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# Cutaneous and Local Radiation Injuries

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## Abstract

The threat of a large-scale radiological or nuclear (R/N) incident looms in the present-day climate, as noted most recently in an editorial in Scientific American (March 2021). These large-scale incidents are infrequent but affect large numbers of people. Smaller-scale R/N incidents occur more often, affecting smaller numbers of people. There is more awareness of acute radiation syndrome (ARS) in the medical community; however, ionizing radiation-induced injuries to the skin are much less understood. This article will provide an overview of radiation-induced injuries to the skin, deeper tissues, and organs. The history and nomenclature; types and causes of injuries; pathophysiology; evaluation and diagnosis; current medical management; and current research of the evaluation and management are presented. Cutaneous radiation injuries (CRI) or local radiation injuries (LRI) may lead to cutaneous radiation syndrome (CRS), a sub-syndrome of ARS. These injuries may occur from exposure to radioactive particles suspended in the environment (air, soil, water) after a nuclear detonation (ND), an improvised nuclear detonation (IND), a nuclear power plant (NPP) incident, or an encounter with a radioactive dispersal or exposure device (RDD/RED). These incidents may also result in a radiation-combined injury (RCI); a chemical, thermal, or traumatic injury, with radiation exposure. Skin injuries from medical diagnostic and therapeutic imaging, medical misadministration of nuclear medicine or radiotherapy, occupational exposures (including research) to radioactive sources are more common but are not the focus of this manuscript. Diagnosis and evaluation of injuries are based on the scenario, clinical picture, and dosimetry, and may be assisted through advanced imaging techniques. Research-based multidisciplinary therapies, both in the laboratory and clinical trial environments, hold promise for future medical management. Great progress is being made in recognizing the extent of injuries, understanding their pathophysiology, as well as diagnosis and management; however, research gaps still exist.



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**Keywords**

radiological; nuclear; local radiation injury (LRI); cutaneous radiation injury (CRI); cutaneous radiation syndrome (CRS); total body surface area (TBSA); nuclear detonation (ND); improvised nuclear device (IND); nuclear power plant (NPP); radioactive dispersal device (RDD); radioactive exposure device (RED); fluoroscopy; radiation dermatitis; radioactive orphan source; radioactive sealed source; electron paramagnetic resonance (EPR); mesenchymal stem cell; stromal vascular fraction (SVF); hyperbaric oxygen therapy; animal models; porcine; medical countermeasures; treatments

## 1. Introduction

The threat of a large-scale radiological incident from a state-owned nuclear device, an improvised nuclear device (IND), or a nuclear power plant (NPP) incident is very real and could result in large numbers of individuals with various degrees of acute radiation syndrome (ARS). A radiation dispersal device (RDD) is a device that, through multiple means, disperses radioactive materials into the environment. In addition to producing thermal burns and traumatic injuries, these incidents may also result in ionizing radiation injuries to the skin, deeper soft tissues, and organs, or radiation combined injuries (RCI), radiation exposure combined with another insult, such as skin wounds from debris, chemicals, and/or thermal burns. More frequently, exposures occur in industrial and occupational settings, either inside or outside the workplace. These sealed or contained sources can cause external radiation exposures, often resulting in cutaneous (C) or local (L) radiation injury (RI). In addition to the frequently seen and expected radiotherapy-induced dermatitis, there are other delayed tissue injuries from radiotherapy. Radiotherapy overexposures can result in injuries that are more severe than radiodermatitis. Fluoroscopy-guided diagnostic and treatment procedures may also cause damage and injuries to the cutaneous and deeper tissues. Knowledge and recognition of these injuries must be accompanied by rapid evaluation and diagnosis to achieve better outcomes for the patients. Below, the authors provide a thorough review of CRI/LRI, including historical perspectives, type or causes of these injuries, their pathophysiology, diagnosis and evaluation, appropriate medical management, and current research developments.

## 2. History of cutaneous injuries

Cutaneous radiation injury was evident in radiation workers from the early days of experiments with radioactivity. Roentgen announced his discovery of X-rays in January 1896, and the discovery of radioactivity from uranium was announced by Becquerel later that year [1]. Around the same time, Grubbé used Crookes tubes to study the fluorescence of chemicals [2]. During these experiments, he noticed pain, erythema, hyperemia, and hyperesthesia on the back of his left hand and, shortly after that, this progressed to dry desquamation and epilation. Realizing the destructive power of X-rays, Grubbé treated a woman with breast cancer in January 1896, only 23 days after Roentgen’s report.

In February 1896, Daniel and Dudley at Vanderbilt University radiographed Dudley’s head, and 21 days later noticed erythema and epilation [3, 4]. The following year, Stone-Scott

[5] reported 69 cases of X-ray-induced skin damage and, in 1902, Codman reported an additional 170 cases of X-ray injury [6]. Even Nobel Laureate Marie Curie developed radiation-related skin burns on her hands, as a result of handling radium samples during her experiments [7]. Further examples of cutaneous injury are described in an early health physics text [8].

