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ORIGINAL ARTICLE

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NECOM 3: A Practical Algorithm for the Management of Radiation Therapy-Related Acute Radiation Dermatitis

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ABSTRACT

Background: In the Nordic European countries in 2020, cancer diagnoses accounted for 175,925 patients. About 50% of cancer patients receive radiation therapy (RT), which may lead to radiation dermatitis (RD). Notably, patients with breast, head, neck, and anal cancers may be prone to developing RD. However, few algorithms exist for the prevention and treatment of RD.

Methods: The Nordic European Cutaneous Oncodermatology Management (NECOM) project aims to improve cancer patient outcomes by offering tools to prevent and treat cancer therapy-related cutaneous adverse events (cAEs). The first 2 NECOM papers presented various cAEs and skincare regimens involving hygiene, moisturization, sun protection, and camouflage products for preventing and managing cAEs. The NECOM 3 practical algorithm for preventing and managing acute RD (ARD) is intended to promote healthy skin and reduce RT-related ARD, improving cancer patient outcomes.

Results: The NECOM advisors discussed the results of a systematic literature review and obtained consensus on the evidence and opinion-based practical algorithm for ARD to support all stakeholders in the Nordic European healthcare setting. The algorithm starts with skin-preserving therapy, followed by skin condition assessment and patient-specific interventions based on the grade of RD present.

Conclusion: ARD may lead to symptoms of pruritus and pain, decreased QoL and morbidity, and treatment interruptions. Patient education on the prevention of RD and treatment recommendations given in the NECOM 3 algorithm may help prevent and manage RD and improve the overall care of patients receiving RT.

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INTRODUCTION

New cancer cases in 2020 in Europe, excluding non-melanoma skin cancer, are estimated at 4 million cases.[1] Breast (530,000 patients), colorectal (520,000), lung (480,000), and prostate (470,000) cancer accounted for almost half of the overall cancer burden in Europe in 2020.[1] The estimated number of cancer deaths in Europe was over 710,000 in males and 560,000 in females.[1] An analysis over the past 50 years confirms the progress in improved cancer control; in 84% of patients, 5-year survival was over 60%.[2] Metastases remain a challenge, emphasizing the need for early detection before metastasis occurs.[2]

In the Nordic European countries in 2020, all cancer diagnoses accounted for 175,925 patients.[3,4]

Of the 1,92 million estimated United States patients diagnosed with cancer in 2022, approximately 50% require radiation therapy (RT).[5] RT's most common side effect is radiation dermatitis (RD), particularly in patients with breast, head, neck, and anal cancers. RD may develop with a broad spectrum in severity and degree and considerable heterogeneity in its management.[5] Few clinical treatment algorithms exist to prevent and treat RD, underscoring the need to develop uniform, evidence-directed recommendations.[6,7] The Nordic European Cutaneous Oncodermatology Management (NECOM) practical algorithm for preventing and managing acute RD (ARD) in patients with cancer and survivors is intended to promote healthy skin and reduce cancer treatment-related cutaneous adverse events (cAEs).

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Status of the Nordic European Cutaneous Oncodermatology Management Project

The NECOM project aims to improve cancer patient outcomes by offering tools for preventing and managing cAEs. A review paper (NECOM 1) explored clinical insights in cAEs and focused on skincare regimens involving hygiene, moisturization, sun protection, and camouflage products.[6] The NECOM 2 publication discussed a skincare algorithm for patients with cancer and survivors to promote healthy skin and reduce cancer treatment-related cAEs.[7] Oncology nurses are central to the cancer treatment ecosystem, bridging patients and other healthcare professionals (HCPs).[7]

Scope of the Nordic European Cutaneous Oncodermatology Management 3 Algorithm

The NECOM 3 publication presents a practical algorithm for preventing and managing ARD using behavioral interventions, diagnostic interventions, prevention and treatment measures, and a skincare regimen involving hygiene, moisturization, and sun protection measures.[6] The algorithm aims to reduce inflammation and promote healing skin areas affected by ARD by applying topical treatments and skincare. In addition, the panel aims to reduce the ARD of patients receiving RT by determining the best approach for oncology skincare programs in Nordic European countries.

