncology, University of Rochester Medical Centre, Rochester, New York, USA

[6] Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands

[7] Department of Dermatology, University Hospitals, Cleveland OH, USA

[8] Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

[9] Department of Radiation Oncology, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

[10] Department of Radiation Oncology, University of Toronto, Toronto ON, Canada

[11] Michael G. DeGroote School of Medicine, McMaster University, Hamilton ON, Canada

Corresponding Author

Tara Behroozian

Michael G. DeGroote School of Medicine, McMaster University, Hamilton ON, Canada

Tara.Behroozian@medportal.ca

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Abstract

Purpose

This systematic review and meta-analysis aimed to evaluate the efficacy of barrier films and dressings in preventing acute radiation dermatitis (RD).

Methods

OVID Medline, Embase, and Cochrane databases were searched from 1946 to September 2020 to identify randomized controlled trials on the use of barrier films or dressings to prevent RD. For comparable outcomes between studies, pooled effect sizes and 95% confidence intervals (CI) were calculated using the random effects analysis in RevMan 5.4.

Results

Fourteen and 11 studies were included in the qualitative and quantitative analyses, respectively. Five types of barrier films used for RD were identified: Hydrofilm, StrataXRT®, Mepitel® Film, 3M™ Cavilon™ No-Sting Barrier Film, and silver leaf nylon dressing. Hydrofilm and Mepitel Film significantly reduced the development of RD grade ≥2 in breast and head and neck cancer patients (RR 0.32, 95%CI 0.19, 0.56, p<0.0001; RR 0.21, 95%CI 0.05, 0.89, p=0.03, resp.). Moreover, Hydrofilm had a beneficial effect on patient-reported outcomes (PROs) (SMD -0.75, 95%CI -1.2, -0.29, p=0.001). The meta-analyses on the other barrier films did not show any significant effect.

Conclusion

This review and meta-analysis demonstrated that Hydrofilm and Mepitel Film could effectively reduce RD severity and improve PROs. The evidence is generally weak for all the studies on barrier films and dressings due to a limited study number, high risk of bias, small sample sizes, and minimal comparable outcome measures. It's potential has been proven, but future research in this field is recommended to confirm the efficacy of these products and assess real-world feasibility.

Keywords

Acute radiation dermatitis; Barrier film; Dressing; Meta-analysis; Radiotherapy; Skin toxicity; Systematic review

1. Introduction

Radiation dermatitis (RD) is a common adverse effect among patients undergoing radiotherapy (RT) for cancer. RD can be characterized as acute or late depending on the timing of onset, whereby the development of acute RD begins within four weeks of initiating RT, and late toxicities arise 90 days or more after treatment completion [1]. Acute RD can range in severity, from mild erythema to moist desquamation and skin ulceration in severe cases, while late toxicity often includes telangiectasia, fibrosis, and edema [1, 2]. To date, there is still no golden standard for the prevention and management of acute RD [3].

The severity of RD is related primarily to aspects of the treatment (e.g., total dose, size of treatment field, fractionation regimen, other therapies, etc.) and patient characteristics (e.g., body mass index, smoking status, comorbidities, racial background, etc.) [4, 5]. Skin abrasion due to friction with clothing or skin-to-skin contact is also an important risk factor for RD [6]. Consequently, a skin barrier protectant may offer a solution to this problem [4, 7].

Skin barrier protectants are topical formulations designed to keep the skin barrier function intact by hindering the desquamation of superficial keratinocytes at the stratum corneum [8, 9]. Moreover, they can protect intact or injured skin from chemical and mechanical insults, such as body and wound fluids, adhesives, friction, and shear. Generally, these products involve a transparent protective coating on the skin and can be applied to intact, broken, or irritated skin [7]. They are formulated from various substances, such as acrylates, organic and inorganic polymers, or silicone. Skin barrier protectants are generally intended for external use only and contraindicated in cases of open or deep puncture wounds. The use of skin barrier protectants is also based on the evidence that a moist wound-healing environment facilitates re-epithelialization, allowing for a 50% increase in wound healing rates [2]. To date, skin barrier protectants are mainly used to manage Moisture Associated Skin Damage (MASD) [10]. However, its use in preventing skin damage, specifically RD, has barely been investigated. Therefore, a meta-analysis on this topic is highly needed [11].

Five types of skin barrier films and dressings have met the inclusion criteria for this review. They have been investigated in RD through multiple randomized controlled trials (RCTs), including Hydrofilm®, StrataXRT®, Mepitel® film, 3M™ Cavilon™ No-Sting Barrier Film, and silver leaf nylon dressings (SLND). Hydrofilm is a waterproof, transparent

polyurethane film coated with a hypoallergenic polyacrylate adhesive [12, 13]. StrataXRT is a semi-permeable, self-drying, transparent silicone gel which forms a thin, flexible, protective coating [14, 15]. Mepitel Film is a sterile, transparent, breathable, and adhesive soft silicone film [16, 17]. No-Sting Barrier Film is a terpolymer-based alcohol-free barrier film that is durable, breathable, fast-drying, non-sticky, waterproof, and hypo-allergenic [18]. Finally, SLND is a nonadherent nanocrystalline silver-coated dressing [19, 20].