It is instructive to describe the radiation pathology of cutaneous injury in two early users of radiation devices, as these injuries serve as prototypical examples of the pathology of cutaneous injury. Clarence Madison Dally (1865–1904) was an associate of Thomas Edison who often demonstrated an X-ray machine at local fairs. Dally noted an early epilation of his anterior scalp, eyebrows, and eyelashes, and he later experienced degenerative changes of the hands. His left hand developed erythema and was extremely painful, eventually leading to moist desquamation and ulceration, requiring multiple skin grafts. Eventually, his left hand was amputated above the wrist due to extensive squamous cell carcinoma (SCC). He later had amputation of both arms, and death followed a recurrence of mediastinal SCC.

Elizabeth Fleischman-Aschheim (1859–1905) was an American woman who purchased an X-ray machine in 1897, including a fluoroscope, to treat patients at the Presidio during the Spanish-American War. She eventually experienced severe radiation dermatitis with ulceration and had multiple SCCs removed. The axilla was noted to be involved with these masses, with more nodules below the acromioclavicular articulation. She eventually had her arm, scapula, and clavicle removed, dying of SCC metastases to the pleura and lung.

Some types of cutaneous damage, such as skin cancer, did not show up for 10–30 years after early radiologists exposed their hands during fluoroscopic examinations. By 1922, it was estimated by Ledoux-Lebard that more than 100 early radiologists had died of occupationally produced cancers, including leukemia [9]. Furthermore, several studies showed that until 1950, the mean lifespan of radiologists was considerably shorter than that of other physicians [8]. A tribute to early victims of X-ray injuries has recently been published [10].

## 3. Types and Causes of Injuries

### 3.1 Types of injuries

There are many terms used to describe radiation injuries to the skin and deeper soft tissues. These can all occur from the absorption of energy after acute or chronic exposure to ionizing radiation, leading to early or delayed injuries, typically limited to a localized area of the body [11]. The intensity, duration, and severity of these lesions follow a dose-dependent pattern; it is considered a deterministic or tissue reaction, affecting the skin and underlying structures [12]. The injury depends mainly on the volume of irradiated tissue, the dose absorbed by that volume of tissue, the radiation quality, and the inherent factors of the exposed individuals (comorbidities) [13]. CRI/LRI, while not normally life-threatening, may cause complications that can have a negative impact on quality of life, including chronic pain and disfigurement. A subsyndrome of ARS, termed cutaneous radiation syndrome (CRS), occurs when there is 1) a large percentage of the total body surface area (TBSA) involved, 2) a deeper depth of injury, and/or 3) a more extensive cutaneous involvement

after acute, whole-body irradiation. CRS can lower an individual's probability of survival. Cases of CRS were seen with 16 of 28 acute deaths in Chernobyl [14, 15]. Another expected outcome anticipated following exposure to a large-scale accident or nuclear detonation, and seen in many of the Chernobyl victims [16] is radiation combined injury (RCI), which involves radiation exposure concomitant with other trauma [17]. Although this other trauma could involve fracture, hemorrhage, and infection, often, the skin is involved, with the presence of thermal burns and/or debris and blunt-force injuries [18].

### 3.2 Causes of injuries

Radiation-induced injuries to the skin, CRI/LRI, are anticipated following the detonation of a nuclear device or radioactive dispersal device (RDD), sometimes called a "dirty bomb", and radioactive exposure device (RED), with the latter generating both beta and gamma exposure. In addition, there is the possibility of beta particle exposure to the skin from the fallout resulting from the initial nuclear detonation, especially if it is a ground burst; as well as "ground shine" dose rates of up to 1 mGy/h from beta and 0.1 mGy/h from gamma [19–21]. CRI/LRI could also result from other scenarios, including over-exposures from radiotherapy or fluoroscopic-assisted diagnostic studies / treatments, or industrial accidents, which could lead to injuries of varying severity. Experience has shown that affected individuals typically belong to one of the following groups: occupationally exposed radiation workers (in accidents derived from the industry), patients (in accidents derived from medical practices), or the general public (in accidents related to industry and the finding of non-controlled sources of radiation, also called orphan sources) [22]. Local external exposure to gamma radiation sources is of significant concern because of its frequency in cases of accidental overexposure to ionizing radiation and the possibility of underlying damage to tissues and other body structures developing into severe injuries.