MATERIALS AND METHODS

A modified Delphi process was used for the algorithm's development, following the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.[8-10] The process entailed preparing the project, selecting the advisors, conducting systematic literature searches, summarizing the literature search results, grading the literature, and drafting the algorithm.[8-10] On September 9, 2022, the panel convened to discuss the systematic literature review results and draft the algorithm by integrating evidence and the clinical expertise of the panelists. A further online process was to refine the algorithm and prepare and review the publication. Even though the current algorithm is adapted to Nordic European countries, it could be applied worldwide to support all healthcare providers treating oncology patients, including physicians, nurses, pharmacists, and advanced providers.

Literature Review

The searches focused on the literature describing current best practices in improving cutaneous health during RT, reducing inflammation, and promoting healing of skin affected by ARD. The search topics were deemed clinically relevant to the algorithm and included guidelines, consensus papers, reviews, and publications describing the current best practice in ARD in the English language from January 2010 to August 2022. A dermatologist and a physician associate/scientist conducted searches on September 6 and 7, 2022, on PubMed and Google Scholar as secondary sources of the English-language literature. Search terms included: *Acute radiation dermatitis AND patients' quality of life OR skincare efficacy, safety, tolerability OR skin irritation OR topical regimes OR prevention OR treatment OR adjunctive skincare for treatment, maintenance OR education of staff and patients.*

The initial search on these terms yielded 122 publications. Two independent reviewers evaluated the literature review results and resolved any discrepancies by discussion. After excluding duplicates and articles that fell outside of the eligibility criteria for the algorithm ([n = 52] such as other subjects, low quality), 70 papers remained. These 70 comprised 1 guideline, 2 algorithms, 18 systematic reviews, 5 review articles, and 45 clinical studies. Of the clinical studies, 18 were randomized controlled trials (Figure 1).

Cancer Treatment With Radiation Therapy

Approximately 50% of cancer patients receive RT as a single modality or combined with cytotoxic therapy, immunotherapy, or targeted therapy.[11-17] RT can be given for curative, neoadjuvant, adjuvant, or palliative cancer treatment.[11-17]

Breast cancer mortality, the most common malignancy in women, has markedly reduced due to earlier screening and improved treatment.[18,19] The standard treatment to reduce breast cancer's local recurrence comprises adjuvant RT combined with surgery.[12,20] This treatment approach has demonstrated efficacy for patients with early-stage breast cancer undergoing breast-conserving surgery or locally advanced breast cancer with positive lymph nodes undergoing a modified radical mastectomy.[12,20] The effects of RT are not selective to tumor cells and may damage surrounding organs and tissues.[21-30] As a result, nearly all patients who receive RT will develop some form of RD.[21-30]

ARD may range from mild erythema to wet desquamation reactions; ulcers and necrosis can occur in severe cases.[22] The severity of RD depends on the host, disease, and treatment-specific factors, such as the individual's genotype, target dose, fractionation regimen, and RT modality.[5-11] ARD can significantly impact patients' quality of life (QoL), as demonstrated in a prospective study in 83 cancer patients (breast cancer, 49%, head, and neck cancer, 45%, and anus cancer, 6%) receiving RT.[13] All patients developed ARD [59% grade 1, 33% grade 2, and 8% grade 3].[13,32] The Skindex-16, a validated instrument for assessing dermatologic-related QoL, was administered pre- and post-RT.[13] The median composite pre-treatment Skindex-16 score was 0 vs 34 post-RT, demonstrating a markedly negative impact on QoL following RT.[13] Another study of patients with breast cancer receiving RT reported that related cAEs negatively impacted physical well-being, body image, emotional and functional well-being, and treatment satisfaction.[31]

Acute Radiation Dermatitis

ARD is an acute cutaneous inflammatory reaction and oxidative stress induced by exposure to biologically effective levels of ionizing radiation.[16,21-26,29,33] Inflammatory markers involved in acute inflammation secondary to ionizing radiation, including IL-1, IL-6, tumor necrosis factor alpha (TNF-α), and transforming growth

