

Review Article

A Review of the Clinical Similarities of the Terms Used to Describe Injury to the Skin Caused by Ionizing Radiation

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Abstract

Injury to the skin caused by ionizing radiation results in a complex sequence of symptoms with non-standard treatment regimens. This process is further complicated by the fact that professionals in radiation treatment, research, and injury prevention use different terms to describe the injury. Though there is broad agreement in the two most commonly used diagnostic scales (the RTOG and the CTCAE), skin injury treated in radiation oncology offices is usually described as radiation dermatitis and is coded under the ICD-10 term, radiation-related disorders of the skin and subcutaneous tissue. If the injury becomes severe, transfer to a wound or burn clinic is likely, where it is often described as a radiation burn and coded as a burn or corrosion. Further compounding the issue, most governmental agencies use the term Cutaneous Radiation Injury (CRI); however, FDA approves products for radiation dermatitis or burns caused by radiation oncology procedures. A review of the literature and comparison of clinical presentation shows that each of these terms has clinically similar symptoms and can be used interchangeably. Though term harmonization within the various stakeholders of radiation injury, treatment, and prevention is unlikely, an obvious first step would involve agreement in the field regarding the clinical similarities of the injuries described by the various terms in use.

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. A literature review of the topic shows that the following terms are often used interchangeably to describe similar skin conditions: cutaneous radiation injury, radiation dermatitis, radiation induced skin injuries, burns caused by radiation oncology procedures, and radiation burns. The predictor for which term is used can usually be traced to occupation or research focus. For example, the various government agencies that are charged with developing mitigation systems for radiation protection, including the Centers for Disease Control and Prevention (CDC), the Department of Defense (DoD), and the Biomedical Advanced Research and Development Authority (BARDA), generally use the term Cutaneous Radiation Injury (CRI), which is well described in the CDC fact sheet on the topic [1]. Radiation oncologists tasked with treating radiation-induced skin injuries use the term radiation dermatitis almost exclusively, while severe radiation-induced skin injuries are often transferred to Burn and Wound Clinics where they are

referred to as burns or even radiation burns. Finally, the Food and Drug Administration (FDA), which is tasked with regulating medical countermeasures and 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 what is known about radiation-induced skin injury described by each of these terms and discuss the similarities of the clinical manifestation of the skin's response described by each.

Overview of Skin Injury Resulting from Irradiation

Researchers and clinicians have both described a common set of responses in the skin after exposure to ionizing radiation. The clinical response ranges in symptom severity as a function of dose, fractionation, and depth of penetration. The broad consensus on the progression of the clinical symptoms, particularly for a severe injury, segregates the injury into early, middle, and late stages of presentation. At a high level, in the early phases of the injury process, erythema,

and sometimes edema, is 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 are known as late effects, which include symptoms such as epilation, skin atrophy, telangiectasias, hypopigmentation, and/or hyperpigmentation. These injury symptoms are discussed more fully below within the context of each of the terms used to describe the injury.

Cutaneous Radiation Injury

The CDC defines CRI as an “injury to the skin and underlying tissues from acute exposure to a large external dose of radiation.” The definition of CRI is further clarified as occurring in individuals exposed to a dose of radiation that is at least 2 Gy (200 rads), independent of exposure source. As described in the CDC fact sheet, 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 (e.g. at a nuclear power plant) as well as the surviving victims of an attack from either a nuclear weapon or a radiological dispersal device (i.e., 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.

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. If CRI were to be used in clinical practice, the likely diagnosis would occur during the manifest illness stage 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. By 6 to 7 weeks, dry desquamation may be present. 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. Later effects include edema of subcutaneous tissues and blisters with moist desquamation, followed by epithelialization. Grade III CRI encompasses the previously discussed symptoms but includes skin erosion and ulceration. Skin presenting with Grade IV CRI will have blisters with early ischemia and dermal necrosis presenting in as few as 2 weeks. 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 (NCI) 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 [2]. 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 literature, radiation dermatitis is used interchangeably with radiation-induced skin injury [3–7].