The present systematic review and meta-analysis was conducted to assess the potential efficacy of barrier films and dressings preventing RD and their impact on RD-associated symptoms.

2. Materials and methods

The full methodology of this study will be reported in a separate publication. In summary, an initial systematic review was conducted to identify original studies on interventions for RD prevention and management for the development of the Multinational Association for Supportive Cancer (MASCC) Clinical Practice Guidelines on RD. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement to search OVID Medline, Embase, and Cochrane literature databases from 1946 to September 2020 [15]. Among the studies identified in the initial systematic review, studies were chosen for inclusion in this review if they (1) investigated a product with one or more RCTs assessing efficacy in the prevention of RD, and (2) assessed a barrier film or dressing versus standard skin care, a placebo, or no intervention. If studies met the inclusion criteria and reported quantitatively comparable outcomes, they were included in the meta-analysis. Data extraction was completed by two independent reviewers (M.A., J.R. and S.B.) to ensure consistency and accuracy.

Forest plots were developed using the Cochrane RevMan 5.4 software, where random effects models were used to generate 95% confidence intervals (CI). Risk of bias was assessed using the Cochrane Risk of Bias (RoB) tool [21]. Two independent reviewers assessed the risk of bias of each trial (S.B. and M.A.). Certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria [22]. For each study, methodological quality of evidence was assessed using the Hadorn criteria [23].

3. Results

3.1. Literature search results

Fourteen studies met the inclusion criteria for this review. They were published between 2004 and 2020, among which the following skin barrier protectants were addressed: Hydrofilm [12, 13], StrataXRT [14, 15], Mepitel Film [17, 24-27], No-Sting Barrier Film [18, 28, 29], and SLND [30, 31]. Of the 14 studies identified, 11 reported comparable outcomes that could be included in the meta-analysis [12-15, 17, 18, 24, 25, 27, 29, 32] (Figure 1).

3.2. Study characteristics

3.2.1. Hydrofilm

Schmeel *et al.* (2018, 2019) evaluated in two prospective, intra-patient randomized studies Hydrofilm in preventing RD with 56 breast cancer undergoing conventional fractionation and 74 hypofractionated RT (Table 1). The irradiated breast of each patient was divided into medial and lateral halves randomized to either Hydrofilm or 5% urea lotion. Hydrofilm was applied before the first RT session and replaced upon detachment (Table 1).

3.2.2. StrataXRT

Two studies investigated StrataXRT in cancer patients undergoing RT [14, 15]. Chan *et al.* (2019) performed a single-blind RCT with 197 head and neck cancer (HNC) patients. Patients either received StrataXRT or Sorbolene cream. Ahn *et al.* (2020) set up a non-blinded RCT with 49 breast cancer patients randomized to StrataXRT or X-derm®. StrataXRT was applied on the irradiated area from the start of RT, twice a day up to 4 weeks post-treatment (Table 1).

3.2.3. No-Sting Barrier Film

Three studies evaluated the role of the No-Sting Barrier Film in preventing RD in patients with breast cancer [18, 28, 29]. Graham *et al.* (2004) performed a prospective, non-blinded, intra-patient RCT with 61 post-mastectomy patients. Patients were randomized to have the No-Sting Barrier Film applied to either the medial or lateral half of their irradiated chest wall, with the other half treated with Sorbolene [18]. Shaw *et al.* (2015) set up a prospective, intra-patient, nonblinded RCT with 30 post-lumpectomy or -mastectomy patients. The patient's chest wall or remaining breast tissue was divided into two skin regions perpendicular to the scar. Patients were divided into one of the two study groups: (1) No-

Sting Barrier Film versus no intervention; and (2) No-Sting Barrier Film versus corticosteroid [28]. Lam *et al.* (2019) performed a prospective, non-blinded, intra-patient RCT with 55 post-lumpectomy patients. The breast was divided into lateral and medial halves and one half received the No-Sting Barrier Film, while the other half received Glaxal Base Cream [29]. In the three studies, a trained nurse applied the No-Sting Barrier Film two to three times weekly from the first until the last RT session. The study by Shaw *et al.* (2015) was not included in the meta-analysis because they did not report outcomes that could be quantitatively compared with other studies (Table 1).

3.2.4. Mepitel Film

We identified five studies that assessed the role of Mepitel Film in RD prevention [17, 24-27]. Two studies tested this product in 157 breast cancer patients [17, 27]. Herst *et al.* (2014) and Møller *et al.* (2018) performed intra-patient RCTs with post-lumpectomy and -mastectomy patients. The breast or chest wall was divided into medial and lateral halves to randomize Mepitel Film on one half and aqueous cream or standard of care on the other half [17, 27]. The three other studies assessed the efficacy of Mepitel Film in 123 HNC patients [24-26] . Wooding *et al.* (2017) performed an open label, intra-patient RCT and was included as two separate studies since separate randomization was done for the New Zealand (NZ) and Chinese cohort. They compared Mepitel Film to Sorbolene in the NZ cohort and to Biafine in the Chinese cohort [25]. Rades *et al.* (2019) evaluated Mepitel Film in a randomized, active-controlled, parallel-group multicenter trial. The control group received a fatty cream with 2–5% urea and a mometasone furoate cream [26]. Yan *et al.* (2020) also used an intra-patient RCT design to compare Mepitel film to Biafine [24]. Mepitel Film was applied at the start of RT by a trained nurse. It was replaced when it curled up too much, ranging from weekly to biweekly, depending on the study setup (Table 1).