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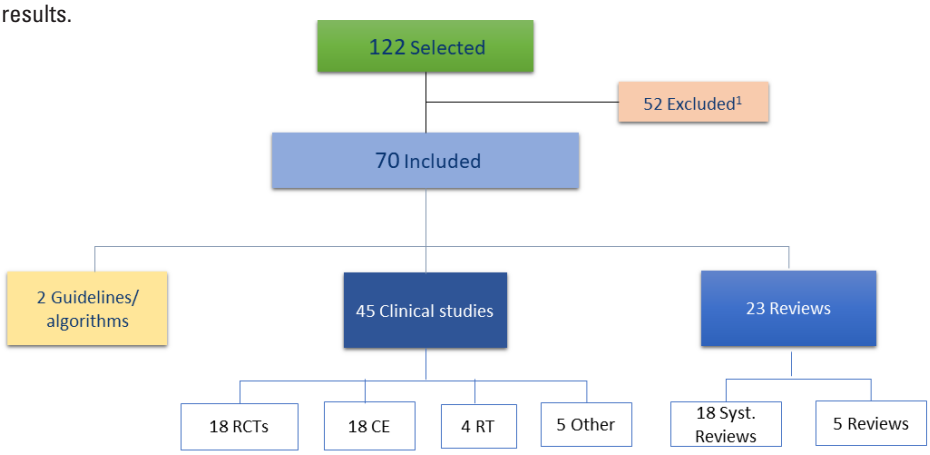
FIGURE 1. Literature results.



[1]Excluded were: Duplications, In case of an update on a review article the latest version was used; Poor quality.

Systematic (Syst.), Randomized controlled trials (RCTs), Randomized trials (RTs), Clinical evaluation (CE)

factor beta (TGF-β), can be expressed within hours after the first fraction of RT.[33] Demographic or disease-related intrinsic patient factors influence the severity of ARD.[33] Several other patient-related risk factors possibly affecting the development or severity of ARD include, for example, smoking, breast size, age, ethnic origin, coexisting diseases, hormonal status, tumor site, and genetic factors.[21-24] RT-treatment-related factors include, for example, beam energy, total radiation dose, treatment techniques, volume and the fraction of radiation, chemotherapy, and tamoxifen therapy.[22-30]

Types and Severity of Radiation Dermatitis

Radiation Therapy Oncology Group (RTOG) and Common Terminology Criteria for Adverse Events (CTCAE) v5 are standard classification tools for grading RD (Table 1).[32,34] The CTCAE scale has 5 grades: 1 = faint erythema and dry desquamation to 5 = death. The scale distinguishes between moist desquamation within skin folds vs flat areas.[32,34]

The RTOG assessment tool has 6 grades (0 = no visible signs of RD, 1, 2, 2.5, 3 to 4 = ulceration, bleeding, and necrosis. The scale separates patchy moist desquamation (grade 2.5) from confluent moist desquamation (grade 3).[32,34] The advisors used the CTCAE v5 grading system for ARD for the NECOM 3 algorithm.[32]

Nordic European Cutaneous Oncodermatology Management 3: A Practical Algorithm for the Prevention and Management of Acute Radiation Dermatitis

The practical algorithm for ARD uses information from the NECOM 2 skincare algorithm for cAEs.[7] The skincare algorithm for cancer patients and survivors starts before cancer treatment with education, skin care, and behavioral measures, followed by an evaluation of cancer treatment-related cAEs (Figure 2).[7] The oncology nurse-led triage determines the condition [life threatening, severe, or not severe], followed by a patient-specific treatment approach.[7] The oncology nurse is central in coordinating the individual cancer patients' care and performing triage of the cAEs, seeking urgent care via an oncologist and/or emergency department (ER) if needed.[6,7] The individual patient's care organization depends on the presented cAEs, the patient's general and skin conditions, and the healthcare system.

