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REVIEW ARTICLE

Comparison of clinical practice guidelines on radiation dermatitis: a narrative review

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Abstract

Purpose Radiation dermatitis (RD) is a common side effect of radiation therapy (RT). While many different treatment strategies are currently used to address RD, there is a lack of consensus and RD prophylaxis and management guidelines have remained largely unchanged over the last 10 years. This review aims to formulate unambiguous supportive care interventions by comparing RD clinical practice guidelines published between 2010 and 2021 by several organizations: Multinational Association for Supportive Care in Cancer (MASCC), British Columbia Cancer Agency (BCCA), Cancer Care Manitoba (CCMB), Oncology Nursing Society (ONS), Society and College of Radiographers (SCoR), and International Society of Nurses in Cancer Care (ISNCC).

Methods Areas of agreement and discordance were assessed among the MASCC, BCCA, CCMB, ONS, SCoR, and ISNCC guidelines.

Results Treatment recommendations across guidelines for acute RD and chronic RT-induced skin toxicities have been summarized. The strongest agreement among the guidelines exists for the use of topical corticosteroids, silver sulfadiazine, washing, and deodorant. All guidelines recommend the use of topical corticosteroids, and washing with water and soap is consistently supported. There is minimal consensus on an optimal dressing or barrier film for RD prophylaxis or management. MASCC weakly recommends prophylactic use of silver sulfadiazine to reduce RD, while BCCA, CCMB, and SCoR recommend its use upon signs of infection. MASCC and CCMB recommend the use of a long-pulsed dye laser to manage telangiectasia, a late effect of RT.

Conclusions Given the extent of discordance among guideline recommendations, further research is recommended to establish optimal treatments for RD prophylaxis and management.

Keywords Radiation dermatitis · Clinical practice guideline · Skin care · Chronic radiation-induced skin toxicities · Radiation dermatitis prophylaxis · Radiation dermatitis management

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Introduction

Radiation dermatitis (RD) is a common side effect of radiation therapy (RT), occurring in approximately 95% of patients [1]. RD is characterized by acute and late skin effects, with the former occurring in the first weeks of RT and the latter manifesting in months to years following treatment [2]. Symptoms of acute RD range from erythema to moist desquamation, a condition characterized by tender, moist, and erythematous skin with leaking serous fluid [3, 4]. Late skin effects are progressive and often irreversible and may include cutaneous fibrosis, telangiectasia, and hyper- or hypopigmentation [5]. These disfiguring changes may significantly reduce patient quality of life (QoL) [5].

The pathogenesis of RD is well understood. Ionizing radiation damages the dermis, causing vasodilation and release of histamine-like substances, leading to the development of erythema [4]. Radiation-induced DNA damage results in the net loss of dividing basal stem cells in the epidermis [6]. Thinning of the skin follows as the superficial layers of the skin that normally shed off are not sufficiently replaced by the deeper basal cell layer, ultimately leading to dry and moist desquamation [6]. The development of late skin effects can be explained by imbalances between profibrotic and pro-inflammatory cytokines [4].

Risk factors related to patient characteristics and radiation treatment play a role in the development of acute and chronic RT-induced skin toxicities. Treatment-related factors include total dose, fractionation schedule, use of a bolus and/or boost, treatment surface area or volume, radiation technique, and use of concurrent chemotherapy or targeted agents [5, 7]. Intrinsic factors that may impact RD severity are chronic sun exposure, breast size, smoking status, diabetes, and obesity [5, 7, 8]. Many tools are used to assess acute RD and chronic RT-induced skin side effects, with scales from the Radiation Therapy Oncology Group (RTOG) and Common Terminology Criteria of Adverse Events (CTCAE) used most commonly [9]. The Late Effects Normal Tissue Task Force subjective, objective, management, and analytic (LENT/SOMA) scale is used to assess late effects [9]. The severity of RD is significantly associated with changes in patients' health-related quality of life (HRQoL) and can result in radiation interruption in severe cases [1, 10], with potential detriment to its anticancer efficacy.

Skin treatments for acute RD span several categories, including topical agents, dressings, barrier films, antibiotics, oral agents, laser therapies, standard care and hygiene, and natural agents. Currently, protocols for addressing RD are highly variable [11, 12]. Many strategies for RD prophylaxis and management have shown promise in addressing RD symptoms, but there is minimal consensus on a "gold standard" intervention. Although a smaller body of evidence exists, the same can be said for late skin effects caused by RD.