3.2.5. Silver leaf nylon dressing

Two studies on SLND in preventing RD were included [30, 31]. Aquino-parsons *et al.* (2010) set up a prospective RCT with 196 breast cancer patients to evaluate the degree of RD in the inframammary fold. Patients in the experimental arm worn the SLND in the inframammary fold from the sixth RT session until 14 days post-RT. The control group received standard skin care [31]. Niazi *et al.* (2012) evaluated the effect of SLND on RD prevention in a prospective RCT with 42 patient lower gastrointestinal cancer patients.

SLND was applied from the first RT session until two weeks post-RT. The control group received sulfadiazine cream from the first signs of RD [30] (Table 1).

3.2.6. Assessment of risk of bias, certainty of evidence, and quality of evidence

The assessment of the risk of bias of the included studies is presented in Figure 2. All fourteen studies were classified as having a high risk of bias, with the main biased domains blinding of participants and personnel and other sources of bias. The GRADE tool was used to assess the certainty of the evidence of the included trials on the different outcome measures. The GRADE level was very low for four and low for eleven outcome measures (Supplementary tables 1-4). All fourteen studies had a doubtful quality of evidence with major flaws according to the Hadorn criteria (Table 1). The common major flaws in most trials were often related to the nonblinding of the patients and outcome assessors and a non-standardization of outcome management.

3.3. Meta-analysis findings

3.3.1. Hydrofilm

Schmeel *et al.* (2018, 2019) showed that Hydrofilm reduced the mean maximum Radiation Therapy Oncology Group (RTOG) grade significantly ($p<0.001$). Moreover, it significantly lowered erythema, moist desquamation, and patient-reported outcome (PROs) ($ps<0.002$) (Table 2) [12, 13].

Based on the meta-analysis of both studies, there was a significant effect of Hydrofilm on the incidence of RTOG grade 0 (RR 3.31, 95% CI 2.08, 5.29, $p<0.00001$), grade 2 (RR 0.32, 95% CI 0.19, 0.56, $p<0.0001$), and grade 2^+ in breast cancer patients (RR 0.28, 95% CI 0.16, 0.48, $p<0.00001$) with no heterogeneity ($Chi^2=0.27$, $df=1$, $p=0.61$, $I^2=0\%$; $Chi^2= 0.67$, $df=1$, $p=0.41$, $I^2=0\%$; $Chi^2=0.08$, $df=1$, $p=0.77$, $I^2=0\%$, resp.). The tests of overall effect showed that patients using Hydrofilm are 5 times more likely to remain at a RTOG grade 0, while they are 4 and 4.61 times less likely to develop RTOG grade 2 and 2^+. Hydrofilm did not influence the development of RTOG grade 1 (RR 0.91, 95% CI 0.69, 1.18, $p=0.47$). The objective evaluation of RD confirmed that Hydrofilm significantly reduced degree of erythema (SMD -0.69, 95% CI -1.14, -0.24, $p=0.003$). Hydrofilm use significantly reduced moist desquamation development (RR 0.08, 95% CI 0.01, 0.63, $p=0.02$), with no heterogeneity ($Chi^2=0.01$, $df=1$, $p=0.94$, $I^2=0\%$). The test of overall effect showed that the risk of developing moist desquamation was 2.4 times less likely with

Hydrofilm. Moreover, the use of topical corticosteroids was significantly reduced due to Hydrofilm (RR 0.08, 95% CI 0.01, 0.63, p=0.02), with no heterogeneity (Chi^2=0.01, df=1, p=0.94, I^2=0%). Patients using Hydrofilm were 2.4 less likely to apply topical corticosteroids (Figure 3a-b).

Regarding PROMs, the analysis of the pooled data showed that Hydrofilm significantly reduced the mean pruritus (SMD -0.75, 95% CI -1.2, -0.29, p=0.001), and limited day-to-day activities score (SMD -0.3, 95% CI -0.58, -0.01, p=0.04), with moderate to low heterogeneity (Chi^2=3.17, df=1, p=0.08, I^2=68%; Chi^2=1.35, df=1, p=0.25, I^2=26%, resp.). The meta-analysis revealed no significant effect of Hydrofilm on the mean pain and burning sensation score (SMD -0.52, 95% CI -1.09, -0.05, p=0.07; SMD -0.56, 95% CI -1.31, 0.19, p=0.15) (Figure 3b).

