Editorial Commentary | Symptom Management in Palliative Medicine and Palliative Care

Mepitel Film for the prevention of acute radiation dermatitis in breast cancer patients: a discussion of recent findings

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Breast cancer is the most common non-cutaneous malignancy, with an estimated 2.26 million cases of invasive breast cancer diagnosed worldwide in 2020 (1). Radiation therapy is a standard component of multidisciplinary breast cancer treatment in the definitive setting and is also used frequently for palliation of more advanced disease presentations (2).

Acute radiation dermatitis (ARD) is one of the most common adverse effects of breast radiotherapy and is characterized by symptoms such as erythema, tenderness, pruritus, dry desquamation, and/or moist desquamation that occur within 90 days of starting treatment (3). Patients who develop acute skin toxicities during or after their treatment, especially those who develop moist desquamation, may be more likely to develop irreversible late toxicities such as fibrosis and telangiectasias, which can negatively impact cosmesis and quality of life (4,5). Additionally, severe ARD can lead to interruptions in the planned radiation treatment schedule, which can potentially compromise locoregional control (6).

Historically, there has been a lack of consensus on optimal interventions in the prevention and management of ARD, leading to variability in clinical practice (3,7). Determining the most effective approach for ARD prevention, mitigation and care is of great interest, as it has the potential to improve both short- and long-term patient outcomes after radiotherapy (3). One proposed method to prevent ARD is the use of Mepitel Film (MF), a thin, silicone-based film utilizing Safetac technology that can be worn during and after radiotherapy (8). The results of a randomized controlled trial (RCT) published in 2014 by Herst *et al.* found that the prophylactic use of MF in patients undergoing breast radiotherapy improved both clinician- and patient-reported outcomes of skin reaction severity compared to patients receiving a standard skin care regimen (9). Moreover, MF completely prevented the occurrence of moist desquamation. The results of a second RCT published in 2018 by Møller *et al.* reported improved patient-reported outcomes but no significant difference in clinician-reported outcomes of skin reactions to breast radiotherapy with prophylactic MF application compared to patients offered a standard skin care option (10).

Thus, a confirmatory RCT was conducted to evaluate the prophylactic use of MF in preventing ARD during and after breast radiotherapy compared to the institution's standard skin care regimen, which included the use of aqueous creams such as Lubriderm and Glaxal. The results of this RCT were published by Behroozian *et al.* in 2023. Unlike

the two previous RCTs, this study chose to focus specifically on two subsets of patients at increased risk for ARD: (I) patients with large breasts who underwent lumpectomy; and (II) patients of any breast size who underwent mastectomy before adjuvant radiation therapy (11).

The study utilized a 2:1 random allocation of patients to receive MF or a standard skin care regimen, with the allocation weighting due to the previously reported superiority of MF. Patients were stratified by surgery type (lumpectomy or mastectomy), radiation treatment regimen (conventional fractionation or hypofractionation), and whether they received a boost or bolus (boost and/or bolus administration versus no boost or bolus). Acute toxicities up to three months post-radiotherapy were analyzed and reported. ARD was graded by healthcare professionals (HCPs) using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, a set of guidelines used to grade adverse treatment effects on a scale from grade 1 (G1) (mild) to G5 (death related to the adverse effect). HCPs and patients were also asked to complete the Radiation-induced Skin Reaction Assessment Scale (RISRAS), a previously validated tool to evaluate skin toxicities (12). Additionally, HCPs and patients were asked to complete the skin symptom assessment (SSA) four-point scale (score of 1= none to score of 4= severe) for the following acute effects: pruritus, pain/soreness, blistering/peeling, erythema, pigmentation, edema, and trouble fitting brassieres. The primary endpoint was the occurrence of CTCAE G2 or G3 ARD events, and secondary endpoints included clinician- and patient-reported outcomes via RISRAS and the SSA (11).