It is necessary that healthcare professionals (HCPs) have accessible and up-to-date guidelines for RD prevention and management, considering its high incidence and impact on QoL. This review aims to compare recommendations from recent RD guidelines and highlights considerations for the development and implementation of future guidelines.

Methods

A literature search was conducted to identify existing clinical practice guidelines for RD published between January 2010 and June 2021. Guidelines were compiled from a search within PubMed, Google Scholar, OVID MEDLINE, and the following clinical practice guideline databases: the Alliance for the Implementation of Clinical Practice Guidelines, Clinical Practice Guidelines Infobase, Turning Research into Practice, National Institute for Health and Care Excellence guidelines, National Health and Medical Research Council's Australian Clinical Practice Guidelines, and New Zealand Guidelines Group. RD guidelines from the American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology (ASTRO), and European Society for Therapeutic Radiology and Oncology (ESTRO) were searched for independently. First, the selection process of strength and grade of recommendations were determined and compared among the guidelines. Next, each guideline's recommendations and rationales were summarized and compared, noting significant similarities and differences. The analysis included a summary of recommendations for acute and chronic RT-induced skin toxicities, along with a consideration of grade-specific guidelines, site-specific recommendations, and risk factors that promote RD.

Results

List of RD guidelines

The six guidelines discussed in this review include the following: Multinational Association for Supportive Care in Cancer (MASCC), British Columbia Cancer Agency (BCCA), Cancer Care Manitoba (CCMB), Oncology Nursing Society (ONS), Society and College of Radiographers (SCoR), and International Society of Nurses in Cancer Care (ISNCC) [13–19]. No RD guidelines from ASCO, ASTRO, or ESTRO were found.

Evidence classification

Each organization employed a unique method in developing its RD guidelines. The respective criteria used to obtain consensus and determine the strength of recommendations are summarized in Table 1. MASCC used methodology based on Somerfield et al. to assign levels and grades of evidence for the literature evaluated [20]. CCMB used a classification scheme from Shekelle et al. to categorize evidence [21]. The system used by ONS is based on the Grading of Recommendations Assessment, Development and Evaluation approach [22]. SCoR used the Cochrane Risk of Bias (RoB) and ROBINS-I tools to measure bias in randomized and non-randomized studies, respectively [23]. ISNCC utilized the RoB 2 tool to critically appraise randomized controlled trials (RCT) [24].

Table 1 Comparison of strength and evidence of recommendations by organization

	Levels of evidence		Levels of consensus/grade of recommendation	
MASCC 2013	Level I	Meta-analyses of randomized controlled trials or randomized trials with high power	Grade A	Level I evidence or consistent findings from multiple studies of level II, III, or IV evidence
	Level II	Randomized trials with lower power	Grade B	Level II, III, or IV evidence with generally consistent findings
	Level III	Nonrandomized trials, such as cohort or case-controlled series	Grade C	Similar to grade B but with inconsistencies or where a single lower power study only is available
	Level IV	Descriptive and case studies	Grade D	Little or no evidence
	Level V	Case reports and clinical examples		
BCCA 2018	Not specified		Not specified	
CCMB 2018	Ia	Evidence obtained from meta-analysis of randomized controlled trials		
	Ib	Evidence obtained from at least one randomized controlled trial		
	IIa	Evidence obtained from at least one well-designed controlled study without randomization		
	IIb	Evidence obtained from at least one other type of well-designed, quasi-experimental study, i.e., studies without planned intervention, including observational studies		
	III	Evidence obtained from well-designed, non-experimental descriptive studies. Evidence obtained from meta-analysis or randomized controlled trials or phase II studies which is published only in abstract form		
	IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities		
ONS 2020	Strong	This recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide information that alters the recommendation		
	Conditional	This recommendation is likely to be strengthened by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional recommendation will help to identify possible research gaps		
	Research and/or knowledge gap	Available evidence is insufficient to determine true effect, and this recommendation may be appropriate for research		
SCoR 2020	Quality assessment approaches: The RoB tool was used to assess the quality of randomized trials and the ROBINS-I tool to assess the quality and risk of bias of nonrandomized studies. Case studies were not assessed for quality and not included in the summary tables. This data has only been used to inform further research recommendations. Systematic reviews were assessed using the Scottish Intercollegiate Guidelines Network checklist for systematic reviews			
ISNCC 2021	High quality Intermediate quality Low quality Insufficient RoB 2 tool used to assess the quality of randomized controlled trials		Strong Moderate Weak	