## 4. Pathophysiology of Injuries

### 4.1 Chronology of injuries

Patients may initially develop primary or transient erythema manifestations on the skin within hours after irradiation, which is related to vascular permeability changes [23]. The time of appearance of transient erythema has a prognostic value. Earlier manifestations after the exposure to ionizing radiation imply higher absorbed doses by the tissues. Correspondingly, its severity serves as a dose indicator [24]. More severe clinical manifestations are observed in the following days or weeks. Lower absorbed doses will be associated with transient and temporary lesions, and higher absorbed doses (>25 Gy) will be followed by tissue necrosis in the following weeks or months [11]. The evolution of CRI/LRI with absorbed doses higher than 25 Gy to the skin has been documented in several radiological accidents [25], and presents the following progression: transient erythema; late erythema, followed by dry and moist desquamation; ulcerative lesions and tissue necrosis in a variable period from one to five weeks, depending on the absorbed doses (See Table 1).

Radiation effects observed in bone and skeletal muscle are predominantly late effects that appear months to years after radiation exposure [23]. Radio-induced rhabdomyolysis and osteonecrosis can be expected when the absorbed doses to muscles and bone are

higher than ~40 Gy [11]. CRI/LRI may continuously develop for several months to years after the radiation exposure as recurrences (radio-induced osteonecrosis is associated with severe chronic recurrences of CRI/LRI) [26]. The main feature of CRI/LRI is its dynamic evolution, with clinical manifestations progressing unpredictably, even several years after initial exposure [11].

### 4.2 Pathophysiological effects

Radiation-induced damage to the different layers of the skin and disruption of the protective barrier can occur directly (e.g., injury resulting from direct energy transfer into the skin) and indirectly (through damage to the underlying vasculature and circulating or skin-resident immune and structural progenitors). With reduced blood flow, fewer immune cells can traffic to the injury site, which can further impact healing and increase susceptibility to wound infection. Disruption of the skin barrier, due to trauma or other exposures such as radiation can lead to poor outcomes following a radiological or nuclear incident. Damage to the skin could occur acutely following exposure – for example, from radiation-induced desquamation – but also from injuries that manifest later and are worsened by other skin damage from other insults, such as failure of wounds to heal, infection, and late cutaneous fibrosis. In addition, in combined radiation injuries (i.e., radiation combined with other forms of trauma that could involve puncture/shrapnel injuries and/or burns), it is established that damaged and irradiated skin will respond in a way that is not seen with the traditional injuries alone. The effects of radiation within the skin can also vary based on the differing radio-sensitivity of skin-resident cells. For example, hair follicle stem cells, melanocytes, and cells located in the basal keratinocyte layer tend to react more strongly to exposure, and thus, contribute to more significant deep dermal injuries [27].

A major consideration in evaluating the severity of CRI is the energy of the radiation to which the skin has been exposed. Although beta particles have lower overall energy than gamma rays, which means that they cannot penetrate as deeply, they deposit all of their energy within the outer layers of the skin [19]. The clinical signs of radiation injury can vary based on the dose and duration of exposure, but generally present in several well-defined ways, which may be distributed over time. These can include:

1. Erythema (redness, similar to a sunburn)
2. Epilation (hair loss due to follicle damage)
3. Dry desquamation (scaly, flaking skin)
4. Moist desquamation (characterized by weeping/loss of fluid)
5. Edema (swelling of the region in which the CRI is located)
6. Hyperpigmentation (skin darkening, often characterized by excessive melanin)
7. Vascular damage (if the wound is deep enough, vessels can be compromised and ischemia can result)
8. Ulceration (presenting as an open sore, and frequently linked to blood flow concerns)

9. Atrophy (thinning and degradation of the skin structure)
10. Telangiectasia (dilation of small vessels in the skin)
11. Fibrosis (over-production of connective tissue)
12. Necrosis (subcutaneous tissue death due to ischemia and other contributing factors)

In some instances, if the dose of radiation is high enough and the penetration is significant, other non-epithelial tissues, such as underlying adipose and muscle, can be damaged. This complication can lead to an even worse prognosis for the patient, in terms of healing and long-term outlook.

Unlike typical thermal burns, CRT/LRI evolve over a longer time and involve periods of latency, interspersed with active inflammation. Cutaneous radiation injuries do not heal as quickly as thermal injuries and the strength of the closed wound is lower and the associated pain of the injury can be much higher. For example, some individuals receiving high radiation doses to their extremities report the development of superficial ulcers in the skin years after exposure, even in areas believed to be fully healed [28]. In general, the higher the radiation dose delivered to the skin, the more rapid the presentation of manifest illness signs and symptoms after exposure. For equivalent radiation doses, a key determinant of the severity and rapidity of the onset of manifest symptoms is the anatomical location of the irradiation, with the face, chest, and neck (areas with relatively thin skin) responding sooner and with more debilitating injury than body regions with thicker skin, such as palms and the soles of the feet [29].