The results of the study showed that MF significantly reduced the combined incidence of G2 and G3 ARD events [odds ratio (OR): 0.20, 95% confidence interval (CI): 0.12–0.34, P<0.0001] with the effect similar across all stratification factors (P=0.85). MF also significantly reduced the incidence of G3 ARD events (OR: 0.19, 95% CI: 0.07–0.45, P<0.0002) and moist desquamation (OR: 0.36, 95% CI: 0.19–0.68, P=0.002). In patient-assessed RISRAS, patients in the MF arm reported significantly lower levels of discomfort/pain (P=0.001), burning sensation (P=0.004), and total RISRAS score (P=0.005), even after adjusting for all stratification factors, compared to patients treated with the standard skin care regimen. In HCP-assessed RISRAS, patients in the MF arm had significantly lower scores for erythema (P<0.0001), moist desquamation (P<0.0001), and total RISRAS score (P<0.0001). Additionally, patients in the MF arm had significantly lower combined patient- and HCP-assessed RISRAS scores (P<0.0001). In patient-assessed SSA, patients using MF reported significantly lower scores in blistering/peeling (P=0.009), erythema (P=0.001), pigmentation (P<0.0001), and edema (P=0.03). In clinician-assessed SSA, patients using MF had significantly lower scores in pain/soreness (P=0.0009), blistering/peeling (P=0.009), erythema (P<0.0001) and pigmentation (P=0.001). Patients in the MF arm were prescribed less antibiotics to manage ARD events than patients in the standard skin care arm (P<0.0001). There was no difference in topical corticosteroid use between groups (11).

This study importantly showed improvements in HCP and patient-reported outcomes of skin reactions in patients using MF, unlike in Møller *et al.*, which only demonstrated improved patient-reported outcomes, although it should be noted that HCP-reported outcomes were blinded in the Møller *et al.* study, unlike in the Herst *et al.* and Behroozian *et al.* studies (9-11). However, as in the study by Møller *et al.*, patients using MF in this current study reported similar reductions in tenderness, discomfort/pain, and burning sensations by RISRAS, as well as reductions in blistering/peeling, erythema, pigmentation and edema by patient-assessed SSA (10,11). While this study demonstrated improvement in HCP-reported outcomes as in Herst *et al.*, this study did not find that MF completely prevented moist desquamation (9,11). However, the differences in findings between this study and the others could be related to the fact that the patient population in this study was at a baseline higher risk for developing moist desquamation and severe ARD (11). In fact, in the report by Møller *et al.*, it was found that the subgroup of mastectomy patients using MF had significantly less HCP-assessed skin toxicity on the last day of radiotherapy compared to mastectomy patients in the standard arm (P=0.005) (10).

While the study clearly demonstrated improved rates of higher-grade skin toxicities including moist desquamation with the use of MF, it also draws attention to some of the limitations in the existing tools and scales for measuring ARD. For example, both the CTCAE and the RISRAS scales grade the severity of dermatitis by the degree of erythema; in the HCP RISRAS scale, erythema may range from dusky pink to dull red, brilliant red, and deep red/purple. By depending on erythema, these scales inherently under-reflect ARD in patients with darker skin tones, who more often develop hyperpigmentation than erythema. Several studies demonstrate that Black patients are more likely than White patients to experience under-recognized radiation dermatitis symptoms, to have discordance between

patient- and provider-reported symptoms, and to experience more severe ARD overall (13-16). Behroozian *et al.* are commended for including multiple toxicity assessment scales reflecting both patient and provider perspectives, and for reporting Fitzpatrick skin types. However, the study was not stratified according to different skin types (11). As lighter skin types (I and II) were overrepresented in the MF group compared to the control group (33.5% and 22.4%, respectively) and darker skin tones have been associated with increased risk for severe ARD, this may have skewed the results of the study in favor of the intervention (11,16). Additionally, the lack of validated scales that apply across the full spectrum of skin tones is a notable limitation within our field and in this study. An objective, operator-independent system for measuring ARD and baseline skin pigmentation is necessary in order to evaluate radiation skin toxicity in skin of color. Multiple tools are under investigation, including colorimetry, spectrophotometry, ultrasound, and others. Studies investigating spectrophotometry have demonstrated success in using this tool, but overall, these novel assessment tools are often costly, difficult to use, and not broadly accessible for routine clinical use (17). Thus, the development of simple, user-friendly and widely available tools that are applicable across skin tones and correlate with patient experience is of great interest. The Michigan Scale for ARD and the gRADient scale are examples of more inclusive scales that are under study and could be utilized in future studies reporting on the potential benefits of MF in skin of color (18,19). Additionally, there has been some evidence supporting the use of deep learning techniques for assessing ARD in head and neck cancers, suggesting that artificial intelligence-based methods have potential as a future method to assess ARD after breast RT in a more efficient and unbiased manner (20).