3.3.2. StrataXRT

Chan *et al.* (2019) showed that StrataXRT significantly reduced the incidence of Common Terminology Criteria for Adverse Events (CTCAE) grade 2 and 3 RD (ps<0.004). They reported no differences in PROMs [15]. On the other hand, Ahn *et al.* (2020) demonstrated only a significant effect of StrataXRT on the degree of erythema and pigmentation (ps<0.015) [14] (Table 2).

The meta-analysis revealed no significant effect of StrataXRT on the maximum CTCAE score (SMD -0.17, 95% CI -0.42, 0.08, p=0.18). StrataXRT did also not influence PROMs, namely pruritus (SMD -0.02, 95% CI -0.27, 0.24, p=0.90). and pain (SMD -0.06, 95% CI -0.31, 0.19, p=0.66) (Supplemental Figure 1).

3.3.3. No-Sting Barrier Film

Graham *et al.* (2004) showed that No-Sting Barrier Film reduced the incidence and duration of moist desquamation (ps<0.05) [18]. The results of Shaw *et al.* (2015) only indicated that No-Sting Barrier film could slow down the development of pruritus, but the effect was not significant [28]. Lam *et al.* (2019) showed that No-Sting Barrier Film could significantly reduce RD on the lateral compartment of the chest wall (p=0.041). Moreover, it significantly reduced pruritus (p=0.035) on the medial part and burning sensations on the lateral part of the chest wall (p=0.047) [29] (Table 2).

The meta-analysis of the studies by Graham *et al.* and Lam *et al*. revealed no significant effect of No-Sting Barrier Film on the incidence of moist desquamation on the lateral (RR 0.96, 95% CI 0.67, 1.36, p=0.80) nor on the medial side of the chest wall (RR 1.06, 95% CI 0.75, 1.50, p=0.75) (Supplemental Figure 2).

3.3.4. Mepitel Film

The studies by Herst *et al.* (2014) and Møller *et al.* (2018) showed that Mepitel Film completely prevented moist desquamation and reduced RD severity in breast cancer patients (ps<0.001) [27, 17]. In addition, Møller *et al.* showed that Mepitel Film reduced PROMs (ps<0.017) [17]. Wooding *et al.* (2017) demonstrated in both cohorts of HNC patients that Mepitel Film significantly decreased the severity of RD based on the Radiation-Induced Skin Reaction Assessment Scale (RISRAS) (ps<0.003) [25]. The study by Rades *et al.* (2019) was prematurely stopped because Mepitel Film was not tolerated well, and results showed no significant effect on RD severity [26]. Yan *et al.* (2020) demonstrated that Mepitel Film significantly reduced the development of moist desquamation and the overall RISRAS score (ps<0.007) [24] (Table 2).

The meta-analysis on the data of Herst *et al*. (2014) and Møller *et al.* (2018) showed that Mepitel Film significantly reduced the development of grade 2^+ RD in breast cancer patients (RR 0.21, 95% CI 0.05, 0.89, p=0.03), with a high level of heterogeneity (Chi^2=5.05, df=1, p=0.02, I^2=80%). Breast cancer patients are 2.12 times less likely to develop grade 2^+ RD. Mepitel Film did not influence RTOG grade 1 and 2 incidences in breast cancer patients (RR 1.12, 95% CI 0.89, 1.41, p=0.35; RR 0.22, 95% CI 0.04, 1.07, p=0.06, resp.) (Figure 4a).

Pooling the data of Wooding *et al.* (2017) and Yan *et al.* (2020) demonstrated that HNC patients using Mepitel film developed significantly more RTOG grade 1 RD (RR 2.99, 95% CI 1.46, 6.12, p=0.003), with no heterogeneity (Chi^2=0.19, df=2, p=0.91, I^2=0%). HNC patients using Mepitel Film are 3 times more likely to develop grade 1 RD. Additionally, the meta-analysis on the same studies demonstrated that Mepitel Film significantly reduced the patient (SMD -0.52, 95% CI -0.86, -0.19, p=0.002), researcher (SMD -0.87, 95% CI -1.24, -0.51, p<0.00001) and total RISRAS score (SMD -0.94, 95% CI -1.29, -0.59, p<0.00001), with no to low heterogeneity (Chi^2=0.43, df=2, p=0.80, I^2=0%; Chi^2=2.19, df=2, p=0.34, I^2=9%, Chi^2=0.65, df=2, p=0.72, I^2=0%, resp.). There was no significant difference in total skin dose between the Mepitel Film and control HNC patients (SMD 0.02, 95% CI -0.31, 0.35 p=0.90) (Figure 4b).

The meta-analysis on the data of Wooding *et al*. (2017), Rades *et al.* (2019) and Yan *et al.* (2020) revealed that Mepitel Film significantly reduced RTOG grade 2 RD in HNC patients (RR 0.81, 95% CI 0.68, 0.97, p=0.02), with no heterogeneity (Chi^2=2.81, df=3, p=0.42, I^2=0%). HNC patients using Mepitel Film are 2.24 less likely to develop grade 2 RD. Mepitel Film did not influence the incidence of RTOG grade 2^+ (RR 0.84, 95% CI 0.64, 1.09, p=0.19), 3 (RR 0.68, 95% CI 0.21, 2.16, p=0.51) and moist desquamation (RR 0.60, 95% CI 0.33, 1.08, p=0.09) in HNC patients (Figure 4a).

