


Review of the Terminology Describing Ionizing Radiation-Induced Skin Injury: A Case for Standardization

Technology in Cancer Research & Treatment
 Volume 20: 1-8
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 DOI: 10.1177/15330338211039681
journals.sagepub.com/home/tct


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Abstract

Ionizing radiation causes injury to the skin that produces a complex clinical presentation that is managed by various paradigms without clear standards. The situation is further complicated by the fact that clinicians and researchers often use different terms and billing codes to describe the spectrum of cutaneous injury. There is, however, general agreement between the two most commonly-used diagnostic scales, the Radiation Therapy Oncology Group and the Common Terminology Criteria for Adverse Events, and in their use to describe skin injury following radiation therapy. These scales are typically used by radiation oncologists to quantify radiation dermatitis, a component of the radiation-related disorders of the skin and subcutaneous tissue family of diagnoses. In rare cases, patients with severe injury may require treatment by wound care or burn specialists, in which case the disease is described as a “radiation burn” and coded as a burn or corrosion. Further compounding the issue, most US government agencies use the term Cutaneous Radiation Injury to indicate skin damage resulting from large, whole-body exposures. In contrast, the US Food and Drug Administration approves products for radiation dermatitis or “burns caused by radiation oncology procedures.” A review of the literature and comparison of clinical presentations shows that each of these terms represents a similar injury, and can be used interchangeably. Herein we provide a comparative review of the commonly used terminology for radiation-induced skin injury. Further, we recommend standardization across clinicians, providers, and researchers involved in the diagnosis, care, and investigation of radiation-induced skin injury. This will facilitate collaboration and broader inclusion criteria for grant-research and clinical trials and will assist in assessing therapeutic options particularly relevant to patient skin pigmentation response differences.

Keywords

cutaneous radiation injury, radiation skin injury, ionizing radiation-induced skin injury, radiation dermatitis, radiation burn, radiation injury terminology

Received: February 24, 2021; Revised: July 15, 2021; Accepted: July 27, 2021.

Introduction

In the fields of radiation oncology and radiation biology, a naming convention issue exists around the terminology used to describe skin injuries caused by ionizing radiation. Multiple terms are often used interchangeably to describe similar skin conditions such as: cutaneous radiation injury (CRI), local radiation injury, radiation dermatitis, radiation-induced skin injuries, burns caused by radiation oncology procedures, and radiation burns. The utilization of each term is closely associated with the context in which the clinician or researcher practices. For example, the various

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government agencies that are charged with developing medical countermeasures for radiation exposure, including the office of the Assistant Secretary for Preparedness and Response, the Department of Defense (DoD), the National Institute of Allergy and Infectious Diseases, and the Biomedical Advanced Research and Development Authority, generally use the term CRI which refers to skin damage that occurs as a result of acute radiation exposure.^{1,2} In the management of routine skin irritation that results from conventionally fractionated radiotherapy, radiation oncologists frequently use the term radiation dermatitis. Burn specialists and wound care physicians commonly refer to this injury as a radiation burn. Finally, the Food and Drug Administration (FDA), which is tasked with regulating treatments for radiation injury, has approved products for the indications of “radiation dermatitis” and “burns caused by radiation oncology procedures.” Though these terms are used with significant overlap within the field, the issue of whether or not they refer to the same injury etiology has not been addressed directly. The goal of this review is to summarize the available literature regarding radiation-induced skin injury and to compare and contrast the manifestations of this injury across the varied terminologies.