In addition to the CTCAE scale, clinicians often use the Radiation Therapy Oncology Group (RTOG) grading criteria to assist the assessment of radiation injury during manifestation of illness [8]. Both of these scales are important tools for oncologists given that literature reports have claimed that as many as 95% of oncology patients receiving radiation therapy for breast, prostate, perineal, and head/neck cancers experience some form of radiation dermatitis [9], though fractionated dosing has reduced this number in recent years. Lower grade injuries are often seen in the clinic and present with symptoms that closely follow the CRI scale used by the CDC. The higher grades of injury are uncommon but are usually associated with high doses used in patients with a larger body mass index, accidental radiation dosage errors, use of certain biologic therapies, or equipment malfunctions. It has been estimated that as many as 20% to 25% of patients, particularly with greater BMI and/or advanced cancers, will experience the higher grade symptoms of moist desquamation and ulceration [7,10].

The NCI’s CTCAE scale ranges from Grade 1 (mild) to Grade 4 (life threatening) symptoms and includes a Grade 5 representing death [2]. 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 mostly 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 of full thickness 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 (death) [8]. 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.

Burns Caused by Radiation Oncology Procedures

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 using this term. 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 (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). In addition to the indication confusion, 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 subtle differences in terminology associated with cutaneous radiation injury, creates challenges both for clinicians and product manufacturers. 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. Additionally, no Current Procedural Terminology (CPT) reimbursement codes exist for products related to the FDA-approved indications of “radiation dermatitis” or “burns caused by radiation oncology procedures.”

Radiation Burn

The term “radiation burn” is not often used by researchers in the field of radiation biology; however, it can be found in literature and is often used clinically. A search of PubMed for the term radiation burn produces thousands of articles, but only a handful (22 by our assessment) are specifically related to the clinical presentation of a radiation injury to the skin. The breakdown of the relevant literature includes articles on “cutaneous radiation burns,” descriptions of medical countermeasures related to nuclear events, case reports of radiation burns sustained in accidental or workplace exposure, radiation burns resulting from the therapeutic use of ionizing radiation, and radiation burns sustained from fluoroscopy or other radiation-guided medical procedures. Further complicating this term’s use in clinical practice is that the 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 thermal burn codes (T20–T25) for “burns and corrosions of 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.

Discussion

Given the increasing threat of a radiation incident around the world, it is imperative that researchers, clinicians, and government agencies operate with a consensus definition of radiation skin injury. It is not the intent of the authors to advocate for one scale or term above the others but rather make the point that having multiple terms to describe the injury is not optimal for stakeholders in radiation research and treatment. Though a single standardized term with a single corresponding grading system would solve this issue, 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 what is required, however, is the field’s agreement on term equivalency, particularly within FDA, which regulates products that are designed to treat the injury regardless of the term used to describe or diagnose it.

The purpose of this review is to begin a discussion between researchers, clinicians, and government agencies regarding the terminology used in their respected 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).

We can further see these similarities in the assessments of the injuries shown in Figures 1 and 2. Injuries such as those shown in Figure 1 are typically seen in radiation oncology settings and are usually diagnosed as dermatitis using the CTCAE or RTOG scales. When radiation injuries are more severe as shown in Figure 2, they are typically referred to as radiation burns and are treated in Burn, Wound, or Plastic Surgery Centers. Though typically not used by burn and wound clinicians, the RTOG, CTCAE, and CDC classifications can all be used to describe these injuries.

In addition to the challenge of treatment referral based on injury scale, it is also important to acknowledge that the various stakeholders of the diagnostic tools, injury terms, and recommended treatment paradigms have different areas of focus. The governmental agencies charged with developing medical countermeasures and response capabilities to radiation threats obviously seek to address the potential of a mass causality scenario. In these scenarios, a patient is likely to receive a full dose of radiation at once; thus, these agencies are focused on the more severe grades of the injury scale described in the CDC CRI fact sheet. Alternatively, radiation oncologists are generally focused on the lower grades of injury most often seen as adverse outcomes of the cumulative effects of irradiation associated with radiation therapy, and these lower grades of injury are more fully described in the CTCAE and RTOG. These areas of focus do not have to be competitive, particularly given the similarities of the various diagnostic scales.