The body’s systemic response to cutaneous radiation injury has not been studied extensively, but conclusions can be drawn from the more fully explored topic of immune responses to radiation therapy. It is known that the immune system responds to the volume of cell death and injury in a localized tissue field. Nonviable cells release inflammatory mediators known as damage-associated molecular patterns (DAMPs). DAMPs can include TNF-α, reactive oxygen molecules, transforming growth factor (TGF) β-1, and other species that can instigate and accelerate the immune system response. The chemokines and cytokines released from these stressed cells stimulate and direct a focused inflammatory response into the radiated tissue. The effects from the immune response triggered by the radiation injury may initially begin a constructive response of the damaged tissues, but the scale of the response can also lead to adverse outcomes of chronic inflammation, fibrosis, and pathological wound healing [30, 31].

In addition to direct damage to cellular DNA, ionizing radiation drives the formation of reactive nitrogen and oxygen molecules that acutely stimulate tissue inflammatory responses. Immune system activation drives the inflammatory response, with TGF-β1 playing a pivotal role in driving chronic wound inflammation. TGF-β1 production is elevated immediately after exposure to ionizing radiation (the quantity of TGF-β1 released appears to correlate to radiation dose) and can remain high for many months. The resulting chronic inflammation leads to an over expression of interleukin (IL) – 4, IL-13 (T-helper 2 cytokines), and platelet-derived growth factor (PDGF), which enables a protracted

myofibroblast presence in the injured tissues. This leads to poor wound healing with a reduced local vascular supply, dense fibrosis, and excess deposition of ECF proteins (collagen, fibronectin, hyaluronic acid) in the injured subdermal tissues. The resulting fibrotic tissue is often cosmetically displeasing, vulnerable to future trauma, and associated with chronic or non-healing wounds [32–35].

A unique correlation appears to exist between radiation dermatitis and trans-epidermal water loss (TEWL) that suggests the use of topical treatments could mitigate the extent of cutaneous symptoms and reduce fibrotic skin changes. It has been noted that overexposure to ultraviolet (UV)-B radiation leads to a disruption of the ability of the stratum corneum to protect from undesired TEWL and results in clinical findings similar to irradiated skin. Quantification of TEWL in UV-B radiation exposure reaches a peak volume (and begins to return to normal levels) within days of injury. Ionizing radiation injury to the skin results in a delayed occurrence (mean = 27 days) of peak TEWL values and correlates with symptoms of erythema, desquamation, and erosions. Interestingly, peak TEWL precedes by 8 days the peak of radiation dermatitis symptoms. The stratum corneum barrier defect (which has been shown to induce cytokine production) may play a causative role in wound fibrosis formation following CRI/LRI and, if so, topical medications with high lipid content may reduce or prophylaxis some of the early CRI/LRI symptoms and late complications related to pathological fibrotic wound healing [36]. While topical corticosteroids may improve epidermal barrier function in the short term, their negative impact on epidermal proliferation makes them less than ideal treatment options outside of the initial inflammatory phase of CRI/LRI. Emollients are a safer treatment option for more protracted treatment regimens [37].

## 5. Diagnosis and evaluation

### 5.1 History and Physical

A thorough history and physical examination of a patient with suspected CRI/LRI should include scenario details, timing and duration of signs and symptoms, a detailed skin examination with a thorough neurological exam, and serial digital color photographs. It is important to consider underlying and closely approximated anatomy, as the injury may be more extensive than initially suspected [11]. If the injury is acute, it is appropriate to perform a complete blood cell count with differential to monitor for any signs of the hematopoietic syndrome of ARS. Biological dosimetry may have a limited role in two indications: 1) depending on the irradiated volume, radiation quality factor and absorbed dose of the partial body irradiation, biological dosimetry can provide additional information that may confirm the local exposure (Harlequin chromosomes) and may eventually perform an estimation of absorbed doses (with limitations)l 2) as a complementary assessment tool, used after the medical evaluation of a CRI / LRI, there are elements that may suggest associated whole-body irradiation and estimate the absorbed dose to whole-body. Another consideration is to collect tissues for electron paramagnetic resonance (EPR). This may have more specific applications, such as nail clippings for finger injuries, excised tissues, or amputated bone [38, 39]. The use of EPR may not currently be rapid enough or widely available for clinical diagnostics, though its use may be helpful retrospectively. Attention to

any other clinical signs or symptoms is important to monitor for a more extensive injury, such as ARS [11].

### 5.2 Imaging – Ultrasound and thermography

It is of medical interest to be able to evaluate both thermal and radiation burns. Ultrasound and thermography have found a place in the clinical setting for evaluation of these injuries and the combination has enabled early detection of subcutaneous pathological changes not easily visible clinically. Thermography systems image skin lesions in the 6- to 14-μm infrared spectrum, thereby visualizing the heat distribution in the skin due to inflammatory processes. These changes are generally due to increased arteriolar flow. Various authors have reported on the usefulness of thermography in determining the extent of ionizing radiation injury ([40–45]. In addition, there is a significant literature on the use of thermography in the management of thermal burns [46–54]).

High frequency ultrasound has also been shown to be an important diagnostic modality to evaluate skin damage, since the technique basically probes tissue density changes. Reflection and transmission coefficients for an incident longitudinal wave are dependent on density changes between different tissue planes, therefore making it possible to visualize pathological changes in real time.

