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REVIEW

Systematic review and meta-analysis on interventions for radiation dermatitis prevention and management: an overview of the methods

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Abstract

Over several decades, research on the prevention and management of acute radiation dermatitis (RD) has continued to emerge, yet there remains no "gold standard" treatment for RD care. Recent guidelines on RD prevention and management were published in 2022 by the Oncodermatology Study Group of the Multinational Association of Supportive Care in Cancer (MASCC). As part of this guideline process, a collaborative effort was undertaken by international RD experts to quantitatively compare commonly studied RD skin interventions through meta-analyses and discern superiority of interventional treatments over another intervention, standard-of-care, or placebo in RD prevention and management. This paper summarizes the materials and methodology used in a set of meta-analysis studies that supplement the 2022 MASCC Clinical Practice Guidelines on RD Prevention and Management.

Keywords Oncodermatology · Radiation dermatitis · Methods · Systematic review · Guidelines · Meta-analysis

Introduction

Acute radiation dermatitis (RD) is a prominent adverse side effect of external beam radiotherapy (RT), with symptoms arising in up to 95% of patients [1]. While RT remains a promising intervention in the prevention of locoregional cancer recurrence, RD can worsen patient's quality of life, lead to interruptions in treatment, and is often characterized by erythema, moist desquamation, edema, pruritus, and pain [2, 3]. Unfortunately, there is no "gold standard" intervention for the prevention or management of RD, despite decades of research on the topic.

Clinical practice guidelines on RD care have been published by the Multinational Association of Supportive Care in Cancer (MASCC) in 2013, along with several other institutions [4, 5]. Due to a lack of definitive guidelines and increasingly new research on RD care in the last decade, an update of guidelines was warranted. A team of experts across the globe, within and outside of MASCC, have developed the 2022 Clinical Practice Guidelines on RD Prevention and Management in accordance with the MASCC Guidelines Development Policy [6] to reflect the current literature and expert opinions on RD care. After a comprehensive literature search, further in-depth, quantitative analyses of certain types of RD interventions were highly warranted due to the high number of randomized trials available. To date, few meta-analyses have been published comparing interventions for RD care due to a lack of comparable evidence, but with increasingly available literature, systematic reviews and meta-analyses were conducted as a sub-study of the MASCC RD Guidelines Development Project. A panel of researchers assisted in the process of conducting meta-analyses to pool data across multiple primary studies. Ultimately, these reviews and meta-analyses will act as independent resources

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to guide clinical decision-making, supplementary to the upcoming MASCC Clinical Practice Guidelines.

The present paper provides an overview of the methodology used in conducting meta-analyses on various interventions used in RD prevention and management. The findings of these reviews will be published in a series of seven subsequent articles (six meta-analyses, one critical review) organized by RD treatment category.

Initial systematic review for guideline development

A comprehensive literature search was conducted for the purpose of developing updated RD guidelines by the MASCC Oncodermatology Study Group RD Guidelines Working Group [7, 8]. All study types were included in the systematic review, regardless of study design or type of skin intervention. The systematic review provided an overview of all interventions used in the prevention or management of RD. An intervention was considered preventive if administered prior to the onset of RD symptoms.

Scope of review

The scope of the review was kept broad to avoid exclusion of any relevant studies. The following inclusion and exclusion criteria were followed.

Inclusion criteria

- Original research studies on an intervention aimed at preventing or managing RD in cancer patients undergoing external beam RT
- English language
- Full-text or abstract available
- Human subjects
- RD severity or RD-related symptoms measured as primary and/or secondary outcomes

Search strategy

A medical librarian conducted a comprehensive literature search of Ovid MEDLINE, Embase, and Cochrane Central Register of Controlled Trials Databases. The search was performed on September 21, 2020 (1946 to September 2020), and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table 1).

Assessment of quality of evidence

In accordance with the MASCC Guideline Policy, quality of evidence was assessed using the Hadorn et al. (1996) criteria based on the presence of "major" or "minor" flaws across several diagnostic criteria (i.e., selection of patients, allocation of patients to treatment groups, study administration, etc.) (Table 2) [9]. Any studies with none or "minor" flaws were assigned a quality of evidence of "Adequate", while studies with "major" flaws were assigned a quality of evidence of "Doubtful", indicating potentially poor study methodology.