Several pragmatic challenges of utilizing MF were brought to light when conducting the trial reported by Behroozian *et al.*, including poor adherence of the MF to the supraclavicular and axillary regions, some impediment in daily activities, the need for very careful application in patients with larger breasts, increased time needed to check the film before treatments, and high relative cost of MF. Some strengths of the study include its use of various assessment methods and the stratification of patients by factors that may impact ARD risk, whereas limitations include its non-blinded design, limited number of patients receiving conventional fractionation, and that many follow-up visits were virtual due to the COVID-19 pandemic. Of note, 6 patients (<5%) switched to standard skin care from MF due to inability to tolerate MF for reasons such as developing an allergic rash (11). Key information about each of the three discussed RCTs is summarized in *Table 1*.

In a systematic review and meta-analysis of the three RCTs, it was concluded that MF reduced the incidence of G3 and G2 or G3 ARD as evaluated by the CTCAE and RTOG scales and reduced mean patient-evaluated and combined RISRAS score, but not the researcher-evaluated RISRAS score. However, the authors noted that these RCTs used different methods to report outcomes and also noted high heterogeneity in the results, which were limitations of the analysis (21). Another recent meta-analysis including studies on both MF and Hydrofilm also concluded that these products are associated with improved patient- and clinician-reported outcomes related to ARD, highlighting that there are barrier films other than MF with the potential to reduce ARD (22). A systematic review on StrataXRT, a gel that forms a barrier film, found that this intervention reduced the risk of developing moderate to severe ARD compared to standard of care (SOC), and the differences between StrataXRT and MF were insignificant (23).

The first of a recently published series of two papers from the Multinational Association of Supportive Care in Cancer (MASCC) Oncodermatology Study Group Radiation Dermatitis Guidelines Working Group was a systematic review of 235 original studies on the prevention and management of ARD (3). It found that MF, in addition to photobiomodulation therapy, mometasone, betamethasone, olive oil, and oral enzyme mixtures, showed promising evidence across multiple RCTs as potential approaches to ARD prevention. However, they reported that due to several limitations, such as high variability in the way that studies assessed symptoms and reported outcomes, they feel that it is difficult to develop any clinical practice guidelines based solely on this evidence. Similarly, a commentary published in 2019 also concluded that there would be difficulty in developing clinical guidelines on the usage of MF based on the studies by Herst *et al.* and Møller *et al.* due to differences in the way that symptoms were recorded and analyzed in these studies (24).

The second paper in the MASCC series utilized a four-round Delphi consensus process to collect and integrate the opinions of 42 international experts on preventing and managing ARD based on the currently available literature. For the prevention of ARD across disease sites, this panel of experts recommended MF and photobiomodulation therapy for breast cancer patients, along with Hydrofilm, mometasone, betamethasone, and olive oil for all

Table 1 Summary of RCTs investigating MF for the prevention of ARD in breast cancer patients