The practical algorithm for ARD starts with skin-preserving therapy, as detailed below, followed by measures on day 1 of RT. After each RT session, the patients are instructed to inspect their skin condition for possible cAEs (ie, erythema, dry or moist desquamation, skin necrosis, or ulceration). If the skin is clear, the skin-preserving therapy is continued. If cAEs are detected, or the patient has concerns, the oncology nurse (in person, by email, or via telemedicine) performs triage. The cleansing and treatment interventions are tailored to the CTCAE grade if ARD is present.[32,34] The oncology nurse seeks urgent care for the patient via an oncologist or ER in case of fever, sepsis, deep ulcers, or severe pain.

Skin Preserving Therapy

Patient education on proactive measures is needed to maintain healthy skin and prevent the development of RT-related cAEs. Therefore, education is an essential first step for clinicians to discuss with patients before starting RT.[6,7] Skin preserving therapy comprises education on skin care, including cleansers, moisturizers, and protection using moisturizing sunscreen (SPF 50+) in combination with avoidance of irritants and sun exposure. Recommendations include avoiding skin irritants, products with an elevated pH (>7), and scented products.[6,7] Patients should avoid skin trauma or friction caused by excessive rubbing or scratching or the use of adhesive bandages and tape that could potentially peel skin upon removal.[6,7] Comfortable clothing made from breathable, non-abrasive fabrics, and supportive bras (for women receiving breast RT) is recommended during RT.[6,7,21,34,35] Using electric shavers for hair removal, waxing, or other depilatory pre-shave and after-shave products is generally not recommended during RT if these

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TABLE 1.

The CTCAE v.5 and RTOG Classification Systems for Acute RD

CTCAE v5		RTOG	
Grade	Definition	Grade	Definition
1	Faint erythema or dry desquamation	0	No visible change to skin
2	Moderate to brisk erythema; Patchy moist desquamation mostly confined to skin folds and creases, moderate edema	1	Faint or dull erythema Soreness, pruritus, and tightness of the skin
3	Moist desquamation in areas other than skin folds and creases, bleeding induced by minor trauma or abrasion	2	Bright erythema / dry desquamation Sore, pruritus, and tight skin
4	Life-threatening consequences; Skin necrosis or ulceration of full-thickness dermis, spontaneous bleeding from the involved site. Skin graft indicated	2.5	Patchy moist desquamation Yellow/pale green exudate Soreness with edema
5	Death	3	Confluent moist desquamation Yellow/pale green exudate, soreness with edema
		4	Ulceration, bleeding, necrosis (rarely seen)

Division of Cancer Treatment & Diagnosis Dermatitis Radiation Grading (DCTD); Radiation Therapy Oncology Group (RTOG)
Grades of Acute Dermatitis (CTCAE – common terminology criteria for adverse events (National Cancer Institute)[32,34]

regions are within the treatment field.[6,7,21,34,35] For example, breast cancer patients are advised to avoid shaving the axilla with straight-edge razors; however, they may continue to use aluminum-based antiperspirants or deodorants during RT.[6,7,34,35]

Clinical studies on skincare have analyzed potential benefits for the prevention and treatment of ARD.[35-44,53-63] Reviews[35,36,38,39-45] of topical agents for treating ARD reported benefits or potential benefits when using formulations containing hyaluronic acid,[39,40,63] epidermal growth factor (EGF),[41,58,61] topical corticosteroids (TCS),[45-52] or statins.[53] A systematic review[35] found no benefits for formulations containing aloe vera,[38] chamomile,[35] ascorbic acid, pantothenic acid, and trolamine.[59] Topical agents that contain soothing ingredients such as niacinamide, panthenol, squalene, glycerin,[62] and allantoin have demonstrated benefits for reducing ARD symptoms.[28,37]

A thermal water-containing skincare regimen comprising 2 types of cleanser, a moisturizer, a healing balm, and an SPF50+ sunscreen has shown benefits for ARD prevention and reduction of symptoms.[37] In this study of 253 women with mostly early-stage breast cancer undergoing postoperative RT, the self-reported frequent users who once-daily used the total skincare regimen showed significantly ($P \leq 0.0001$) less incidence of severe RD (grade 3 CTCAE v. 5[32] and higher) than those who self-reported using parts of the skincare regimen infrequently.[37]

The application of moisturizers in moderation just prior to daily administration of RT has not been shown to interfere with or increase the radiation dose to the skin.[54] Encouraging patients to apply skincare daily and liberally without restrictions will likely improve adherence to the skincare regimen and QoL.[6,7]

Day 1 of Radiation Therapy

At day 1 of RT, patients are recommended to continue with skin-preserving therapy and apply mid-potency topical corticosteroid (TCS) cream (such as mometasone furoate 0.1% or triamcinolone 0.1%) for up to 2 weeks after completion of RT.