Overview of Skin Injury Resulting From Irradiation

Researchers and clinicians have described a common set of changes in the skin after exposure to ionizing radiation. The severity of symptomatology varies with dose, fractionation, and beam energy. Generally speaking, the time course of injury may be categorized into early and late phases. The early phase of the injury process is characterized by erythema and cutaneous edema, followed by epilation, dry desquamation, and hyperpigmentation. As the injury progresses, patients may experience pruritus, tingling, and a sensation of heat, followed by vesiculation, moist desquamation, erosion, ulceration, and/or necrosis of the epidermis, dermis, or both. Following the most visible and severe symptoms, patients will often experience what is known as late effects, which include symptoms such as epilation, skin atrophy, telangiectasia, hypopigmentation, and/or hyperpigmentation. The International Commission on Radiological Protection has outlined the general progression of radiation-induced skin irritation to include dry desquamation at 3 to 6 weeks and moist desquamation at 4 to 6 weeks. Dry desquamation occurs due to the loss of keratinization due to a decrease in the number of basal layer dermal cells. Moist desquamation occurs due to epidermal loss related to loss of basal layer clonogens. In the later phases at > 6 weeks, ulceration occurs as a result of secondary damage after protracted moist desquamation, dermal necrosis occurs at > 10 weeks due to vascular insufficiency and the death of dermal tissues, dermal atrophy occurs at > 26 weeks related to fibrosis and contraction, and telangiectasia occurs at > 52 weeks due to dilation of dermal capillaries and fibrosis and scar formation.³ These are discussed in greater detail below within the context of each of the terms that are used to describe the injury.

Cutaneous Radiation Injury

The Centers for Disease Control and Prevention (CDC) defines CRI as an “injury to the skin and underlying tissues from acute exposure to a large external dose of radiation”.^{1,4} The definition of CRI is further clarified as occurring in individuals exposed to an acute dose of greater than 2 Gy, independent of exposure source. As described, most cases of severe CRI occur from inadvertent contact with unsecured radiation sources or accidental overexposure from irradiation equipment. CRI can also occur in individuals involved in industrial accidents (eg, at a nuclear power plant) as well as the surviving victims of an attack from either a nuclear weapon or a radiological dispersal device (ie, a “dirty bomb” that combines radioactive material with conventional explosives). The term CRI is not used clinically to describe the skin response to oncology or fluoroscopy procedures, despite the similarities between the resultant physical injury and clinical presentation/symptomatology.

The severity of CRI is expressed using a grading scale that classifies injuries from Grade I to IV based on the number and type of observable symptoms. The symptoms associated with each of these grades are outlined by the CDC for the prodromal, latent, manifest illness, third wave of erythema, recovery, and late effects of the injury.¹ It is important to note that while the clinical syndrome described for acute radiation exposures is analogous to skin injury from conventional therapeutic radiation, the time course and severity of the injury are often different. If CRI definitions were to be applied to routine clinical practice, acute radiation dermatitis would likely be diagnosed days to weeks following initiation treatment, within the manifest illness stage. This is often when symptoms become clinically relevant and require care.

The manifest illness stage for Grade I CRI occurs 2 to 5 weeks after exposure and includes symptoms of skin redness, slight edema, and possible increased pigmentation.¹ By 6 to 7 weeks, dry desquamation may be present.¹ CRI symptoms classified as Grade II present up to a week sooner in the injury process for reasons that are unknown. In addition to the symptoms associated with a Grade I injury, patients with a Grade II injury may report a sense of heat, and the skin around the injured area may become darker in color.¹ Later effect include edema of subcutaneous tissues and blisters with moist desquamation, followed by epithelialization. Grade III CRI encompasses the previously discussed symptoms but also includes skin erosion and ulceration.¹ Skin presenting with Grade IV CRI will have blisters with early ischemia and dermal necrosis presenting in as few as 2 weeks.¹ Further, Grade IV is expected to have extensive complications and will likely require a skin graft.