Systematic reviews and meta-analyses

Study selection and logistics

The literature search results are summarized in Fig. 1. After the initial systematic review, 240 studies were identified for inclusion in the development of RD guidelines (151 randomized, 89 non-randomized). Each of the RD interventions assessed within the 240 articles were compiled in a list. If a skin intervention was investigated by two or more independent randomized controlled trials (RCTs) and reported quantitatively comparable data, those RCTs were included to be further analysed through meta-analyses. Only full-texts were included. Thus, 51 RCTs were chosen for inclusion in quantitative analysis. The rationale for solely including RCTs can be explained by the fact that RCTs are considered to be of higher quality than non-randomized studies. Additionally, studies were only included if they were one of two or more studies investigating the same intervention because two or more comparable studies are required to conduct a meta-analysis. If a quantitative analysis could not be done on a given skin intervention due to a lack of comparable outcomes between RCTs, a narrative review was synthesized.

Among the RCTs included for quantitative analysis, a total of six RD intervention categories were identified: barrier films and dressings, photobiomodulation therapy, topical non-steroidal agents, topical steroidal agents, antiperspirant/deodorant, washing with water/soap, and natural and miscellaneous agents. A team of researchers across 10 countries was convened to lead each meta-analysis, with two to three co-leaders assigned to a single intervention category. Co-leaders led all stages from data collection to manuscript drafting under supervision of an advisory team within the MASCC Oncodermatology Study Group.

Data collection

Per intervention category, data extraction was completed by two to three independent reviewers to ensure consistency and accuracy. Data was collected on the patient and

Table 1 Search strategy

Database	Search strategy
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) < 1946 to September 21, 2020 >	1 exp Neoplasms/rt [Radiotherapy] (174980) 2 exp Neoplasms/ (3362351) 3 (cancer* or neoplasm* or carcinoma*).mp. (3475990) 4 exp Radiotherapy/ (186199) 5 (radiotherap* or radiation therap*).mp. (357550) 6 1 or ((2 or 3) and (4 or 5)) (315336) 7 exp Radiodermatitis/ (2369) 8 (radiation dermatitis or radiodermatitis or dermatitis).mp. (93850) 9 ((skin or dermatol*) adj3 (toxic* or react* or burn* or rash* or damage* or injur* or irritat*)).mp. (43024) 10 or/7–9 (132040) 11 th.xs. (7087210) 12 pc.fs. (1294186) 13 ((manag* or treat* or alleviat* or avoid* or lessen* or prevent* or prophyla* or control*) adj5 (skin or dermatol* or dermatitis or radiodermatitis)).mp. (59405) 14 or/11–13 (7115355) 15 6 and 10 and 14 (3522) 16 limit 15 to english language (3061) 17 limit 16 to yr = "1980-current" (2908)
Embase Classic + Embase < 1947 to 2020 Week 38 >	1 exp cancer radiotherapy/ (252364) 2 exp malignant neoplasm/rt [Radiotherapy] (255066) 3 exp malignant neoplasm/ (3730883) 4 (cancer* or neoplasm* or carcinoma*).tw,hw,kw. (4452135) 5 exp radiotherapy/ (607771) 6 exp cancer radiotherapy/ (252364) 7 (radiotherap* or radiation therap*).tw,hw,kw. (540025) 8 1 or 2 or ((3 or 4) and (5 or 6 or 7)) (583450) 9 exp radiation dermatitis/ (4502) 10 (radiation dermatitis or radiodermatitis or dermatitis).tw,hw,kw. (144407) 11 ((skin or dermatol*) adj3 (toxic* or react* or burn* or rash* or damage* or injur* or irritat*)).tw,hw,kw. (111930) 12 or/9–11 (245052) 13 th.fs. (1607011) 14 pc.fs. (1183743) 15 ((manag* or treat* or alleviat* or avoid* or lessen* or prevent* or prophyla* or control*) adj5 (skin or dermatol* or dermatitis or radiodermatitis)).tw,hw,kw. (96613) 16 or/13–15 (2724312) 17 8 and 12 and 16 (3090) 18 limit 17 to (english language and yr = "1980 -Current") (2834)
EBM Reviews—Cochrane Central Register of Controlled Trials < August 2020 >	1 exp Neoplasms/rt [Radiotherapy] (1184) 2 exp Neoplasms/ (78769) 3 (cancer* or neoplasm* or carcinoma*).mp. (201806) 4 exp Radiotherapy/ (5926) 5 (radiotherap* or radiation therap*).mp. (35854) 6 1 or ((2 or 3) and (4 or 5)) (32664) 7 exp Radiodermatitis/ (200) 8 (radiation dermatitis or radiodermatitis or dermatitis).mp. (8687) 9 ((skin or dermatol*) adj3 (toxic* or react* or burn* or rash* or damage* or injur* or irritat*)).mp. (8983) 10 or/7–9 (16685) 11 th.xs. (402320) 12 pc.fs. (91081) 13 ((manag* or treat* or alleviat* or avoid* or lessen* or prevent* or prophyla* or control*) adj5 (skin or dermatol* or dermatitis or radiodermatitis)).mp. (23405) 14 or/11–13 (419173) 15 6 and 10 and 14 (928) 16 limit 15 to english language (748) 17 limit 16 to yr = "1980-current" (739)