3.3.5. Silver leaf nylon dressing

The results of Aquino-Parsons *et al.* (2010) showed that SLND did not reduce the development of moist desquamation in the inframammary fold. However, it did reduce the degree of pruritus in the final week of RT and one-week post-RT (ps<0.019) [31]. Niazi *et al*. (2012) demonstrated a significant effect of SLND on the mean dermatitis score in rectal and anal cancer patients (p=0.01) (Table 2) [30]. A meta-analysis on SLND was not possible because there were no comparable outcome measures available.

4. Discussion

The present paper is a systematic review and meta-analysis assessing the effect of barrier films and dressings in preventing RD in cancer patients. According to our findings, Hydrofilm and Mepitel Film significantly reduced RD clinical signs in breast cancer and HNC patients. Additionally, Hydrofilm had a beneficial effect on PROs (e.g., pruritus and limited day-to-day activities score) and topical corticosteroid use in breast cancer patients. The StrataXRT and No-Sting Barrier Film meta-analyses revealed no significant effect on RD severity or PROs. No meta-analysis on SLND was possible.

The research and use of barrier films and dressings in general wound care have increased, resulting in various options, including semi-permeable films, foam dressings, hydroactive dressings, hydrocolloids, hydrogels, alginates, and smart textiles. The benefits of wound dressings and films are multiple. They include building a barrier against infection and abrasion, maintaining a moist environment, absorbing excessive extracellular fluid, maintaining proper temperature, and ameliorating patient symptoms (e.g., pain, pruritus, burning sensation, etc.). Choosing the most appropriate wound dressing or film depends on the wound characteristics, such as the origin, pathophysiology, and condition of a wound [33, 34].

Hydrofilm, Mepitel Film, No-Sting barrier film, and StrataXRT are semi-permeable film dressings with similar functions, i.e., superficial skin protection. The main difference between them is the construction and adhesion material. Hydrofilm is built out of polyurethane and is applied to the skin via a hypoallergenic polyacrylate adhesive, resulting in a more permanent attachment and difficult premature removal. Mepitel Film is a silicone barrier film that uses the Safetac® technology to minimize pain and trauma when changed or removed. StrataXRT is silicone gel that allows a perfect adaptation to body surfaces and does not need removal. No-Sting Barrier Film is a terpolymer and flexible barrier film that does not need to be removed. These film barriers are not suited for moderately to highly exuding wounds [35]. On the other hand, SLND are nonadherent and easy to remove silver-based dressings, mainly used in burn wound management [19, 36].

Fernández-Castro *et al.* (2017) evaluated the effectiveness of semi-permeable dressings, including Mepitel Film, for RD prevention in a systematic review. They concluded that the evidence is weak and more rigorous trials are needed to provide more substantial evidence [11]. Wan *et al.* (2019) evaluated the evidence of Mepitel Film in a short communication, stating that the evidence to include it in standard clinical guidelines for RD is not possible due to missing multi-centered RCTs and the high heterogeneity of the available studies [37]. Micheli *et al.* (2017) assessed the effectiveness of No-Sting Barrier Film in protecting skin integrity in various wound models including RD. They concluded that No-Sting Barrier Film could be used in post-mastectomy patients, but the evidence is weak, and future studies should consider more robust designs with appropriate controlled interventions, larger sample sizes, more extended follow-up periods, and validated skin assessment tools [38]. Rosenthal *et al.* (2019) reviewed the evidence regarding the management of RD and presented a treatment algorithm for clinicians. They concluded that SLND demonstrated to be beneficial in RD management and recommended them in standard clinical practice. A meta-analysis by Chan *et al.* (2014) concluded that there is too limited evidence to make a concrete conclusion about dressings for RD management [39]. The systematic review and meta-analysis by Ginex *et al.* (2020) combined the different studied barrier films in one analysis and showed a significant reduction in RD severity and PROs [40].

Recommendations regarding barrier films and dressings to prevent RD are highly variable across existing guidelines on RD care [41]. The Multinational Association for Supportive Cancer (MASCC) Skin Toxicity Study group (2013) made a weak recommendation against SLND due to weak evidence [42]. The updated version of the MASCC RD guidelines is being developed and will be published in 2022. The Oncology Nursing Society (ONS) made a conditional recommendation suggesting semi-permeable dressings in addition to standard of care to reduce RD in their 2020 guidelines. The certainty in the overall evidence was considered low due to concerns regarding the risk of bias and imprecision [43]. The International Society of Nurses in Cancer Care (ISNCC) panel (2021) made a weak recommendation to use StrataXRT to prevent RD. They had insufficient evidence to support or refute Hydrofilm, Mepilex Film, No-Sting Barrier Film, and SLND [44].