Study characteristic	Herst *et al.* [2014]	Møller *et al.* [2018]	Behroozian *et al.* [2023]
Inclusion	Any patient receiving RT for breast cancer	Women receiving adjuvant RT for breast cancer	Post-mastectomy patients and patients with breast size ≥36 band or ≥ C-cup undergoing adjuvant RT for breast cancer
Stratification	None	Medical center	Surgery type, RT regimen, boost or bolus administration
Number of patients receiving MF (n)	78	79	243
Number of patients in control arm (n)	Patients served as their own control	Patients served as their own control	124
Data collection methods	Patient- and HCP-assessed modified RISRAS, HCP-assessed ARD via RTOG scale	PROM, PREM, HCP-assessed ARD via RTOG/EORTC scale	HCP-assessed ARD via CTCAE v5.0, patient- and HCP-assessed RISRAS, patient- and HCP-assessed SSA
Follow-up	Three times weekly during RT, once weekly for 4 weeks post-treatment	Final day of treatment and 2 weeks post-treatment	Weekly during RT; weekly for 6 weeks post-treatment; 3, 6, 12, and 24 months post-treatment (only data up to three months post-treatment currently reported)
Results	Reduced severity of overall skin reaction severity (as assessed by RISRAS) by 92% (P<0.0001) with MF *vs.* SOC	Patients using MF reported lower levels of pain (P<0.001), itching (P=0.005), burning sensation (P=0.017) and sensitivity (P<0.001) with MF *vs.* SOC	Reduced combined G2–3 ARD with MF (15.5%; 95% CI: 11.3–20.6%) *vs.* SOC (45.6%; 95% CI: 36.7–54.8%), OR: 0.20, P<0.0001
	Decreased moist desquamation with MF *vs.* SOC (0% *vs.* 26% respectively, P<0.001)	Lower severity of ARD at RT completion (P=0.005) for post-mastectomy patients using MF *vs.* SOC	Decreased G3 ARD (2.8%; 95% CI: 1.1–5.7%) *vs.* (13.6%; 95% CI: 8.1–20.9%), OR 0.19, P<0.0002
		No difference in HCP-assessed ARD in patients using MF *vs.* SOC (P=0.1)	Decreased moist desquamation (8.0%; 95% CI: 4.9–12.0%) *vs.* SOC (19.2%; 95% CI: 12.7–27.1%), OR: 0.36, P=0.002

RCTs, randomized controlled trials; MF, Mepitel Film; ARD, acute radiation dermatitis; RT, radiation therapy; HCP, healthcare professional; RISRAS, Radiation-induced Skin Reaction Assessment Scale; RTOG, Radiation Therapy Oncology Group; PROM, Patient-Reported Outcome Measures; PREM, Patient-Reported Experience Measures; EORTC, European Organization for Research and Treatment of Cancer; CTCAE, Common Terminology Criteria for Adverse Events; SSA, skin symptom assessment; SOC, standard of care; CI, confidence interval; OR, odds ratio.

disease sites included. MF for breast cancer patients was recommended by 76% of the panel, barely surpassing the 75% consensus threshold, and as such, the panel expressed caution to clinicians when using it. Additionally, MF narrowly missed the consensus threshold for use in patients undergoing head and neck cancer radiation therapy. Of note, 94% and 97% of the expert panel recommended using the topical corticosteroids mometasone and betamethasone for the prevention of ARD, respectively, the highest levels of consensus received by any of the approaches for preventing ARD (7). Like the RCT by Behroozian *et al.*, the papers in the MASCC series also expressed concerns about the cost of MF, which was estimated to be 91.15 CAD (about 67.52 USD) on average in the Behroozian *et al.* trial, and the time associated with administering it. The concern was raised that an intervention like MF might not be easily accessible to all institutions and to those living in lower income areas (3,7,11). In addition, the availability of MF has been called into question, as acquisition of MF has proven to be a challenge in some geographic areas. Another practical issue is the relatively poor adherence of MF to the axillary and supraclavicular regions, and thus

optimization of the film and/or application techniques are needed or an additional method to prevent ARD needs to be utilized for these regions (11). The issues of film adherence and cost may be exaggerated depending on the climate, and it should be noted that all three of the RCTs published to date were performed in regions of low humidity and cool temperatures. As adherence of the film may vary by temperature and humidity, further study of the efficacy of MF in more tropical climates is also warranted.

The results for MF are most impressive for breast cancer patients at high risk for ARD, and further study will be revealing to understand the impact of MF in preventing ARD for lower-risk patients and for patients being treated with radiotherapy for other disease sites, such as head and neck cancers. The ongoing Alliance RCT comparing the use of MF to SOC skin care management (allowing the use of mometasone furoate in the SOC arm) in the post-mastectomy setting will also add valuable insight (NCT04989504). Of note, all published and ongoing studies investigating MF have been performed in patients undergoing photon RT. As the utilization of proton therapy grows across disease sites, including for breast cancer patients, future investigation into the efficacy of MF in reducing ARD in patients receiving proton therapy will be of value (25). Additionally, studies directly comparing MF to other interventions, such as topical corticosteroids and other barrier films, would be extremely valuable for the development of clinical guidelines. Given the promising data to date, opportunities to improve the time and cost efficiency of administering MF should be explored to allow this intervention to be a more accessible SOC treatment option for patients.

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Footnote

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