Thickness thermal burns were used in a live porcine model [55, 56]. The work was extended shortly thereafter to evaluate efficacy in a medical environment, and to evaluate the spectral content of ultrasound signals reflected from thermal burn interfaces [57]. Since that time, various investigators have described the ultrasound characteristics of thermal injury and extended this technique to evaluate burn depth [57–64]. At the time of the research conducted into thermal burns, it was clear that evaluation of cutaneous radiation injuries was a much more difficult problem because of the diffuse nature of damage and the prolonged time interval for the development of clinical signs and symptoms. The high frequency ultrasound technique previously developed at ORNL has now been extended to analyze radiation-induced cutaneous injury. This has been possible because of improved instrumentation since the 1970’s and the development of image analysis and texture algorithms to define the diffuse injury.

Case studies for three patients will be presented to illustrate various ultrasound and thermography techniques for evaluation of CRI/LRI. Patient P is a young, 65 kg Yorkshire swine, studied in a collaborative project at the University of Tennessee College of Veterinary Medicine (UTCVM). Patient S is a 46-year-old female industrial radiologist who experienced radiation injury after briefly touching a 22-Ci, Ir-192 source during a routine change-out procedure. Patient D is a 56-year-old male who experienced a myocardial infarction, which resulted in percutaneous coronary intervention (PCI), who subsequently experienced two significant CRI/LRIs on his back from extended fluoroscopy procedures.

In the UTCVM studies, porcine patient P was irradiated locally in four 2×2 cm squares, 3 sites for analysis and one control site. Dose to the sites was 15 Gy using 6 MeV electrons from the UTCVM LINAC facility. Ultrasound evaluation of the cutaneous injury was performed using a 12 MHz linear array ultrasound transducer. Tissue characterization

using image and spectral analysis was performed offline and was useful to visualize the extent, depth, and time dependence of the radiation-induced lesions. Figure 1 illustrates infrared visualization of early transient erythema in Patient P, 15 minutes after irradiation. Figure 2 presents grayscale ultrasound images (4 cm depth) of one of the sites before irradiation (control) and at 15 minutes post-irradiation. From top to bottom in control and subsequent images, there is epidermis, dermis, a well-demarked fat layer, a muscle insertion, and various anatomic layers of muscle. After irradiation, the immediate cellular response was significant tissue edema. In Figure 2, water density is black. Some tissue fluid is normal (Figure 2, left) but a large amount of tissue edema is present at 15 minutes post-irradiation (Figure 2, right). Therefore, it is clear that it is possible to visualize radiation-induced damage evolving in real time. In Figure 3, water density is colored red, making the tissue edema easier to visualize. By days 1 and 2 post-irradiation, the irradiated areas are flooded with fluid, obscuring multiple anatomic structures. By Day 6, the situation appears to resolve.

Evaluation of ultrasound data involved image analysis of frames saved in a standard 800- by 600-pixel format. The grayscale distribution function (Figure 4 - derived from algorithms in the National Institutes of Health (NIH) computer image analysis suite, ImageJ version 1.51i.) is very sensitive to radiation-induced tissue edema, particularly in the first 5 days after irradiation. Since edema fluid is colored black in the grayscale image, the pixel distribution shifts to the left and is narrower in the irradiated areas. The pixel distribution in irradiated areas is statistically different from that in the control ($p < 0.0001$; two sample Kolmogorov–Smirnov test) within 15 minutes post-irradiation. This difference continues through the conclusion of the experiment at 24 days.

The Kolmogorov–Smirnov test (K-S test [65–67]) is a nonparametric statistical test to evaluate the equality of a continuous, one-dimensional statistical distribution against a reference Gaussian probability distribution (one-sample K–S test) or to compare two experimental distributions (two-sample K–S test), as in this case. In this case, the two-sample K–S test and the corresponding D statistic are ideal and robust for comparing the control distribution versus the irradiated-tissue distributions at various days post-irradiation. The two-sample KS test is one of the most useful and general nonparametric methods for comparing two samples because it is sensitive to differences in both location and shape of the empirical cumulative distribution functions of the two samples. It is also considered robust and distribution-free.

Patient S is a 46-year-old female industrial radiologist whose left index finger briefly touched a 22-Ci, Ir-192 source. She presented to the Radiation Emergency Assistance Center/Training Site (REAC/TS) 3 weeks post-event and, at that time, severe edema and blistering was noted on the palmar side of the left index finger (Figure 5). No additional pertinent medical history or accident information was available. The initial presentation of the finger on Day 27 post-incident is shown in Figure 5, and the ultrasound image with a 12-MHz transducer is shown in Figure 6. The REAC/TS health physics team estimated a 15- to 20-Gy dose to the index finger.