The current systematic review and meta-analysis strength is a robust methodology based on a comprehensive search of literature and precise inclusion and exclusion criteria. On the other hand, the primary limitation of the present paper is that, in the meta-analysis, we could only include studies with comparable outcomes. Indeed, since there is no standardization of RD assessment, all outcome data extracted from the trials could not be compared quantitatively. Therefore, the width of the confidence interval for the included studies is broad, as is for the meta-analysis, which depends on the precision of the individual study estimates and the number of combined studies. Moreover, across the studies included, the quality of evidence was doubtful and there was a high risk of bias. A potential limitation of this analysis could also be comparing outcomes reported by slightly different scales. Behroozian et al. (2021, n=777) demonstrated that clinician-reported outcomes (CROs) and PROs have a low level of agreement. Clinicians significantly underreport RD symptoms compared to patients [45]. Studies often did not use scoring systems for HRQoL or RD symptoms. It would be interesting for future trials to include both CROs and PROs. Moreover, control arms were considered together to improve comparability across trials, even if the standard arm partially differed between each study. Finally, most included studies focused on breast cancer patients, while also other patient groups suffer from RD, which should also be considered in future research.

5. Conclusion

This systematic review and meta-analysis on the use of barrier films and dressing to prevent RD demonstrated that Hydrofilm and Mepitel Film had beneficial effects on RD severity. Moreover, Hydrofilm improved PROMs and reduced the use of topical corticosteroids in breast cancer patients. The meta-analysis revealed no significant effects of No-Sting Barrier Film and StrataXRT. No meta-analysis on SLND was possible. The high risk of bias, low patient numbers, and limited comparability of outcomes require increased standardization in outcome assessment across trials on RD. Future studies should investigate larger patient populations with a wider variety of cancer types in well-designed trials (e.g., double-blind RCT), combining CROs and PROs. Moreover, studies should also focus on the cost-effectiveness, comparative effectiveness, potential adverse effects, and patients' satisfaction with the studied barrier films.

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Figure captions

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Fig. 2 Summary of risk of bias assessment

Fig. 3 a) Forest plot of comparison: Hydrofilm versus control. Outcome: Incidence of RTOG grade 0, 1, 2, 2+, moist desquamation, and topical corticoid use**. b)** Forest plot of comparison: Hydrofilm versus control. Outcome: Mean pruritus score, mean pain score, mean burning sensation score, mean limited day-to-day activities score, mean objective erythema score.

CI, confidence interval; IV, inverse variance; M-H, Mantel-Haenszel; SD, standard deviation; Std., standardized; RTOG, Radiation Therapy Oncology Group

Fig. 4 a) Forest plot of comparison: Mepitel Film versus control. Outcome: Incidence of RTOG grade 0, 1, 2, 2+ in breast cancer patients and RTOG grade 1, 2, 2+, 3 and moist desquamation in head and neck cancer patients

CI, confidence interval; M-H, Mantel-Haenszel; RTOG, Radiation Therapy Oncology Group

Fig. 4 b) Forest plot of comparison: Mepitel Film versus control. Outcome: Mean RISRAS patient, researcher and total score and mean total skin dose in head and neck cancer

CI, confidence interval; IV, inverse variance; SD, standard deviation; Std., standardized; RISRAS, Radiation-Induced Skin Reaction Assessment Scale

Table 1 Study Characteristics

First author (ref.)	Blinding	Experimental arm (n)	Control arm (n)	Mean age (range)	Cancer type	RT regimen (dose, fractionation, type of technique)	Timing of administration	Methods used to assess RD	Methodological Quality of Evidence	Risk of Bias
Chan et al., 2019 (10)	Single-blind	StrataXRT (100)	Sorbolene (97)	63.8 (50.8-75.9)	Head and neck cancer	D: >50 Gy F: - T: VMAT	Twice daily, starting from the first day of RT up to 4 weeks post-RT	CTCAE Skindex-16	Doubtful	High
Ahn et al., 2020 (9)	Nonblinded	StrataXRT (21)	X-derm (28)	47.5 (29-60)	Breast cancer	D: 60 Gy F: 2 Gy T: External beam RT	Twice daily, starting from the first day of RT up to 4 weeks post-RT	CSSP CTCAE RTOG PROMs (dryness, itchiness, burning sensation, and pain) Objective skin measures (erythema, melanin, TEWL)	Doubtful	High
Schmeel et al., 2018 (7)	Nonblinded	Hydrofilm (56)	Urea lotion (56)	62 (36-82)	Breast cancer	D: 66 Gy F: 2 Gy T: IMRT or VMAT	Before the first RT session on the medial or lateral side of the irradiated breast, and replaced upon detachment or at least every two weeks	RTOG/ EORTC, RISRAS	Doubtful	High
Schmeel et al., 2019 (8)	Nonblinded	Hydrofilm (74)	Urea lotion (74)	60.31 (37-84)	Breast cancer	D: 40.05 – 56.05 Gy F: 2 Gy T: IMRT or VMAT	Before the first RT session on the medial or lateral side of the irradiated breast, and replaced upon detachment or at least every two weeks	CTCAE, RISRAS	Doubtful	High
Graham et al., 2004 (13)	Non-blinded	No-Sting Barrier Film (61)	Sorbolene (61)	58 (30–88)	Breast cancer	D: 50-60 Gy F: 2 Gy T: -	Twice weekly if allocated to the medial compartment and three times weekly if allocated to the lateral compartment of the chest wall	RTOG PROMs (pain, pruritus)	Doubtful	High
Shaw et al., 2015 (23)	Nonblinded	No-Sting Barrier Film (30)	- No intervention (13) - Corticosteroid (17)	51 (30-79	Breast cancer	D: 60 Gy F: 2 Gy T: -	Every other day during RT (except weekend)	RTOG PROMs (pain, pruritus)	Doubtful	High
Lam et al., 2019 (24)	Investigator blinded	No-Sting Barrier Film (55)	Glaxal Base cream (55)	62.1 (45-86)	Breast cancer	D: 42.5 -50 Gy F: 2 - 2.66 Gy T: -	Twice weekly from the first RT session in the lateral or medial half of the breast	STAT RTOG PROMs (itching, burning, pulling, tenderness)	Doubtful	High
Herst et al., 2014 (22)	Nonblinded	Mepitel Film (78)	Aqueous cream (78)	58 (30-88)	Breast cancer	D: 40-54 Gy F: 2 - 2.66 Gy T: -	From the first RT session and was replaced when curled up too	RISRAS RTOG Skin dose measurements	Doubtful	High