Abbreviations: MASCC, Multinational Association for Supportive Care in Cancer; *BCCA*, British Columbia Cancer Agency; *CCMB*, Cancer Care Manitoba; *ONS*, Oncology Nursing Society; *SCoR*, Society and College of Radiographers; *RoB*, risk of bias; *ROBINS-I*, Risk of Bias in Non-randomized Studies—of Interventions

Guideline recommendations

Guideline recommendations for acute RD from each organization are summarized by skin treatment category in Table 2.

MASCC

In 2013, MASCC published guidelines for acute RD prophylaxis and management, as well as management of chronic RT-induced skin toxicities [13]. Fifty-six RCTs, two

Table 2 Comparison between MASCC, BCCA, CCMB, ONS, SCoR, and ISNCC acute radiation dermatitis guidelines

Treatment type	MASCC 2013	BCCA 2018	CCMB 2018	ONS 2020	SCoR 2020	ISNCC 2021
Natural and miscellaneous agents	Almond cream: (P-) Aloe vera: (P-) Ascorbic acid: (P-) Calendula: (P-) Camomile cream: (P-) Dexpanthenol: (P-) Raygel: (P-) Theta cream: (P-)	Baby powder/cornstarch: (-)	Aloe vera: (-) Baby powder/cornstarch: (-) Talcum: (-)	Aloe vera: (P?) Calendula: (P-) Curcumin: (P?) Emu oil: (P-)	Other natural and miscellaneous agents: (?)	Aloe vera: (M-) Silymarin-based cream: (?)
Barrier films and dressings	Dressings: (M?) Silver leaf dressing: (P-, M-)	Absorbent dressing: (+) Hydrocolloid dressing: (+) Non/low adherent dressing: (+) Silicone dressing: (+) Tape/adhesive bandages: (-) Moisture-retentive barrier ointment after saline soak: (+)	Absorbent dressing: (+) Framycetin dressing: (+)** Hydrocolloid dressing: (+) Non/low adherent dressing: (+) Mepitel film: (+) Non-sting barrier film: (-) Tape/adhesive bandages: (-)	Semipermeable dressing: (P+)	Barrier film: (?) Non-adhesive dressing: (+) Paraffin/petroleum-based dressing: (-) Silicone low adhesion dressing: (+) Silver leaf dressing: (?)	Silicone-based film forming gel dressing: (P+) 3M Cavilon no-string barrier film: (?) Mepilex Lite dressings: (?) Mepitel film: (?) Silver Nylon dressing: (?)
Analgesics	-	Analgesics: (+)	Analgesics: (+)	-	Analgesics: (+)	-
Oral agents	Pentoxifylline: (P?) Proteolytic enzymes: (P?) Sucralfate: (P-) Zinc: (P?, M?)	-	Antihistamines: (+)	-	-	-
Topical corticosteroids	Corticosteroids: (P+)	Corticosteroids: (+)	Corticosteroids: (+)	Corticosteroids: (P+, M+)	Corticosteroids: (+)*	Betamethasone 17-valerate: (M+) Mometasone furoate: (M+) Hydrocortisone: (?)
Non-steroidal topical agents	Gentian violet: (?) Hyaluronic acid: (P?) Petroleum-based ointment: (P?) Sucralfate: (P?, M-) Trolamine: (P-, M-)	Hydrogel: (+) Petroleum-based ointment: (-)	Hyaluronic acid: (-) Hydrogel: (+) Petroleum-based ointment: (-)	Non-steroidal topical agents: (P-, M-)	Non-steroidal topical agents: (?) Gentian violet: (-)	Artovastatin 1%: (?) Doxepin cream: (?) Heparinoid moisturizer: (?) Topical lactokine-based R1 and R2: (?)
Laser therapy and electrosurgery	Light-emitting diode lasers: (P-)	-	-	-	Photobiomodulation therapy: (?)	-
Antibiotics	Silver sulfadiazine: (P+, M+)	Polysporin: (+)** Silver sulfadiazine: (+)**	Polysporin/neosporin: (+)** Silver sulfadiazine: (+)** Oral antibiotics: (+)**	Silver sulfadiazine: (M+)	Topical antibiotics: (+)**	Silver sulfadiazine: (?)