Table 2 Hadorn criteria (1996) for quality of evidence assessment [9]

Study design variable	Major flaws	Minor flaws
1. Selection of patients	a. Diagnostic criteria for the disease under study were not described b. The criteria for admission to and exclusion from the study were not specified c. The decision regarding inclusion or exclusion from the study was sometimes made after treatment was initiated d. The study population was not representative of the majority of patients with the condition under investigation e. For cohort studies, the study groups were not treated concurrently	a. The diagnostic criteria for the disease under study were inadequately described b. The criteria for admission to and exclusion from the study were inadequately described c. Patients were excluded from participation in the study, but no list or table of the reasons for exclusion was given
2. Allocation of patients to treatment groups	*For randomized clinical trials only:* a. Statements in the paper suggest that patients were not randomly assigned b. Known prognostic factors or confounders for the outcome of interest were not measured at baseline, or there was no comparison of the values for these variables for the study groups *For cohort or registry studies only:* a. Known prognostic factors for the outcome of interest or possible confounders were not measured at baseline	*For randomized clinical trials only:* a. Patients were not allocated to the study groups in a truly randomized fashion (e.g., randomization by birth date, every other patient given placebo) *For cohort or registry studies only:* a. None
3. Therapeutic regimen	None	a. The mean daily dose actually taken by patients during the trial was not recorded b. The actual dosing schedule was not described and only the total daily dose is given c. Titration end points were not described d. Other therapeutic maneuvers were not described adequately enough that the study could be repeated
4. Study administration	a. Patients were crossed over into the other group outside of the study design b. Medications were used that were not part of the original study design c. Other breaks in the study protocol occurred	a. In a multicenter study, methods of diagnosis, treatment, or outcome measurement were not identical among the participating centers
5. Withdrawals from study	a. Patients withdrew from the study, and the reasons for withdrawal were not listed. This includes an unexplained reduction in the number of patients recorded in the tables b. Sensitivity analysis shows that the number of withdrawals with unknown or unlisted outcomes could significantly bias the results. For example, if three patients in the treatment group who were lost to follow-up or not recorded had actually died, a significant reduction in mortality in the treated group would be made insignificant	a. There was an excessive number of withdrawals regardless of the reasons: 10% for studies lasting less than 3 months or more than 15% for studies lasting for more than 3 months
6. Patient blinding *(randomized controlled trials only)*	a. A placebo was not used for the control group b. For a study that used patient self-reported health status or symptoms as an end point, a study that claimed to be placebo controlled gave no description of how the placebo was administered	a. For a study that used mortality as an end point, a study that claimed to be placebo controlled gave no description of how the placebo was administered b. For a study that used patient self-reported health status or symptoms as an end point, the physical characteristics, side effects, or method of administration of the placebo differed from that of the active drug so that It was possible for the patlent to discern the treatment assignment

