

Peer Review File

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Reviewer A

This is a well-written commentary summarising the recent publications on Mepitel film for preventing radiation dermatitis in high-risk breast cancer patients. The authors have highlighted in detail the strengths and weaknesses of the studies and their implications for clinical practice.

To enrich the discussion, I would suggest the authors to consider adding the following points:

1. A systematic review and meta-analysis of the three randomised controlled trials on Mepitel film was recently published (DOI: 10.1007/s00520-023-07982-2). The pooled results of the randomised controlled trials should be discussed in this paper.

Reply: Thank you for this valuable suggestion. The results of this systematic review and meta-analysis are now included beginning at line 161 in the revised copy.

Changes in the text: Added - *“In a systematic review and meta-analysis of the three RCTs, it was concluded that MF reduced the incidence of grade 3 and grade 2 or 3 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).”*

2. It should be discussed that while Mepitel film has shown significant benefits in reducing radiation dermatitis in the chest wall or breast, the supraclavicular region has not been addressed in the studies. In clinical practice, other methods to prevent radiation dermatitis may be required for this area, or the film has to be modified to better adhere to this region for future clinical trials.

Reply: Thank you for this comment. A sentence was added beginning in line 202 discussing this important point.

Changes in the text: Added – *“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).”*

3. The exact costs of the film will be a useful piece of information for the reader and should be discussed. This can be referred to in the feasibility study by Yee et al. (DOI: 10.1016/j.prro.2020.09.004)

Reply: The exact cost of the film as estimated in the Behroozian et al. study was included in line 197 of the revised copy.

Changes in the text: *“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.”*

4. The authors may consider discussing that the tolerance to the film may vary depending on the humidity and temperature of the region that the patients live in. The existing three studies were performed in areas with a relatively cool and dry climate. Further validation of the effectiveness and tolerability of the film needs to be performed in more tropical areas.

Reply: Thank you for this raising this important point. A discussion on this has been added beginning in line 204.

Changes in the text: *“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.”*

5. The authors may consider discussing that published and ongoing studies on Mepitel film are performed in patients undergoing photon irradiation. Proton therapy may be associated with greater skin toxicities, and future clinical trials should evaluate the effectiveness in patients undergoing this type of treatment.

Reply: Thank you for this comment. A discussion on this has been included beginning in line 214.

Changes in the text: *“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).”*

6. StrataXRT is a silicone-based film-forming gel with some evidence of preventing breast radiation dermatitis. A small study published in abstract form has shown that it is non-inferior to Mepitel film (Chao et al. ESTRO 2019). The authors may consider adding it to the section on agents that should be compared to Mepitel film in future clinical trials.

Reply: Thank you for this comment. Discussion on a recently published systematic review and meta-analysis on StrataXRT was cited and discussed beginning in line 169.

Changes in the text: *“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 SOC, and the differences between StrataXRT and MF were insignificant (23).”*

7. With regards to assessment methods for radiation dermatitis, the authors may consider adding a discussion on artificial intelligence-based assessments, which has some evidence in head and neck cancers (DOI: 10.1016/j.ijrobp.2022.03.011.Epub 2022 Mar 15)

Reply: Thank you for this comment. A sentence discussing the potential of AI-based assessments with the suggested citation has been included beginning in line 146.

Changes in the text: *“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).”*

Reviewer B

Chakraborty et al. provide a comprehensive overview of the emerging evidence on Mepitel Film for the prevention of acute radiation dermatitis in breast cancer. The work is well-written and concise.

The reviewer has some minor suggestions:

- Line 43: As APM is an international journal, consider providing worldwide data on breast cancer/DCIS prevalence instead of just for the USA.

Reply: Thank you for this important suggestion. The introductory sentence was changed to include worldwide breast cancer incidence data instead of just for USA.

Changes in the text: *“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).”*

- Lines 50 and 93: Pruritus instead of pruritis.

Reply: Thank you for noting this mistake. These instances of “pruritis” were changed to “pruritus.”

- Line 58: Consider adding a reference (e.g. 10.1007/s00520-022-06829-6 or 10.1007/s00066-023-02074-w).