These issues are also important considerations for FDA when assessing new topically applied treatments. 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 CDC’s 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. CDC’s CRI Grade IV injuries appear 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 (PMA) or a Biologics License Application (BLA) for a biologic.

Table 1. Clinical Presentation and management of skin injuries associated with ionizing radiation exposure.

	Grade I	Grade II	Grade III	Grade IV
Clinical Presentation at Manifestation of Injury				
Cutaneous Radiation Injury (CDC)	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 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
Management of Injury				
	<ul style="list-style-type: none"> – Prevent trauma to the involved area – Topical application of antipruritic topical preparations, corticosteroids, creams, and hydrogels 	<ul style="list-style-type: none"> – Protect involved area from further trauma – Topical application of antipruritic topical preparations, silver sulfadiazine, hyaluronic cream, corticosteroids, hydrogels 	<ul style="list-style-type: none"> – Protect involved area from further trauma – Topical application of antipruritic topical preparations, silver sulfadiazine, hyaluronic cream, corticosteroids, hydrogels 	<ul style="list-style-type: none"> – Prevent further trauma to the involved area and maintain principles of moist healing – Debridement of the injury, amputation of the injured limb, plastic/reconstructive surgery, full-thickness grafts

Table 2. Comparison of Radiation Injury Terms at an exposure dose of 2 Gy.

	Cutaneous Radiation Injury (4)	Radiation Dermatitis (15)	Burns from Radiation Oncology Procedures (16)
Definitions	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
Symptoms	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

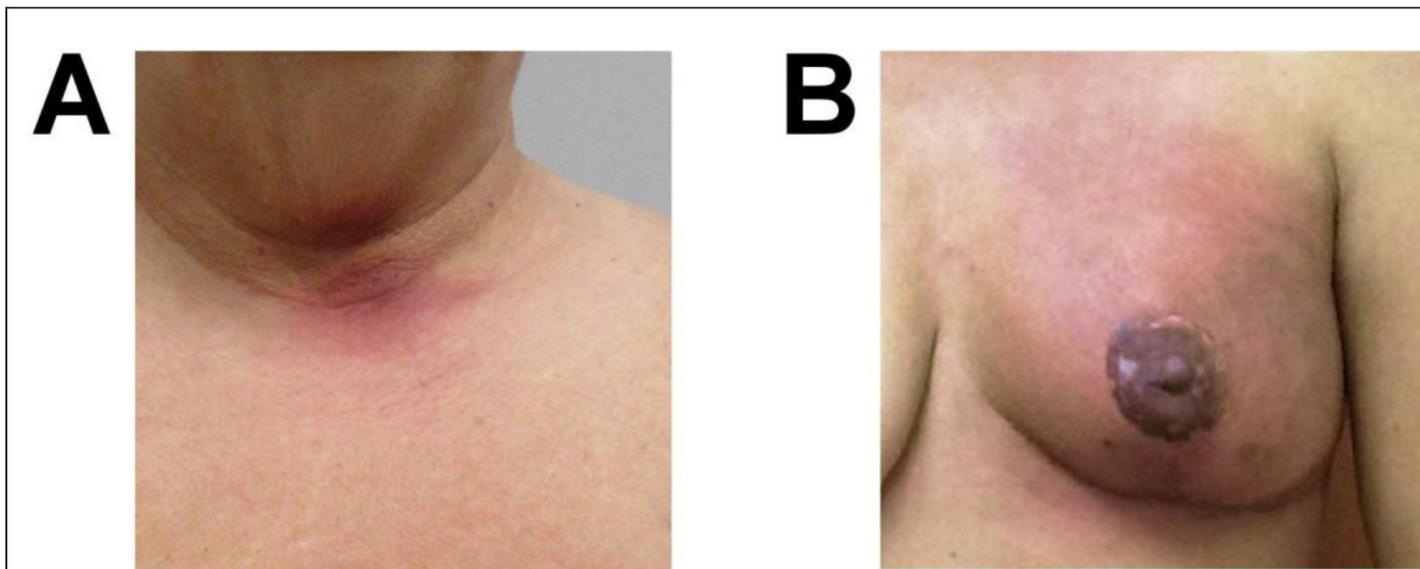


Figure 1. Radiation-induced injuries commonly treated in radiation oncology offices. (A) Grade I Radiation dermatitis as measured by CTCAE and RTOG scales. (B) Grade II Radiation dermatitis as measured by CTCAE and RTOG scales.