Table 2 (continued)

Treatment type	MASCC 2013	BCCA 2018	CCMB 2018	ONS 2020	SCoR 2020	ISNCC 2021
Standard care and hygiene	Antiperspirant/deodorant: (P+) Washing with water and soap: (P+)	Antiperspirant/deodorant: (+) Body lotions or creams: (+) Washing with water and soap: (+) Electric shaver: (+) Saline compress: (+) Sitz bath (perineal/rectal cancer): (+)	Antiperspirant/deodorant: (+) Electric shaver: (+) Aqueous cream (late reaction scaling): (+) Washing with water and soap: (+) Saline compress: (+)	Antiperspirant/deodorant: (P+) Washing with water and soap: (P+)	Antiperspirant/deodorant: (+) Moisturizer: (+) Washing with water and soap: (+) Shaving: (-)	-

(+) Recommended. (-) Not recommended. (?) Unsure or insufficient evidence/knowledge gap. *P* prophylaxis, *M* management. *Recommends preventative use of steroid cream be reserved for patients deemed at high risk to develop RD. **Recommends only in the presence of infection

guideline papers, and six systematic reviews are included in the evidence base for acute reactions. Studies on interventions designed to mitigate RD severity which had skin toxicity grade as an outcome were included. One randomized trial and three prospective single-arm studies inform the late effect guidelines for management of telangiectasia and cutaneous fibrosis. Prophylactic corticosteroids are strongly recommended to reduce acute discomfort and/or acute burning and itching (level 2, grade B). MASCC weakly recommends silver sulfadiazine for acute RD prevention and management in breast cancer (level 2, grade B) and strongly recommends washing with or without soap or shampoo (level 2, grade B).

BCCA

BCCA's most recent RD update was published in 2018, wherein the 2012 RD symptom management guidelines were revised [14]. BCCA organizes their recommendations based on a "step-up approach" that provides recommendations for each skin toxicity grade according to NCI CTCAE (version 4.03) criteria [25]. The updated guideline resembles the 2012 version with a few key changes. First, the present guideline recommends silver sulfadiazine use upon evidence of infection. Furthermore, it has a section for silicone dressings under *treatment procedures*. For patients with grade 1 acute RD, corticosteroid cream is recommended to reduce inflammation. In patients with grade 2 or 3 acute RD, BCCA recommends hydrogels and hydrocolloid dressings for moist desquamation with minimal and moderate exudate, respectively. Silicone dressings, low or non-adherent dressings, and moisture-retentive dressings are recommended for moist desquamation.

CCMB

The 2018 CCMB RD symptom management guidelines are a five-part series titled *Evidence Based Recommendations for the Assessment and Management of Radiation-Induced Skin Toxicities in Breast Cancer*. The analysis describes content from parts 4 and 5, *Management of acute radiation-induced skin toxicities* and *Management of long-term effects*. Eighty-six studies are included, and recommendations from BCCA, Cancer Care Ontario, and Winnipeg Regional Health Authority (WRHA) were evaluated against current consensus and adapted into the CCMB guidelines [26–28]. CCMB divides these guidelines based on the following symptom categories: erythema, pruritus, and dry desquamation; moist desquamation; ulceration and necrosis; and late reactions. CCMB recommends topical corticosteroids to reduce erythema and pruritus (level IV evidence). Applying a non-adherent initial dressing as a primary contact dressing is recommended for the management of moist desquamation (level IV evidence). The use of silver sulfadiazine,

Polysporin®, or oral antibiotics is recommended to treat infection (level IV evidence).

ONS

ONS published guidelines for acute RD in 2020 [15]. Evidence from this guideline was informed by a 2020 systematic review by Ginex et al. that includes 22 articles, 11 of which are RCTs [29]. Recommendations are made for minimizing RD development or RD treatment. ONS recommends washing with water and soap (strong recommendation), use of antiperspirant/deodorant (conditional recommendation), and semipermeable dressings (conditional recommendation) for the minimization of RD development. Topical corticosteroids are conditionally recommended for RD prevention and management.