Radiation Dermatitis or Radiation-Induced Skin Injury

The National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) is accepted as a standard classification and grading scale for adverse events in clinical trials and

other oncology settings.⁵ This classification tool defines radiation dermatitis as a “cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation.” In the clinical literature, radiation dermatitis is used interchangeably with radiation-induced skin injury.^{6–10} Consequently, the available outcomes-based research is extremely heterogeneous, making it very difficult to draw conclusions regarding consensus guidelines and standards of care.¹¹

In addition to the CTCAE scale, clinicians often use the Radiation Therapy Oncology Group (RTOG) grading criteria as a standardized tool in the assessment of radiation injury severity during the manifestation of illness.¹² Both of these scales are important tools for clinical oncologists, given the high prevalence of radiation-induced skin injury of variable severity and can be applied to patients across many primary tumor sites. These include breast cancer,^{13–16} head and neck cancer,^{17–19} anal carcinoma,^{20,21} lung cancer,²² and sarcoma.²³ Low-grade injuries (Grade 1–2 by the CTCAE and RTOG scales) are often seen in the clinic as somewhat unavoidable yet manageable consequences of definitive therapy and present with symptoms analogous to the CRI scale used by the CDC, though advances in treatment delivery and fractionation have reduced this burden in recent years. Higher grades of injury (\geq Grade 3) are relatively uncommon but may be associated with patient risk factors such as higher body mass index, concurrent radiosensitizing chemotherapeutics,¹⁸ biologics,²⁴ radiotherapeutic factors such as beam energy, dose heterogeneity, target proximity to the skin surface,¹⁶ and very rarely, equipment malfunction or misadministration. Approximately 23% to 49% of patients treated with chemoradiotherapy will experience higher-grade symptoms including moist desquamation and ulceration.^{15,18,20,25}

The CTCAE version 5 defines radiation dermatitis as “a finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation”.⁵ The severity of skin injury ranges from Grade 1 (mild) to Grade 4 (severe, life-threatening) to Grade 5 (death). Briefly, a Grade 1 injury indicates that faint erythema or dry desquamation is present. Grade 2 radiation dermatitis includes moderate to brisk erythema, with patchy moist desquamation and edema that is largely confined to skin folds and creases. Patients presenting with Grade 3 may exhibit moist desquamation in areas other than skin folds, and often report excessive bleeding caused by minor trauma or abrasion. Grade 4 is a life-threatening condition with skin necrosis or ulceration across the full thickness of the dermis with spontaneous bleeding from the involved site. Grade 4 injuries often require skin grafting or advanced wound care.

Similar to the CTCAE scale, the RTOG scale includes 4 grades of symptoms, omitting Grade 5.¹² Grade 1 includes dermatitis marked by faint or dull erythema, dry desquamation, epilation, and diminished sweating. Grade 2 encompasses injuries that present with tender or bright erythema, patchy moist desquamation, and moderate edema. When injuries progress to Grade 3, they present as confluent moist desquamation that

extends beyond skin folds with pitting edema. Finally, Grade 4 includes ulceration, hemorrhage, and necrosis that may be life-threatening and may require skin grafting. In general, the majority of cases of radiation dermatitis caused by modern radiotherapy for the treatment of cancer can be categorized as grade 1 to 2, with grade 3 to 4 skin injury noted in a small subset of potentially genetically or phenotypically predisposed patients. It should be noted that cases of radiation-induced skin injury after standard radiotherapy requiring hospital admission for urgent treatment, hyperbaric oxygen, or surgical intervention such as skin grafting are exceptionally rare.

Further complicating the terminology used for this injury is that several researchers have added a descriptor to delineate the extent of the injury size by using the term “local” to specify that the injury they are describing is focal.²⁶ However, this does not seem to apply to a larger injury where the use of more general terms such as “partial body”²⁷ or “whole or total body”²⁸ are only used to describe the irradiation exposure mechanism, not the resulting injury. This term can also be applied to a radiation combined injury where radiation and penetrating trauma are used in the same model, an injury that is highly relevant to potential casualties of a nuclear conflict.²⁸ Several perturbations of the use of the term local can be found including “local CRI”,²⁹ local cutaneous injuries induced by ionizing radiation”,²⁹ and “local radiation injury”.^{26,30}

“Radiation Burn”