							much (every 1 or 2 weeks)			
Wooding et al., 2017 (20)	Nonblinded	Mepitel Film (33)	NZ cohort: Sorbolene (22) Chinese cohort: Biafine (11)	-	Head and neck cancer	D: 60-66Gy (NZ), 74 Gy (Chinese) F: 2 -2.2 Gy T: IMRT or VMAT	From the first day of RT and was changed when curled up	RISRAS RTOG Skin dose	Doubtful	High
Møller et al., 2018 (12)	Investigator-blinded	Mepitel Film (79)	Standard skin care (79)	61.9 (31-82)	Breast cancer	D: 40 Gy F: 2.66 Gy T: IMRT	From the first RT session and was changed every 1 or 2 weeks	RTOG/EORTC PROMs (pain, itching, burning, edema, sensitive skin, flaky skin, effect on work/daily activities)	Doubtful	High
Rades et al., 2019 (27)	Nonblinded	Mepitel Film (23)	Standard skin care (28)	-	Head and neck cancer	D: 50 Gy F: 2 Gy T: VMAT	From the first day of RT and continued until moist desquamation or grade 3 RD occurred, otherwise until one week post-RT	CTCAE PROMs (pain)	Doubtful	High
Yan et al., 2020 (19)	Nonblinded	Mepitel Film (39)	Biafine (39)	54 (37–69)	Head and neck cancer	D: 70-74 Gy F: 2 Gy T: VMAT or IMRT	From the first day of RT and was replaced if it came off the skin overnight or if significant areas curled up at the edges	RISRAS RTOG Skin dose	Doubtful	High
Aquino-Parsons et al., 2010 (26)	Nonblinded	Silver leaf nylon dressing (93)	Standard skin care (103)	57	Breast cancer	D: 42.5 -50.4 Gy F: 1.8-2.66 Gy T: -	From the sixth fraction of RT until 14 days post-RT	RTOG PROMs (itching, pain, burning)	Doubtful	High
Niazi et al., 2012 (25)	Investigator-blinded	Silver leaf nylon dressing (19)	Standard skin care (19)	62.45	Gastro-intestinal cancer	D: 50.4-59.4 Gy F: 1.8 Gy T: 3D-CRT	Day 1 of RT, 24 hours per day 7 days per week, except during RT delivery time, up to 2 weeks post-RT	CTCAE	Doubtful	High

Abbreviations. 3D-CRT, Three-dimensional conventional radiotherapy; CSSP, Catterall skin scoring profile; D, dose; EORTC, European organization for research and treatment of cancer; F, fractionation; IMRT, Intensity-modulated radiation therapy; -, not specified; PROM, patient-reported outcome measure; RISRAS, Radiation-Induced Skin Reaction Assessment Scale; RT, radiotherapy; RTOG, radiotherapy oncology group; T, technique; TEWL, transepidermal water loss; VMAT, Volumetric-Modulated Arc Therapy