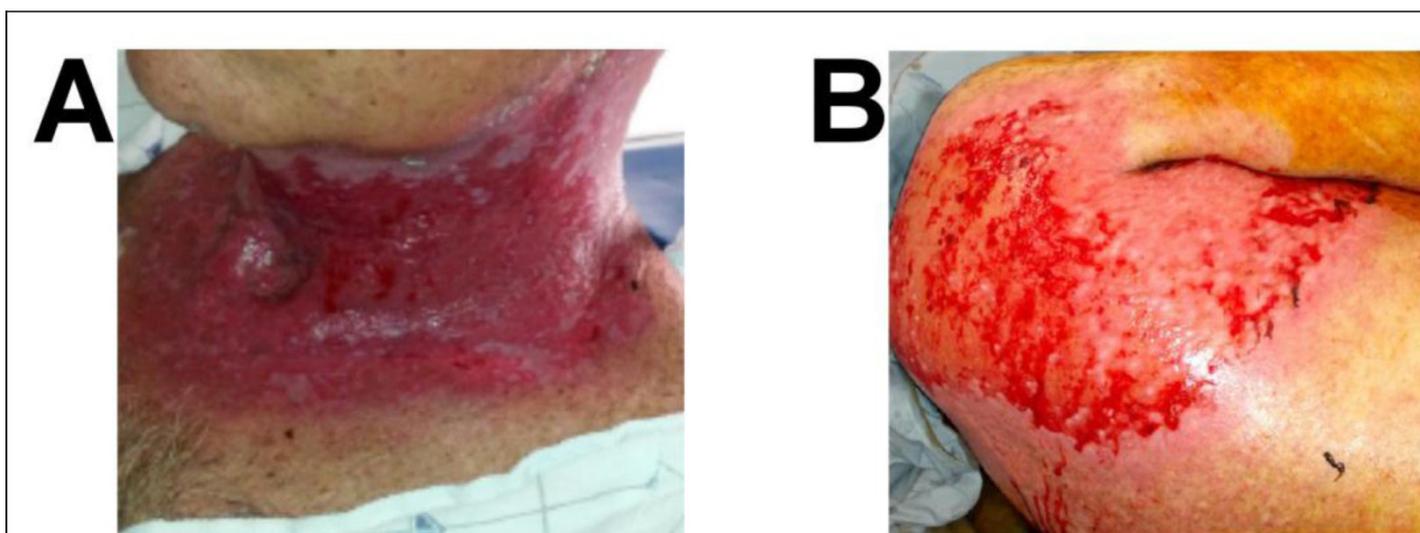


Figure 2. Radiation-induced cutaneous injuries described as radiation burns commonly treated in Burn Centers, Wound Centers, or surgery clinics. (A) Grade III Radiation Burn as measured by CTCAE, RTOG and CDC CRI scale that shows moist desquamation that has not progressed to ulceration. (B) Grade III Radiation Burn showing active areas of ulceration.

In conclusion, CRI, radiation dermatitis, and burns caused by radiation oncology procedures describe equivalent injuries to skin that result from exposure to ionizing radiation. While the source associated with injury varies, 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 can begin a discussion on the equivalency of the terms and their usage relating to skin injury resulting from ionizing radiation. This issue is becoming more relevant as radiation injury becomes a greater threat internationally, requiring the use of common terminology and a common understanding of the definitions of that terminology to ensure stakeholders in the US and abroad can accurately communicate results and issues without confusion.

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