The term “radiation burn” is not often used by radiation oncologists or researchers in the field of radiation biology; however, it can be found in the literature and is often used clinically by practitioners outside the field of radiotherapy who may be less familiar with the pathophysiology, diagnosis, and management of such skin injury. The term is used occasionally in the surgical literature,³¹ despite the marked differences in the underlying radiation “burns” in comparison to electrical, thermal, and chemical burns.^{32,33} Relevant literature describing “radiation burns” includes descriptions of medical countermeasures related to nuclear events,³⁴ case reports of radiation burns sustained in accidental or workplace exposure,³⁵ radiation burns resulting from the therapeutic use of ionizing radiation,³⁶ and radiation burns sustained from fluoroscopy or other radiation-guided medical procedures.³⁷ Further complicating this term’s use in clinical practice is that the International Classification of Diseases, 10th Revision (ICD-10) provides codes for “radiation-related disorders of the skin and subcutaneous tissue”, but not radiation burn. Additionally, patients who develop severe injuries are often referred to wound or burn care specialists who are likely to use the thermal burn codes (T20–T25) for “burns and corrosions of the external body surface, specified by site” to direct treatment. The explanation for this is complicated, but one likely cause is that wound treatment is expensive, so coding must be precise and within acceptable reimbursement paradigms. Taken together, the diagnostic, treatment, and terminology differences of radiation injury result

in difficulties in assessing and providing continuous care for these injuries.

The term “burns caused by radiation oncology procedures” is not found in the body of any of the literature returned in searches conducted in both PubMed and Web of Science. However, FDA has approved several products for this indication in addition to the more commonly used indication, radiation dermatitis. Products approved by the 510(k) premarket notification pathway for “burns caused by radiation oncology procedures” include NU-GEL® Wound Dressing (FDA product number K983362) and Healadex®-P Wound Dressing (K063517). FDA has also cleared other emulsified products for “radiation dermatitis,” including Biafine® Wound Dressing Emulsion (K964240), Tropazone Lotion (K090337), and HydroPermeate™ Topical Emulsion (K122595) and KeraStat® Cream (K192386). Currently, there are several products that have been or are being tested, in studies of radiation dermatitis including: Siverlon® wound dressing (clinical trial number NCT04238728, product not currently indicated for radiation dermatitis by FDA), Biafine (NCT00006481 and NCT02729324), and KeraStat Cream (NCT03559218 and NCT04173247). In addition to the variability in the terminology used for producing medical indications, a larger challenge is that these products have been given a variety of product classification codes that include MGQ (Dressing, Wound And Burn, Hydrogel W/Drug And/Or Biologic), FRO (Dressing, Wound, Drug), and KGN (Dressing, Wound, Collagen). This ambiguity, coupled with the differences in terminology associated with CRI, creates challenges both for clinicians and product manufacturers despite the fact that each term is meant to describe an essentially singular spectrum of cutaneous pathology. The ICD-10

provides codes for “radiation-related disorders of the skin and subcutaneous tissue” (L55-59), which introduces yet another term for the injury, highlighting the discrepancy between the terms and reimbursement codes clinicians use to describe these injuries, and the indications that are used by product developers and the regulatory bodies that review their efforts.

Discussion

Given the threat of a radiation incident around the world, it is imperative that researchers, clinicians, and government agencies operate with a consensus definition of radiation-induced skin injury. The use of multiple terms to describe the same phenomenon, whether in the therapeutic arena or in the context of public safety/radiation protection, puts the clinical and research communities at risk of duplicating efforts due to a failure of adequate communication across all involved parties. This may lead to costly inefficiencies in the allocation of research funding. Though a single standardized term with a single corresponding grading system would mitigate these issues, we acknowledge that CRI and radiation dermatitis are terms that are not likely to be replaced in daily use. However, it is the opinion of the authors that the field’s agreement on term equivalency is important, particularly within the FDA, which regulates products that are designed to treat the injury regardless of the term used to describe or diagnose it. Furthermore, this consensus may be more easily achievable using a broad umbrella term “radiation-induced skin injury,” analogous to other terminologies defining the toxic effects of radiation on organ systems like radiation-induced lung injury³⁸ and radiation-induced liver disease.³⁹

Table 1. Comparison of Three Commonly Used Scales for the Classification of Skin Injuries Associated With Ionizing Radiation Exposure.