Table 2 (continued)

Study design variable	Major flaws	Minor flaws
7. Outcome measurement	a. For a study that required investigators to rate patient clinical status or measure clinical parameters, the investigators were not blinded to the patient treatment group. (Double-blind methodology was not used.) b. For a study that required investigators to rate patient clinical status or measure clinical parameters, the method of administration or the effects of the study drug and the placebo differed enough that investigators were likely to guess the patient treatment. (Double-blind methodology was attempted, but it suffered from serious flaws.)	a. For a study that measured mortality, the investigators were not blinded to the patient treatment group. (Double-blind methodology was not used.) b. For a study that measured mortality, the method of administration or the effects of the study drug and the placebo differed enough that investigators were likely to guess the patient treatment. (Double-blind methodology was attempted, but it suffered from serious flaws.)
8. Statistical analysis	a. The analytical techniques described are incorrect and there is inadequate information to perform a correct analysis b. A significant difference was found in one or more baseline characteristics that are known prognostic factors or confounders, but no adjustments were made for this in in the analysis	a. The analytical techniques described are incorrect, but there is adequate information to perform a correct analysis b. Means and tests for statistical significance are presented with no measure of the variance c. Results are presented in graphical form and tests for significance are presented without giving the actual mean values used to create the graph d. Withdrawals are not handled appropriately e. Post hoc subgroup analysis is performed f. One-sided tests are inappropriately used for testing statistical significance

treatment characteristics (e.g., cancer site, type of RT, dose fractionation schedule) and the study characteristics (e.g., blinding versus open-label). Outcome measures and results were collected as categorical variables (i.e., event proportions) and/or continuous variables (i.e., mean scores). The number of patients who experienced an outcome of interest or mean scores in the experimental and control arms were collected to estimate the OR and 95% CI. Data from the intention-to-treat and per-protocol analyses was collected where available, and the study's corresponding author was contacted in the event that both data sets were not readily available. Subgroups were determined a priori and analyses were conducted where applicable to assess the efficacy of interventions in different cancer sites or modes of administration (e.g., topical vs oral). Given the extensive variability in outcome assessment across RD trials, independent reviewers aimed to maximize the number of outcomes that could be compared across studies by assigning certain outcomes as equivalent where appropriate.

Certainty of evidence and risk of bias

To assess the certainty of evidence of each study included, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework was followed, whereby a certainty of evidence could be assigned as "very low", "low", "moderate", or "high" based on the independent assessment of two to three reviewers per intervention category [10]. GRADE ranks certainty of evidence based on several domains: risk of bias, imprecision, inconsistency, indirectness, publication bias, magnitude of effect, dose–response gradient, and residual confounding [10]. The risk of bias of each study was also assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) by two to three independent reviewers [11]. Five domains in the RoB 2 were considered: bias from the randomization process; bias from deviations from intended interventions; bias from missing outcome data; bias in outcome measurement; and bias in selection of results reported [11]. Any disagreements between reviewers on a study's uncertainty of evidence or risk of bias were resolved by consulting a third party to reach a consensus.

Statistical analysis

Forest plots were developed where possible using the Cochrane RevMan 5 software. Random effects models were used to generate 95% confidence intervals (CI). When categorical variables were included, the Mantel–Haenszel method was used to generate odds ratios (OR). When continuous variables were included, standard deviation and mean values were generated. I^2 statistic was