TCS has anti-inflammatory properties, which may prevent and prolong the ARD development time when combined with other skincare products.[6,7,45-52] The recommendation is supported with high-level evidence, including a meta-analysis demonstrating that mild to potent TCS significantly prevented the incidence of any RD and moist desquamation.[42] TCS use during RT has been shown to prolong the time to development of grade 3 RD.[45-52] High potency TCS should not be used on the face, neck, or genitalia, and can lead to skin atrophy and permanent striae.[48,52,55] Prolonged TCS use may lead to rare cAEs, such as atrophy, purpura, tearing of the skin, telangiectasias, hypertrichosis, and localized infections.[48,52,55]

Using zinc-containing healing balm at the RT-treated site may be resumed post-treatment the next day. However, if RT continues with several rounds over a week, then the use of zinc-containing products should be held off until the course of RT is over.

Topical Treatment of Acute Radiation Dermatitis

Pain can be managed by non-prescription non-steroidal anti-inflammatory drugs (NSAIDs). For CTCAE grade 1-2 RD with erythema and no desquamation, patients may continue their prescribed course of RT. On an ongoing basis, the patients' understanding of pre-RT education and compliance with the skincare regimen and TCS should be checked and reinforced (Table 2).[6,7]

For patients with CTCAE grade 2 with moist desquamation or grade 3 ARD, daily cleansing of the wound and peri-wound skin with a gentle cleanser or saline soaks was recommended.[6,7] Culturing the desquamated region, especially if purulent, should be considered.[6,7]

Skincare with moisturizers is continued in the skin areas around the moist desquamation.[6,7] Discontinuing TCS should be considered,

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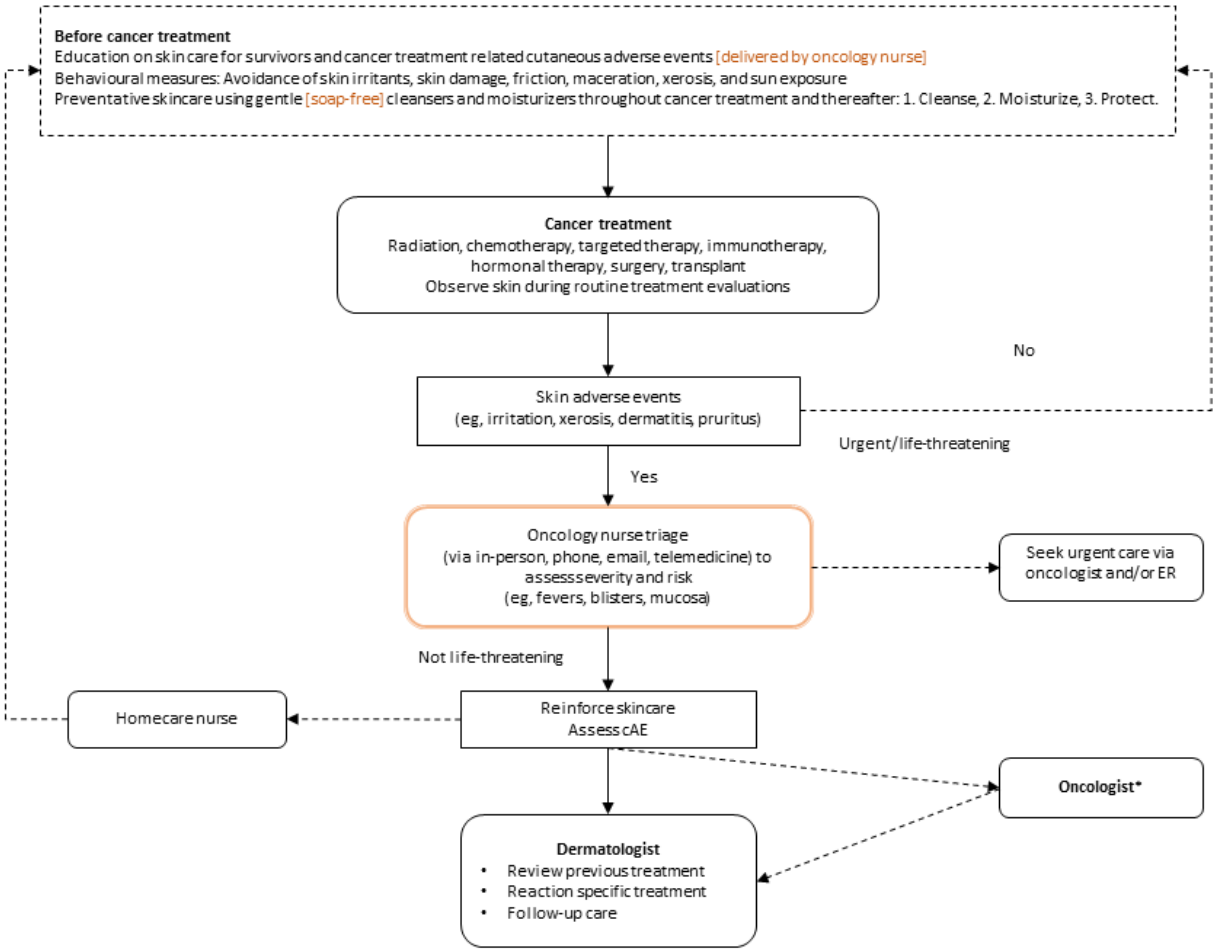
FIGURE 2. NECOM skincare algorithm for cancer patients and survivors.