Reply: Thank you for this suggestion. References were added as suggested.

- Line 68 and other: The correct name of the author is Møller, not Moller.

Reply: Thank you for noting this. All instances of “Moller” were changed to “Møller”.

- Line 70: It should be mentioned that the clinician-reported outcome in the trial by Møller et al. was blinded (contrary to Herst and Behroozian).

Reply: Thank you for this comment. This information was added to a sentence beginning at line 102.

Changes in the text: *“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).**”*

- Line 75: Consider removing the word initial, as full follow-up on all patients was provided.

Reply: Thank you for this suggestion. The word “initial” was removed (line 65).

Changes in the text: *“**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: 1) patients with large breasts*

who underwent lumpectomy, and 2) patients of any breast size who underwent mastectomy before adjuvant radiation therapy (11).”

- Line 91: The original work by Noble-Adams could be cited (10.12968/bjon.1999.8.19.1305).

Reply: Thank you for this suggestion. A citation to the original work by Noble-Adams was added.

- Line 115: It should be mentioned that the rate of topical corticosteroid use, another endpoint in trials investigating ARD prevention methods, was not different between groups.

Reply: Thank you for this comment. The text was modified beginning starting at line 100 to incorporate this important point.

Changes in the text: *“There was no difference in topical corticosteroid use between groups (11).”*

- Line 143: Behroozian et al. did not stratify patients according to Fitzpatrick skin type, an established risk factor for ARD (e.g., 10.3390/cancers12092444). Lighter skin types (I and II) were overrepresented in the MF group (33 vs. 22%; $p = 0,0556$), which might have skewed the results in favour of the intervention. This should be discussed as a potential limitation of their trial.

Reply: Thank you for this comment. A discussion on this important point has been incorporated beginning in line 129.

Changes in the text: *“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).”*

- Line 149: Multiple trials have successfully investigated the use of spectrophotometry in the context of breast ARD and could be cited (e.g. 10.1007/s00066-005-1345-3, 10.3390/cancers12092444).

Reply: Thank you for this suggestion. The text was modified to include this point beginning in line 139, and the citation was added.

Changes in the text: **“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).”

- Line 202: Treated instead of treatment.

Reply: Thank you for noting this. The text has been edited from “treatment” to “treated.”

- A recently published meta-analysis of the trials by Herst, Møller, and Behroozian should be cited, as it summarises the topics mentioned in this editorial

(10.1016/j.breast.2023.07.001). Apart from MF, it also included two trials on the use of Hydrofilm, another barrier film with the same mechanism of action, which shows similar results and included objective assessment methods. The existence of other barrier films for ARD prevention could be discussed briefly.

Reply: Thank you for this comment. The results of this meta-analysis were mentioned beginning in line 166, and the existence of other barrier films such as Hydrofilm was mentioned. StrataXRT, a film-forming gel, was also discussed briefly.

Changes in the text: *“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 SOC, and the differences between StrataXRT and MF were insignificant (23).”*

Reviewer C

The authors are commended for helpfully summarising the clinical trials published on Mepitel Film prior to the recent paper by Behroozian et al., and providing a critical and well-balanced analysis of the RCT by Behroozian et al. Table 1 gives a succinct summary of the three published papers in this field.

Minor comment:

In table 1, the "inclusion" under Behroozian et al. has the following criteria "patients with breast size > 36 band or C cup...". Please check the original paper by Behroozian et al. whether it should be " \geq 36..." and " \geq C"

Reply: Thank you for this comment. The original paper by Behroozian et al. was checked and it should be " \geq ". The text in the "Inclusion" row for the "Behroozian et al." column was changed accordingly.

In table 1, the "number of patients in control arm (n)" under Herst and Moller are "patients served...own controls" and "patients served...own control" respectively. Please consider aligning whether "control" will be in singular or plural form.

Reply: Thank you for this helpful suggestion. In the "Number of Patients in Control Arm (n)" row, the "Herst et. al" column text was changed so that control is now in the singular form (so it matches with the "Møller et al." column text).