SCoR

RD guidelines from SCoR were released in 2020 based on a 2019 systematic review, with articles published from 2014 to 2019 [16]. This review consists of 33 articles, including 21 RCTs [16]. SCoR recommends the use of moisturizer on intact skin. Washing and bathing are recommended during RT, and continued use of the patients' usual deodorant is supported. Corticosteroids may be recommended at the clinician's discretion for use on intact skin, whereas low adhesion or non-adhesive silicone dressings are recommended for broken skin. Topical antibiotics are recommended if infection is indicated. Insufficient evidence exists to assign recommendations on silver leaf dressings, natural or topical products, and photobiomodulation therapy. SCoR advises against shaving, gentian violet, paraffin, or petroleum-based dressing use.

ISNCC

ISNCC released guidelines for the prevention and management of acute RD in 2021 [19]. The guidelines are based on a systematic review that included 36 RCTs published between 2012 and 2020. A three-step modified Delphi consensus was conducted, resulting in four recommendation statements in the finalized guidelines. ISNCC recommends against the use of aloe vera for RD management (intermediate quality, strong). Two recommendations are made for corticosteroid use: betamethasone 17-valerate cream to manage acute RD (high quality, moderate) and mometasone furoate cream for high-grade RD (intermediate quality, weak). Lastly, ISNCC recommends the use of silicone-based film forming gel dressing for patients upon RT initiation for prevention of acute RD (intermediate quality, weak).

Comparison of recommendations of acute RD across guidelines

Natural and miscellaneous agents

MASCC strongly recommends against the use of prophylactic aloe vera for RD based on evidence from three randomized trials and a systematic review that find no benefit for its use (level 1, grade A). CCMB cites Heggie et al., claiming that aloe vera has no moisturizing effect and should only be used on intact skin for soothing and cooling purposes [30]. ISNCC strongly recommends against aloe vera use to manage acute RD. ONS makes no recommendation on aloe vera due to lack of standardization among studies in their evidence base, but notes that a review by Chan et al. shows no benefit of aloe vera for prevention and management of RD [31]. Of 15 studies of emollients examined by SCoR, no recommendation is made for any product, including aloe vera.

Barrier films and dressings

There is minimal consensus among the guidelines concerning the use of barrier films and dressings. MASCC cites insufficient evidence to provide recommendations on dressings such as hydrocolloid dressings. Similarly, SCoR reports insufficient evidence to recommend changes in practice for the use of barrier films and dressings and acknowledges the difficulty of designing such studies without introducing bias. Moreover, since literature is limited in assessing barrier films and dressings using hypofractionated RT regimens, SCoR abstains from recommending any product because conventional fractionation becomes a confounding variable. In contrast, BCCA and CCMB recommend the use of silicone-based dressings to reduce trauma and minimize pain due to moist desquamation. Mepitel® is the choice product of CCMB for an initial contact dressing for moist desquamation, based on results from an article by Glove and Harmer (2014) [32]. ISNCC makes a weak recommendation for use of silicone-based film forming gel dressing prophylactically upon RT initiation.

Analgesics

There is consensus among BCCA, CCMB, and SCoR for the use of analgesics to reduce painful RD. BCCA recommends analgesics be administered as ordered by the physician for grade 2–4 RD (CTCAE v4.03), for chronic RT-induced skin toxicities, and for radiation recall phenomenon. CCMB states that analgesics promote comfort with level IV evidence for erythema, pruritus, dry desquamation, and moist desquamation, specifying that topical analgesics are an option for pain not well controlled with oral analgesics.

SCoR states that over-the-counter or prescription analgesics should be considered during RT.

Oral agents

Oral agents do not commonly appear among the RD guidelines. Based on clinical experience, CCMB recommends oral antihistamines for managing pruritus, despite the lack of evidence to support antihistamine use for breast radiation-induced pruritus. In assessing proteolytic enzymes, MASCC examined three RCTs that show significantly lower rates of grade 2 or higher skin reaction versus controls. However, MASCC deems the evidence insufficient due to inadequate study design.

Topical corticosteroids

Each guideline recommends the use of topical corticosteroids for acute RD. MASCC recommends prophylactic use of topical agents based on evidence from five studies that demonstrate favorable results. The strongest evidence comes from an RCT by Miller et al. that demonstrates a statistically significant reduction in skin irritation and itching following administration of topical corticosteroids [33]. ONS recommends using topical corticosteroids for the minimization of RD development and symptom (e.g., pain, pruritus) treatment on intact skin. This recommendation is informed by 6 studies within a systemic review by Ginex et al. that shows a relative risk of 0.64 (95% confidence interval [0.42, 0.96]) for reducing the development of grade 2 or greater RD [29]. CCMB and BCCA recommend corticosteroid use to alleviate discomfort from grade 1 symptoms such as erythema, pruritus, and dry desquamation. SCoR recommends corticosteroid use at the advice of physicians and states that corticosteroid creams should be reserved for prophylactic use in patients at high risk of RD. ISNCC recommends betamethasone 17-valerate cream and mometasone furoate cream to manage acute RD during RT while urging discontinuation should the skin become disrupted.