The texture of a clinical image contains information regarding disease processes and this technique is becoming widely used in clinical medicine [68–74]. Since diffuse cellular injury with tissue edema was noted in this case, some measure expressing texture and complexity of the image would appear to be useful. Image entropy H is such a measure, defined by:

$$H = -\sum_{k} p_k log_2(p_k)$$

where k is the number of gray levels in the image and $p_K$ is the probably associated with gray level k. Image entropy in this study was calculated using algorithms in the NIH image analysis suite, ImageJ version 1.51i.

Normally in thermodynamic processes, disorder and entropy increase in non-isentropic cycles. However, in irradiated tissue with edema, the image becomes more uniform due to the outpouring of fluid and it is expected that image entropy would decrease. Figure 6 (inset graph) illustrates the exponential decrease in image entropy along the distal aspect of the patient S's finger.

Patient D is a 56-year-old male who had an emergent cardiac stent placed under fluoroscopic guidance or a percutaneous coronary intervention (PCI). He subsequently had a stent revision and 'definitive therapy', in a procedure that took as long as 5 h total, at 0.01- to 0.1-Gy/min skin dose. Total dose to areas of his back was estimated to be between 40–50 Gy. After the procedure, he developed two large lesions, one necrotic, on his back (Figure 7a). Figure 7b shows a thermography image of the lesions at the time of initial presentation. This is the first case where REAC/TS personnel were able to use ultrasound, infrared thermography, and clinical medical techniques simultaneously. Patient D had an extended recovery over several years, involving 120 hyperbaric oxygen therapy dives and ultimately, wide local excisions. Skin grafting was done on the left lesion and extensive wound therapy, including vacuum-assisted wound closure, on the right lesion, Figure 8 presents an ultrasound image of late radiation fibrosis on his back, next to an area of more normal tissue. The fibrotic area is outlined for aid of visualization. Substantial literature exists on ultrasound analysis of skin fibrosis [75–78]. Fluoroscopic injury from medical procedures continues to be a significant safety issue. A review of radiation injuries due to fluoroscopy has been presented by Mettler and colleagues [79–81]. Additional clinical recommendations and a review of the fluoroscopy injury literature have also been presented [82–87].

From these examples we see that ultrasound and thermography, combined with image analysis, can provide additional diagnostic modalities for the medical management of CRI/LRI. Several texts on image analysis are available, which the authors have found useful [88–90].

### 5.3 Imaging – other techniques

In addition to ultrasound and thermography, other imaging modalities have been found useful in the clinical management of radiation injury to the skin and deeper tissues. Mettler

and colleagues [91] have investigated the use of three-phase radionuclide bone scanning in the management of CRI/LRI. These authors describe the use of radionuclide imaging in the evaluation of a patient who developed necrosis of his distal digits following a radiation accident. In addition to determining the vascular status of the hands, imaging helped indicate an appropriate level for amputation. Raina and Samuel [92] have reported two cases using isotope angiography and blood pool scanning in the management of cutaneous injury. Patients developed necrosis of the distal digits after exposure to 22–25 Ci from Co-60 sources over 2 to 3 minutes. In addition to determining the vascular status of the hands, imaging helped indicate an appropriate level for amputation. The authors conclude that isotope angiography followed by delayed blood pool imaging is a simple, non-invasive procedure to assess radiation-induced damage to extremities and evaluate deterioration or improvement during follow-up.

In past experiences, computed tomography (CT) and magnetic resonance imaging (MRI) have demonstrated to be significant imaging methods for diagnostic and dose reconstruction purposes in the evaluation of CRI/LRI in affected patients.

## 6. Current Clinical Management

There are currently no drugs specifically approved/cleared by the U.S. Food and Drug Administration (FDA) to treat CRI/LRI, such as those that can occur during a radiological or nuclear incident. Approaches currently used to treat thermal burns, including topicals, wound dressings, and cellular therapies, are under study for potential efficacy in a radiation emergency medicine setting. These are frequently in use in clinical scenarios involving small-scale, accidental exposures. To repurpose existing burn treatments for a new radiation indication is often the foundation of treatment, however, the nature of radiation-induced skin trauma is very different than thermal burn and other wounds in a number of key areas (see Section 4. Pathophysiology of Injuries). Current standards of care for clinical management of CRI/LRI come from many areas, such as experiences in accidents, radiotherapy over-exposures, burn therapies, animal research, and clinical trials.