Table 2 Primary and secondary outcomes

Study	Topical agent	Cancer type	Sample size	Primary outcomes	Secondary outcomes
Chan et al., 2019 (10)	StrataXRT	Head and neck cancer	197	StrataXRT patients experience lower mean skin toxicity at the end of RT (P = 0.002). At the end of RT, 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 (RR = 0.876,95% CI: 0.778–0.987, P=0.031); and a 36% lower risk of experiencing grade 3 skin toxicity (RR = 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 respective 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.
Ahn et al., 2020 (9)	StrataXRT	Breast cancer	49	Two-way repeated- measures ANOVA revealed different patterns of changes in the erythema index (F=3.609, p=0.008) and melanin index (F=3.475, p=0.015).	The post hoc analysis demonstrated a significantly lower erythema index and melanin index in the patients allocated to the StrataXRT group.
Schmeel et al.2018 (7)	Hydrofilm	Breast cancer	56	In the Hydrofilm compartments, mean maximum RTOG/EORTC radiation dermatitis severity grades were significantly reduced from 1.33 to 0.35	The photospectrometric measurements showed significantly reduced erythema severity compared to the control compartments (overall response rate, 89.3%). Hydrofilm prevented moist desquamation and significantly reduced patients' experience of itching and pain.
Schmeel et al.2019 (8)	Hydrofilm	Breast cancer	74	Compared to the control compartments physician- assessed radiation dermatitis severity was reduced in the Hydrofilm compartments (mean 0.54 vs. 1.34; p≤0.001)	Objective photospectrometric skin measurements showed decreased erythema (p = 0.0001) and hyperpigmentation (p= 0.002) with Hydrofilm. Hydrofilm prevented moist desquamation and significantly reduced patients' experience of itching and pain
***Graham et al. 2004* (13)**	No-Sting Barrier Film	Breast cancer	61	Rates of moist desquamation were significantly different statistically (p=0.002 and 0.049, Respectively for No-Sting Barrier Film and Sorbolene)	No statistically significant differences were noted in the pain scores. The pruritus scores were significantl y reduced in the No-Sting Barrier Film area (area under the curve, p 0.011).
***Shaw et al. 2015* (23)**	No-Sting Barrier Film	Breast cancer	39	No statistically significant difference; P: 0.072 between No-Sting Barrier Film and Elomet application, in later occurrence of Grade 1 pruritus than the use of Elomet.	No statistically significant difference; p: 0.289 between No-Sting Barrier Film and corticosteroid.
***Lam et al. 2019* (24)**	No-Sting Barrier Film	Breast cancer	55	No significantly difference in the time-to- onset of grade 2 dermatitis between No-Sting Barrier Film and standard of care treated halves, (p= 0.89).	A statistically significant difference in burning sensations on the lateral compartments (p= 0.047) and pruritus on the medial compartments (p= 0.035) when 3M ™ Cavilon was applied
***Herst et al. 2014* (22)**	Mepitel film	Breast cancer	78	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).	Mepitel Film significantly decreased the combined, researcher and patients RISRAS scores (p< 0.0001) by 92% compared with aqueous cream.
Wooding et al. (Chinese cohort) (20)	Mepitel film	Head and neck cancer	11	The differences in reaction severity of the combined and researcher components of RISRAS were statistically significant (p=0.003 for both), whilst the patient component of the RISRAS showed no statistically significant difference in skin reaction severity between Mepitel Film and Cream covered skin patches (p = 0.185).	No statistically significant difference between patches covered in Mepitel Film or Cream
Wooding et al. (NZ cohort) (20)	Mepitel film	Head and neck cancer	22	The difference in skin reaction severity between Mepitel Film and Cream skin patches was statistically significant for combine d, researcher and patient	No statistically significant difference between patches covered in Mepitel Film or Cream

				components of RISRAS for the NZ cohort (p-values of <0.001, 0.001 and <0.001 respectively).	
Møller et al., 2018 **(12)**	Mepitel film	Breast cancer	79	A statistically significant lower level of pain (p<0.001), itching (p=0.005), burning sensation (p= 0.005) as well as edema (p=0.017) and reduced sensitivity (p <0.001) in patient treated with Mepitel Film compared to standard of care.	
Rades et al. 2019 **(27)**	Mepitel film	Head and neck cancer	51	No significant difference in grade ≥ 2 RD between Mepitel Film and standard of care (fatty cream with 2–5% urea and mometasone furoate cream).	No difference between Mepitel and standard of care (fatty cream with 2–5% urea and mometasone furoate cream) in pain scores.
Yan et al. 2020 (19)	Mepitel film	Head and neck cancer	39	A statistically significant, 41% decrease in moist desquamation incidence (P < 0.001) in favour of Mepitel Film-covered skin.	A statistically significant decrease in skin reaction severity for combine d, researcher and patients RISRAS components of 30%,32% and 23%, respectively (P < 0.001, 0.001 and 0.007, respectively. No significant difference in skin dose between Mepitel Film- covered skin and Biafine cream- covered skin (P = 0.925
Aquino-Parsons et al. 2010 **(26)**	Silver Leaf Nylon	Breast cancer	196	No significant difference in the presence of moist desquamation, erythema or RTOG skin toxicity scores between silver nylon leaf dressing and standard of care (hydrogel or sulfadiazine cream).	
Niazi et al. 2012 **(25)**	Silver Leaf Nylon	Lower gastrointestinal cancer	38	The mean dermatitis score for the standard arm was 2.53 and 1.67 for silver leaf nylon dressing (SD, 1.2). The difference between these mean scores was statistically significant (P=0.01).	

CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; NZ, New Zealand; RD = radiation dermatitis; RISRAS, Radiation-induced skin reaction assessment scale; RR, relative risk; RTOG, Radiation Therapy Oncology Group; SD, standard deviation.