Non-steroidal topical agents

No guideline makes a recommendation to use petroleum-based products. MASCC reported several studies that used Aquaphor as a control group which lacked information on the product's efficacy. BCCA recommends hydrogels to manage moist desquamation with minimal exudate, while CCMB states hydrogels should be used post-RT for non-infected ulcerating and necrotic tissue. ONS strongly recommends a standard washing and skincare regimen over non-steroidal products for both prevention and management of RD. SCoR states that there is insufficient evidence to recommend any product for topical application. ISNCC reports insufficient evidence to support or refute non-steroidal topical agents.

Laser therapy and electrosurgery

SCoR cites two studies investigating photobiomodulation therapy that each demonstrate a statistically significant reduction of moist desquamation: Robijns et al. included 120 breast cancer patients and used a placebo group, while Strouthos et al. included 70 breast cancer patients and a control group with no intervention [34, 35]. Notwithstanding this evidence, photobiomodulation is not recommended for use in practice by SCoR because it is unclear if results from the two cited studies could be replicated using hypofractionated RT schedules.

Antibiotics

All guidelines other than ISNCC recommend silver sulfadiazine to manage infection. Additionally, MASCC makes a weak recommendation for the prophylactic use of silver sulfadiazine based on a randomized trial by Hemati et al., which shows a statistically significant decrease in skin injury in patients using silver sulfadiazine prophylactically [36]. ONS considers silver sulfadiazine to be standard of care for treating moist desquamation [15]. CCMB and BCCA recommend using silver sulfadiazine only with evidence of infection. CCMB indicates a concern for potential antibiotic resistance with using silver sulfadiazine, and BCCA states the product may delay wound healing.

Standard care and hygiene

The strongest agreement among the guidelines exists for standard hygiene and care; most emphasize the importance of maintaining a clean treatment area. Routine washing with water and soap and use of deodorant/antiperspirant during RT are consistently supported.

Management of chronic radiation-induced skin toxicities and additional information on skin care

Guideline recommendations for chronic RT-induced skin toxicities from MASCC, BCCA, and CCMB are summarized in Table 3.

MASCC and CCMB recommend the use of a long-pulsed dye laser to manage telangiectasia based on a randomized trial of 13 patients by Nymann et al., which used intense-pulsed light as the comparator [37]. MASCC rates the evidence level 3, grade B, and CCMB rates it IIb. CCMB also recommends the use of intense-pulsed light, despite evidence from Nymann et al. wherein a long-pulsed dye laser exhibited superior efficacy over intense-pulsed light [37].

Table 3 Comparison between MASCC, BCCA, and CCMB chronic radiation-induced skin effect guidelines

MASCC 2013	BCCA 2018	CCMB 2018
Cutaneous fibrosis Vitamin E ± pentoxifylline: (M?) **Telangiectasia** Long-pulsed dye laser: (M+)	**Maintain skin flexibility** Lotions or creams: (+) **Prevent injury** SPF 30+ sunscreen: (+) **Manage pain** Analgesics: (+) **Prevent infection** Antibacterial/antifungal products: (+)	**Cutaneous fibrosis** Vitamin E + pentoxifylline: (M+) **Fibronecrosis** Hyperbaric oxygen therapy: (M+) **Telangiectasia** Intense pulsed light: (M+) Long-pulsed dye laser: (M+) Hyfrecator-based treatment: (M+) **Promote cleanliness** Wash with water and mild soap: (+) **Maintain skin flexibility** Moisturizing cream: (+) **Protect from environment** SPF 30+ sunscreen: (+)

(+) Recommended. (?) Unsure or insufficient evidence/knowledge gap. *M* management

MASCC states that there is insufficient evidence to recommend pentoxifylline to manage cutaneous fibrosis, citing two studies that lacked control groups [38]. In contrast, CCMB recommends pentoxifylline and vitamin E for fibrosis while acknowledging mixed results in the literature. CCMB also lists hyperbaric oxygen chamber therapy as a treatment option for fibronecrosis. Additionally, BCCA and CCMB provide guidance to prevent injury, promote cleanliness, prevent infection, manage pain, and maintain skin flexibility for chronic RT-induced skin toxicities. Recommendations for chronic RT-induced skin toxicities are not described in the guideline documents of SCoR, ONS, or ISNCC. Also, BCCA and CCMB guidelines include information on radiation recall phenomenon, and both recommend this condition be treated in the same manner as acute RD.