Any radiation injury should result in the engagement of radiation health and protection experts and a multidisciplinary team of medical and health professionals, including health and medical physicists; nuclear and radiation medicine specialists; surgeons (plastic, reconstructive, oncologic, and burn); hematologists; nuclear medicine physicians, radiologists, and radiation oncologists [11, 93]. Medical management of severe cases of CRI/LRI (i.e., radionecrosis) will likely require hospitalization in specialized plastic and reconstructive surgery or burn departments, with experience in managing this kind of injury [11]. Primary treatment of CRI/LRI has evolved in the last 20 years. Initially, a “wait and see” strategy was used to treat CRI/LRI as conventional burns, waiting for their spontaneous evolution. This approach often resulted in dramatic consequences for the health of the affected patients and amputations on several occasions [25, 26, 94, 95]. At the end of the 1990s, after the radiological accident in Yanango (Peru), in which the patient had a hemipelvectomy [96], scientists began exploring the possible use of bone marrow derived mesenchymal stem cells (MSCs) to treat radiation-induced skin lesions. In 2005, a radiological accident occurred in Nueva Aldea (Chile), when a construction worker found a

sealed radioactive $^{192}$Ir source from an industrial radiography device on scaffolding and put it in his pocket while taking it to his supervisor. The incident resulted in severe CRI/LRI to the hands and gluteus after the worker held the source in his hands and kept it in his back trouser pocket. On day 15 after the accident, following the request from the Chilean authorities and in line with the recommendation of an IAEA Assistance Mission, the patient was transferred to France for his treatment [97].

A treatment using a new approach was successfully applied, developed by the Institut de Radioprotection et de Sûreté Nucléaire (IRSN) and Percy Hospital, based on dosimetry-guided surgery and cellular therapy, united local dose assessment with early conventional surgery guided by dosimetry and the administration of mesenchymal stem cell (MSC). This combination yielded impressive results and a new paradigm based on the treatment was consolidated (Figure 9) [13, 98, 99], and is positioned to provide excellent outcomes for cases with known exposure histories.

Dosimetry-guided surgery is applied as an early procedure in cases of severe local radiation exposure, when deep ulceration or necrosis can be expected [99]. Isodoses are calculated using a ‘dosimetric map’, that shows the dose distribution on the skin surface and underlying tissues obtained by a personalized voxel phantom. The resulting map informs surgeons of soft tissue areas of high radiation dose (>25 Gy) where necrosis is likely to occur. Dose reconstruction provides valuable information for determining the prognosis and the best treatment strategy [11]. MSCs are injected during surgery in different areas, and again in several sessions following surgery, to deliver paracrine factors like anti-inflammatory cytokines, growth factors, and microvesicles that contribute to the healing [13, 25, 26, 99].

Pharmacological management of pain with conventional analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), central action analgesics, opioids, and sedatives has been indicated, especially during the initial phases of CRI/LRI. Also, neuroleptics, antihistaminic drugs, anxiolytics, and antidepressants have an accessory role in pain management. One of the most promising developments in pain management has been observed with stem and stromal vascular fraction cellular injections [97]. The use of autologous, MSCs (bone marrow-derived and cultured) and autologous, adipose-derived stromal vascular fraction (SVF) injections (adipose-derived, non-cultured cells), with or without surgery, show promise in animal models, humanitarian use, and in clinical trials for decreasing healing time, pain control and resolution of healing without repeated exacerbation of the injury (Figure 10) [100–102].

Conservative therapy consists of use of artificial skin and dermal constructs (Integra®, Terudermis®), with or without growth factors (e.g., TGF-β). Pentoxifylline, a methylxanthine, which reduces blood viscosity and improves perfusion at the microcirculation level, alone and in combination with α-tocopherol, provides a synergistic effect [103, 104]. Topical treatments in the form of antihistamines (oral and/or topical), NSAIDs, silver-based therapies, debridement [12, 105, 106], and topical steroids (class II and III) [107] are useful therapies, alone and in combination. Other approaches, such as treatments in a hyperbaric chamber, have reported promising results in the management of CRI/LRI [102, 108], although in the REAC/TS experience, two of the authors have observed

that it requires many more hyperbaric dives (treatments) than indicated for other wound care (personal communication[5]).

Experience demonstrates that the involvement of other professionals, such as nutritionists, physiotherapists and mental health support teams, may improve the treatment results in the medical management of patients with CRI/LRI and should always be considered in the treatment process [11, 102]. Arrangements for the medical follow-up of these patients should be considered, especially on severe CRI/LRI cases, intending to the early detection of recurrences and timely treatment of complications. Previous radiological accidents have shown recurrences after one to thirty years after the accidental exposure (Figure 11) [26, 28, 95]. All of these treatments may be combined with surgical techniques: wide local excision of damaged tissues with healing by secondary intention, vacuum-assisted wound closure, or with partial- or full-thickness grafts; local flaps including advancement flap, rotation flap, transposition flap and the interpolation flap; and the free flap where tissue is transplanted from another area; and on occasion, amputation.

## 7. Current Research

Because assessment of candidate medical countermeasures (MCMs) for radiation injuries requires that efficacy studies be carried out in animal models (since conduct of such studies in humans would be unethical and unfeasible), it is critically important that appropriate animal models be selected that most closely mimic anticipated human responses. In addition, identification of biomarkers in the skin that could be useful to determine severity of an injury (e.g., to guide early treatment decisions or predict potential for late complications) are best carried out in appropriate species. For these reasons, development of animal models is an important step in the study of any approaches as potential treatments for CRI/LRI.