*Whether an oncology nurse proactively contacts dermatology or consults with an oncologist first depends on the health system.

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especially if desquamation developed after applying TCS.[6,7] The advisors acknowledged a lack of evidence for recommending one particular dressing over another for treating moderate to severe ARD cases.[6,7] Wound dressings that maintain a moist wound bed and control exudate while not adhering to the wound bed are widely used.[6,7,33,64-69] Depending on the condition and level of exudate, various dressings may be used, such as a hydrocolloid, a foam dressing, or a non-adherent silicone-coated dressing.[6,7,64-69] Silicone-based agents may have anti-inflammatory properties and are available as a gel or coated wound dressing.[64-68] Dressings comprising a hydrogel may offer soothing and cooling.[6,7] The frequency of dressing changes depends on exudate level and is typically every third day.[6,7]

Clinically manifest secondary bacterial infections may be treated with oral antibiotics based on microbial sensitivities. Still, prophylactic topical antibiotics are generally discouraged for antimicrobial stewardship preventing antibiotic resistance.[6,7] Topical hypochlorous acid (HOCl), available as a liquid, spray, or gel, is highly active against bacteria, viruses, and fungal organisms, and has favorable effects on fibroblast and keratinocyte migration.[70]

Silver sulfadiazine cream to the desquamated region may be used until complete healing, although evidence is lacking.[71-73] Although silver sulfadiazine cream is safe, it may slow down re-epithelization.[72] A pseudo eschar may form, which requires debridement.[72] The use of a silver-containing dressing for secondary infected moist desquamation may be a more favorable option than a cream.[73]

Experience with a sodium carboxymethylcellulose dressing in partial-thickness burns showed that, when left on the burn for a prolonged period, the dressing developed a parchment-like structure; and once the underlying wound had re-epithelialized, it still allowed for easy removal from the wound site.[74,75] This type of dressing is also available as a silver-containing dressing for infected wounds.[75]