Discussion

To the best of our knowledge, this is the first comprehensive overview that compares international guidelines on the prevention and management of RD. Research demonstrates that guideline recommendations for RD across organizations have moderate concordance. There is high variability in the outcomes chosen to measure and the treatments included to address RD. Moreover, high-quality, comprehensive, and randomized studies measuring RD outcomes are scarce. Each guideline, excluding ISNCC, recommends the use of silver sulfadiazine to manage infection due to RD. Each guideline recommends topical corticosteroids for prevention and/or management of RD, although there is no consensus for any specific product or dose. Existing guidelines acknowledge that corticosteroids should be used only on intact skin due to potential side effects, thus urging caution for clinical use. BCCA, CCMB, SCoR, and ISNCC show consensus for the use of silicone-based dressings to reduce trauma from moist desquamation, but limited consensus exists for the use of other barrier films or dressings. The strongest consensus exists for standard hygiene and care: washing skin with water and soap and routine deodorant/antiperspirant use are consistently recommended during RT. SCoR, ONS, and ISNCC do not provide recommendations for chronic RT-induced skin toxicities; therefore, limited consensus exists for that group of recommendations. MASCC and CCMB recommend a long-pulsed dye laser to treat telangiectasia, but there is no consensus for management of cutaneous fibrosis.

Guideline development methodologies and symptom assessment methods

Each guideline described presently has associated development methodologies available except for BCCA. Comprehensive literature searches and interdisciplinary panels are used by each organization to amass available evidence and establish consensus for recommendations. An important component for trustworthy guidelines is the inclusion of ratings for the quality of evidence and the grade of recommendations [39]. ONS, MASCC, and ISNCC include both these parameters, CCMB and SCoR assess only the quality of evidence, and BCCA does not include ratings for quality of evidence or grading of recommendations. Standardized methods for quality of evidence assessment, such as the Cochrane RoB 2 for randomized studies, should be considered when developing future clinical practice guidelines.

Guideline panels may have difficulty standardizing treatment protocols due to the high variability of RD assessment methods. Studies commonly use traditional tools such as the RTOG score and the CTCAE scale to assess RD [9]. While these clinical assessment tools are validated, they are inherently subjective and lack patient-reported outcomes (PROs) such as pain, pruritus, and discomfort. Subsequently,

guidelines incorporate PROs as adjunct outcomes with variability in assessment methods used in individual studies. With no gold-standard preventative method for RD, focus should be turned towards treating the impact RD has on patients' HRQoL [40]. One symptom assessment method that incorporates both clinician-reported outcomes (CROs) and PROs is the Radiation-Induced Skin Reaction Scale (RISRAS) [41]. Moreover, there is low concordance between CROs and PROs [42]. Clinicians consistently underreport RD symptom severity in patients who receive breast irradiation [42]. Using objective RD assessment methods may help standardize outcomes in future studies, improving comparability and reproducibility. These include, among other tools, the use of reflectance spectrophotometry to measure erythema and skin pigmentation, as well as corneometry to measure skin hydration [43–46]. A new, standardized tool that incorporates CROs, PROs, and the measurement of biophysical parameters would be beneficial.

Grade-specific recommendations

MASCC, ONS, SCoR, and ISNCC largely make recommendations regarding the general outcome of RD, which may lead to ambiguity upon interpretation. In contrast, BCCA and CCMB list their recommendations in a grade- and symptoms-based approach, both using the CTCAE (v4.03) grading scale to categorize their RD guidelines [25]. ISNCC has one grade-specific recommendation for mometasone furoate cream. Standardized, grade-specific approaches to preventing and managing RD should be considered by panels and institutions since ambiguous recommendations may reduce adherence to clinical practice guidelines [47] and thereby the quality of supportive care. According to a 2017 survey of practice patterns for the treatment and prophylaxis of acute RD, 97.3% of providers determine treatment choice for acute RD by severity of RD [11]. This demonstrates the clinical importance for clear and concise grading scales. Bernier et al. proposed grade-specific recommendations based on a modified CTCAE v4.03 scale in patients receiving cetuximab and RT for head and neck squamous cell carcinoma [48]. Bernier's proposition demonstrates that the grading and management of skin reactions in those receiving cetuximab plus RT must be tailored to the patient's reaction [48]. A grade-specific approach in RD guidelines is patient-centered and should be used in future RD guideline development.