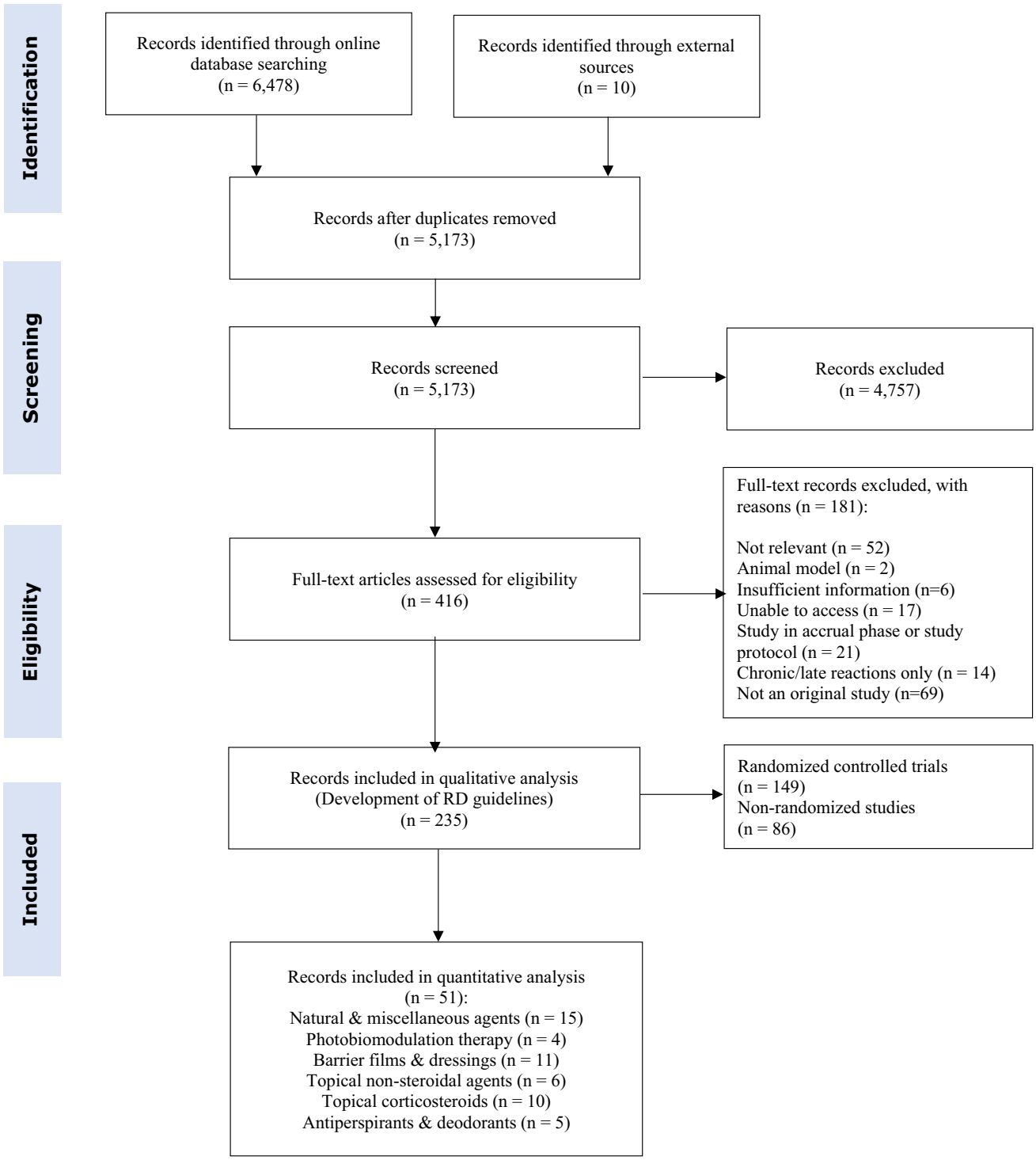

Fig. 1 PRISMA diagram

measured to indicate low heterogeneity ($I^2 < 0.25$), moderate heterogeneity ($I^2 = 0.25$–0.50), and high heterogeneity ($I^2 > 0.50$). A p-value of less than 0.05 indicated statistical significance in the test for overall effect (Z). Based on the outcome of interest that was assessed between studies, a summary OR below 1.00 indicated that the intervention under study lowered the odds of having the outcome, while a summary OR above 1.00 indicated that the intervention increased the odds of having the outcome.

Conclusion

The methods described in this paper have allowed for the findings across many RCTs on various RD interventions to be pooled together. Findings of these systematic reviews and meta-analyses will supplement the updated MASCC RD Guidelines, which will be used to guide clinical decision-making in RD care.

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Data Availability Not applicable for this manuscript.

Declarations

Ethical approval Not applicable.

Competing interests The authors declare no competing interests.

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