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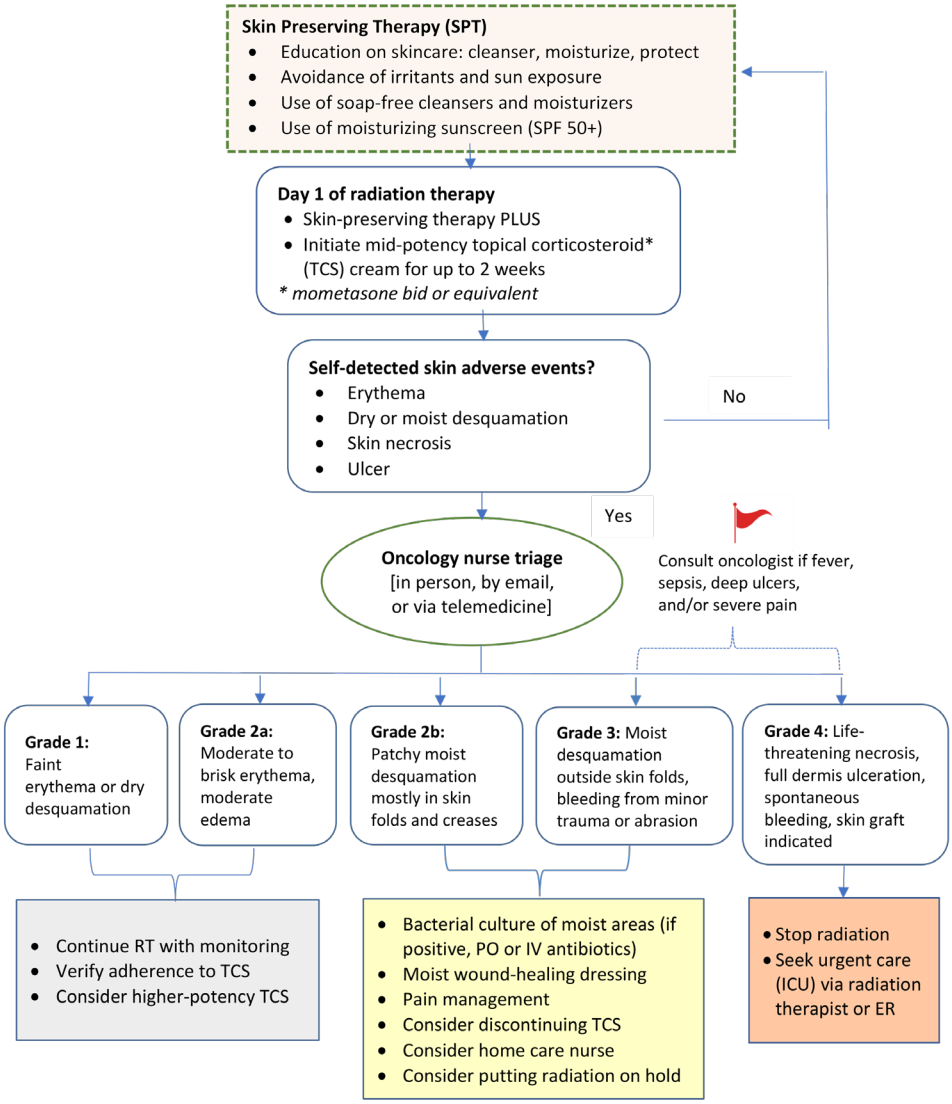
FIGURE 3. A practical algorithm for the prevention and management of acute radiation dermatitis.



Radiation therapy (RT), skin preserving therapy (SPT), Topical corticosteroid (TCS), Sun protection factor (SPF), Per os (PO), Intravenous (IV), Intensive care unit (ICU), Emergency room (ER)

For CTCAE grade 4 RD and any cAEs deemed possibly dangerous or life-threatening, such as skin necrosis, ulceration of the full-thickness dermis, or copious bleeding, further fractions of RT and/or bolus should be held off until the desquamated region is clinically improved.[6,7,23,32,33,35,36] The decision to hold off RT must be made by the radiation oncologist, who will need to weigh the consequence of a treatment break for cutaneous healing vs potentially reducing the efficacy of RT.[76-78] Treatment breaks may negatively impact prognosis in highly proliferative tumors, such as head and neck cancer and inflammatory breast cancer, which have high rates of local recurrence.[76-78]