Site-specific recommendations and RD risk factors

RT delivered to specific anatomical locations is likely to produce site-specific symptoms [49]. In a survey characterizing radiation-induced skin reaction and pain, breast cancer patients demonstrated increased pain and skin reaction, while patients receiving head and neck RT experienced increased skin reaction severity, but minimal pain [50]. Additionally, anatomical regions with skin folds and creases or friction-prone areas are more susceptible to radiation-induced skin reactions, such as the inframammary fold, axilla, perineum, head and neck region, or skin folds in obese patients [51, 52]. The aforementioned guidelines provide minimal site-specific recommendations. Exceptions include MASCC, which recommends the use of silver sulfadiazine cream for breast cancer, and BCCA, which recommends sitz bath daily upon RT initiation for perineal and rectal cancers. Each guideline acknowledges risk factors for the development of RD, but it remains unclear how treatments may be optimized for an individual's risk. One solution to this issue is implementing a risk stratification algorithm to help with decision-making in practice, an idea promoted by SCoR [16]. Assessing individual patients' risk of RD development may inform management and potential prophylactic strategies. For example, SCoR suggests that prophylactic corticosteroids be reserved for patients evaluated as high-risk for RD development. A weakness in this recommendation is that SCoR does not clearly define how particular patients are deemed as "high-risk." As is the case in ONS, MASCC, and ISNCC guidelines, RD guidelines should additionally include a clear distinction between preventative and management methods to address RD. Also, recommendations regarding prophylactic treatment initiation should be provided.

Implementing guidelines into practice

With any newly developed guideline, steps must be taken to increase HCPs' awareness and subsequent uptake [53]. Implementing guidelines into clinical practice would help curtail clinician recommendations that are not evidence-based. However, several barriers for implementation exist, including the lack of trust in evidence or research, resistance from peers and superiors, difficulty changing routine practice, time limitations, and patient financial considerations [53, 54]. No investigation has determined whether adhering to current RD treatment guidelines reduces the severity of acute RD and chronic RT-induced skin toxicities. However, guideline adherence has led to positive outcomes in other settings. For example, multiple studies on chemotherapy-induced nausea and vomiting have reported improved outcomes when participants adhere to antiemetic guidelines [55–57].

Improving consensus among various organizations would likely improve adherence to evidence-based practice. The Delphi method provides an effective way of engaging a large number of participants to achieve consensus during guideline development [58]. This is a process in which a panel of experts arrive at "consensus" through multiple rounds of online questionnaires [58]. Including a larger group of

international panel members for guideline development could reduce bias in recommendations and lead to improved consensus among organizations.

Guideline implementation can be further improved by including the necessary implementation information and tools within the guidelines themselves [59]. Additionally, increasing guidelines' accessibility through public online publishing may improve adherence, promote informed decision-making for treatment, and involve patients during guideline development, all of which promote successful guideline implementation [60, 61]. According to Armstrong and Bloom, there is a substantial gap between patient and public involvement standards for guideline development [62]. ONS and SCoR report having patient representation on their guideline panels. The development and successful dissemination of current, evidence-based guidelines among institutions, HCPs, and patients may improve RD treatment outcomes.

Conclusion

RD is extremely common among patients undergoing RT to regions where the tumor is close to the skin, and its acute and chronic skin manifestations have a significant impact on HRQoL. The RD guidelines published by MASCC, BCCA, CCMB, ONS, SCoR, and ISNCC reflect recommended practices by HCPs according to available evidence. As new evidence becomes available for RD prophylaxis and management, new guidelines must be published and implemented into practice in order to optimize patient outcomes. Future guideline documents should consider individual risk factors for developing RD, incorporate grade- and site-specific recommendations, include updated guidance on managing chronic RT-induced skin toxicities, and include PROs.

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