Scale	Grade I	Grade II	Grade III	Grade IV
Cutaneous radiation injury (CRI)	Redness of skin, slight edema, possible increased pigmentation (2-5 weeks following exposure, lasting 20-30 days); dry desquamation (6-7 weeks following exposure)	Redness of skin, sense of heat, edema, skin may turn brown (1-3 weeks following exposure); edema of subcutaneous tissues and blisters with moist desquamation (5-6 weeks following exposure); possible epithelialization later	Redness of skin, blisters, sense of heat, slight edema, possible increased pigmentation (1-2 weeks following exposure) followed by erosions and ulceration as well as severe pain	Blisters (1-4 days following exposure) with early ischemia (tissue turns white, then dark blue or black with substantial pain) in most severe cases; tissue becomes necrotic within 2 weeks following exposure, accompanied by substantial pain
Radiation dermatitis (CTCAE)	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full-thickness dermis; spontaneous bleeding from the involved site; skin graft indicated
Radiation dermatitis (RTOG)	Follicular, faint or dull erythema, epilation, dry desquamation, and decreased sweating	Tender or bright erythema, patchy moist desquamation, and moderate edema	Confluent moist desquamation, other than skin folds, and pitting edema	Ulceration, hemorrhage, necrosis

Table 2. Comparison of Common Terms Used to Describe Radiation-Induced Skin Injury.

	Cutaneous radiation injury ¹	Radiation dermatitis ^{8–10}	Burns from radiation oncology procedures
Definition	Injury to the skin and underlying tissues from acute exposure to a large external dose of radiation	A radiotherapy-induced skin condition	Burns that result from the high dosage of radiation used to destroy cancer cells, which also destroys healthy cells
Presentation	Itchiness, tingling, erythema, edema, inflammation, dry desquamation, moist desquamation, damage to hair follicles causing epilation, intense reddening, blistering, ulceration, tendency to bleed	Erythema, dry desquamation, moist desquamation, edema, skin necrosis, ulceration, bleeding not induced by minor trauma or abrasion	Erythema, dry desquamation, hyperpigmentation and hair loss, skin atrophy, dryness, telangiectasia, dyschromia, dyspigmentation, fibrosis, and ulcers.
Sources and exposure	Can be caused by any radiation source. Exposure is acute	Caused by radiotherapy. Exposure depends on treatment. Doses are often fractionated	Caused by radiotherapy. Exposure depends on treatment. Doses are often fractionated
Management	Antihistamines, topical antipruriginous preparations, anti-inflammatory medications, slight sedatives, proteolysis inhibitors, antibiotic prophylaxis, topical corticosteroids, locally acting antibiotics and vitamins	Topical steroidal treatment, intralesional steroids, nonsteroidal anti-inflammatory drugs, topical antibiotics, systemic antibiotics, silver sulfadiazine, aloe vera, hyperbaric oxygen therapy, skin grafts, amputation	Topical steroidal treatment, intralesional steroids, nonsteroidal anti-inflammatory drugs, topical antibiotics, systemic antibiotics, silver sulfadiazine, aloe vera, hyperbaric oxygen therapy, skin grafts, amputation

The purpose of this review is to begin a discussion between researchers, clinicians, and government agencies regarding the terminology used in their respective fields to describe radiation injury. When viewed comparatively (as shown in Table 1), there is significant agreement around the clinical manifestation of the skin's response to ionizing radiation within the various classifications systems used (RTOG, CTCAE, and CDC). In addition, there are also significant similarities in the definition, symptoms, sources, and clinical management within the terms CRI, radiation dermatitis, and radiation burns at equivalent doses of radiation (as shown in Table 2).