Patients with large areas of moist desquamation, bleeding, or bullae should be referred to a wound-healing specialist or onco-dermatologist.[7] Breast cancer patients with a tissue expander or implant reconstruction and moist desquamation in any part of their chest wall or axilla should be carefully assessed for secondary infection of the prosthesis by their plastic surgeon.[6,7] Adequate pain control is essential, with a low threshold for offering narcotic medications as needed. Mucosal involvement, thinning of a flap with exposure to a breast prosthesis, and the presence of systemic symptoms such as fever, uncontrolled pain, and laboratory abnormalities – like elevated white blood cell counts or decreased hemoglobin and hematocrit – signal urgent evaluation at an urgent care facility with subspecialty consultation by a dermatologist, plastic surgeon, infectious disease specialist, or wound-healing specialist.[6,7]

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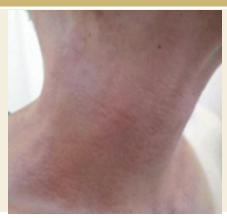
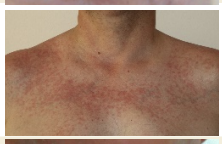
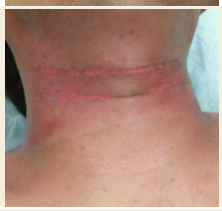
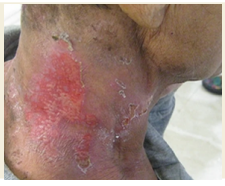
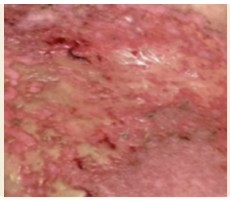
TABLE 2.

Grading of Useful Topical Products Grouped By Level of Evidence			
CTCAE grade		**Topical treatment**	**References**
Grade 1: Faint erythema or dry desquamation		Continue SPT. Check the use of skincare and TCS.	6,7
Grade 2a: Moderate to brisk erythema, moderate edema		Continue SPT. Check the use of skincare and TCS. Saline soaks for cooling the affected area.	6,7
Grade 2b: Patchy moist desquamation mostly in skin folds and creases		Continue SPT on the skin around the areas with desquamation. Consider discontinuing TCS. Saline soaks for cooling the affected area. For moist desquamation apply a wound dressing suitable for the condition. The frequency of dressing changes depends on exudate level and is typically every third day.	6,7,56-61,73,74
Grade 3: Moist desquamation outside skin folds, bleeding from minor trauma or abrasion			
Secondary infection of ARD		Clinically manifest secondary bacterial infections may be treated with mupirocin. Topical HOCl available as liquid, spray, or gel is highly active against bacteria, viruses, and fungal organisms is another option or a silver-containing dressing.	69-72
Grade 4: Life-threatening necrosis, full dermis ulceration, spontaneous bleeding		Seek urgent care (ICU) via radiation therapist or ER. RT and/or bolus should be held until the desquamated region is clinically improved. Patients with large areas of moist desquamation, bleeding, or bullae should be referred to a wound-healing specialist or oncodermatologist	6,7,32

Skin Preserving Therapy (SPT): Education on skincare: Daily gentle cleanser, moisturizer use, and protection of treated areas. Avoidance of irritants and sun exposure. Use of soap-free cleansers and moisturizers and use of moisturizing sunscreen (SPF 50+). Topical corticosteroid (TCS), *Staphylococcus aureus* (*Staph aureus*), Hypochlorous acid (HOCl), Radiation therapy (RT), Emergency room (ER)
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Limitations

Prospective clinical trials that evaluate the efficacy of a practical algorithm for ARD are currently unavailable. Furthermore, the evidence base lacks supporting recommendations for preventing and treating ARD.

CONCLUSION

Frequently, cancer patients receiving RT suffer from ARD leading to pruritus and pain, decreased QoL and morbidity, and treatment interruptions. Patient education on the prevention of ARD and treatment recommendations given in the NECOM 3 algorithm may help prevent and manage ARD and improve the overall care of cancer patients receiving RT.

DISCLOSURES

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