Low-grade injuries are typically seen in radiation oncology clinics and are easily categorized using the CTCAE or RTOG scales. In rare circumstances as a result of modern cancer therapy, and usually in the setting of accidental occupational exposures or other radiation incidents, these injuries are typically referred to as radiation burns and are treated by a burn, wound care, or plastic surgery specialists that may not be familiar with the differential progression of radiation injuries. This issue can be mitigated using a treatment team approach, and by more widely using one of the currently available standardized scales such as the RTOG, or the CTCAE, that can be used to describe these injuries more systematically across the multiple radiotherapy treatment domains.

It is important to acknowledge the differences in the level of familiarity with radiation-induced skin injury and diagnostic and therapeutic expertise across the multidisciplinary treatment teams. These teams often include radiation oncologists, wound care physicians, and burn, plastic, or reconstructive surgeons, all of whom may be involved in the care of patients with radiation-induced skin injury. Additional stakeholders include the governmental agencies charged with developing medical

countermeasures and response capabilities to radiation threats to address the potential of a mass causality event. In these scenarios, the exposure of the total or near-total body is likely, and thus these agencies are focused on the more severe grades of injury described by the CDC CRI scale. A threshold dose of approximately 3.5 Gy has been applied to the cutaneous radiation syndrome, which can complicate the course of recovery in patients with radiation-induced multi-organ failure.⁴⁰ Patients with total body exposures in this absorbed dose range are likely to also be treated aggressively for hematopoietic syndrome in addition to cutaneous injury that is predisposed to bleeding, infection and wound healing complications, all of which increases the risk of death in these patients.⁴¹ Alternatively, radiation oncologists are generally focused on the more commonly-encountered low-grade injury most often seen as adverse outcomes of the cumulative effects of irradiation for cancer therapy, which are fully described in the CTCAE and RTOG. Despite significant differences in their clinical context, these areas of focus need not be mutually exclusive, particularly given the similarities of the various diagnostic scales.

These issues are also important considerations for the FDA in its assessment of new topical therapeutic agents. When used as indications for cleared devices, the terms "radiation dermatitis" and "burns caused by radiation oncology procedures" appear to encompass injuries that would be classified as Grade III or lower on the CDC CRI grading scale. These injuries, which include erythema, dry and moist desquamation, and vascular injury are similar to superficial or partial thickness skin injuries, which are appropriately reviewed within the 510(k) regulatory pathway. The CDC CRI Grade IV injury appears to be similar to a full-thickness skin injury where skin grafts

are typically indicated, and products addressing these needs may be more appropriately reviewed under the Premarket Approval or a Biologics License Application for a biologic.

A significant limitation for all of the current definitions of CRI is the lack of attention to how the injury impacts the skin of differing pigmentation. The standard scale for skin pigmentation is the Fitzpatrick Scale.⁴² The Fitzpatrick Scale was originally intended to assess the impact of exposure to ultraviolet radiation, such as from the sun, but it has significant limitations with respect to CRI or radiation injury. Recent work has shown that skin reactions to clinical radiation therapy varies by skin type, and that differences in skin morphology between black and white skin types may account for the varied response.^{43,44} These differences are also highlighted by the observation that spontaneous desquamation is more likely to occur in black skin types.⁴⁴ Despite the difficulties in addressing skin type, addressing this deficit is critical as the demographic profiles of many countries include an increasing number of individuals with pigmented skin.⁴⁵

In conclusion, CRI, radiation dermatitis, “radiation burn,” and “burns caused by radiation oncology procedures” describe a biologically equivalent injury to the skin that results from exposure to ionizing radiation. While the source of the injury may vary, we propose that the basic etiology and resultant clinical presentation are similar regardless of the nomenclature or classification. Though it may be difficult to completely harmonize terminology and classification tools in the short term, stakeholders should begin a discussion on the equivalency of the terms, and their usage relating to skin injury resulting from ionizing radiation. The authors propose the use of radiation-induced skin injury, a uniform term that encompasses all forms of skin injury due to the biologic effects of radiation which could be used across the various stakeholders to harmonize the various terminology used.


Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The Corresponding Author states a conflict as a board member and shareholder of KeraNetics Inc.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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