### 7.1 Preclinical animal model development

Underway in earnest for over a decade, advanced development of both small and large animal models for CRI/LRI has focused on certain species that possess dermal properties that are most similar to humans. Although mice were initially sought for study of radiation-induced cutaneous injuries, due in part to their relatively low cost and minimal housing requirements, they do not necessarily represent the best model to study CRI/LRI [109]. This is because they heal skin wounds by contracture, unlike humans, whose wounds close through re-epithelialization [110]. In addition, other aspects of their dermal properties can impact the degree to which products can be absorbed across the skin They can; however, be used as an initial proof-of-concept model to determine potential efficacy of a medical countermeasure to address some aspects of skin injury. For example, one murine CRI/LRI model involves irradiating the hindleg with high doses of radiation (~30–50 Gy), and contracture/leg-extension at time points weeks-to-months later is assessed to ascertain the impact of any treatment on mitigation of late soft tissue fibrotic events [111–114]. Another well characterized mouse model involve combined injuries, in which an animal exposed to total-body irradiation and concomitant skin trauma (burns or wounds) is assessed for

[5]Carol Iddins (REAC/TS) and Ronald Goans (REAC/TS)

survival as well as other end points such as rate [115] or strength [116] of wound healing. A somewhat larger rodent, guinea pigs, have also been sought out as a possible model to assess MCM efficacy for CRI/LRI. Their dermal structure is similar to humans [117], in that they have “tight” skin (unlike mice, that have loose), and the means with which they heal a wound is also similar to humans [118]. Although some early work was done to establish this model [119–121], newer studies have clearly shown the utility of this animal to look at efficacy of products to address CRI [122].

Pig models, in general, are useful to study radiation-induced skin injuries. Minipigs have served as an appropriate model for CRI/LRI MCM development. Midway in size between rodents and full-size commercial pigs, there are several strains (Yucatan [123], Göttingen [124–126] and Sinclair [123]), whose cutaneous radiation responses have been investigated. A new model under consideration is the red Duroc pig: this particular strain is important because its epidermis has high levels of melanin, and therefore, could simulate responses in pigmented skin [127]. Commercial variety swine such as the Large White, Oxford or American Yorkshire breeds have been used for decades as models for human skin, in the testing and development of dermatologic products, as their similarity to humans has been well characterized [128]. They were also studied in the 1990s and 2000s for their responses to different types of radiation [129, 130]. Often, multiple wounds are created on the skin on the dorsal surface of the animal, and different wounds can either be vehicle- or drug-treated within the same animal. Their more recent use in studies to assess CRI/LRI has included repurposing of several approaches that are now in advanced development, with funding from the U.S. Biomedical Advanced Research and Development Authority (BARDA). These products include Silverlon® (Argentum), a wound dressing cleared by the U.S. Food and Drug Administration for treatment of burns and wounds [131]. In 2019, this wound dressing was also cleared as a care product for injuries resulting from sulfur mustard exposure of the skin, and the company is recruiting patients for a clinical trial for radiotherapy-induced dermatitis (National Clinical Trial (NCT) 04238728). Other BARDA support of MCMs for CRI/LRI includes studies on KeraStat® Cream (purified, human keratin), which has been studied for wound management of pig [132] and human CRI/LRI. Kerastat completed a clinical trial in 2018 (NCT03559218) and was cleared for a radiation dermatitis indication in 2020. The company continues to advance the product for treatment of CRI/LRI during a radiological or nuclear incident, using a large white pig model [133].

Adding to the animal models available for study of CRI/LRI are human skin representations, that help to bridge the gap between rodent and porcine data, and clinical work in human volunteer and/or patient populations. There are human simulants of skin injury that have been used extensively such as *in vitro* models (e.g., StratiCELL, and EpiDermFT™ (MatTek Life Sciences), and there are other more novel approaches under development such as *ex vivo* perfused, human skin flaps [134], and xeno-transplants using human skin grafted to mice[6].

[6] https://reporter.nih.gov/search/5KkxkW_xR0q73WUcQCTauA/project-details/9870169

### 7.2 Skin utility in radiation biodosimetry

As one of the largest organs of the human body, the skin is eminently poised for study of biodosimetry approaches of triage, definitive care, and predictive capabilities. The skin is an immunologically active barrier tissue that is visually observable, accessible to non-invasive testing and easily sampled, making it amenable to a variety of biodosimetry testing modalities. ANOD SCID gamma (NSG) mouse model has been developed that is engrafted with human adult skin or neonatal foreskin [135] and retains normal skin morphology, intact stem cell populations, functional human vascular beds, and an intact cutaneous immune system. This model is useful in the study of biomarkers of radiation exposure and predictors of tissue injury. In this unique xenotransplant construct, investigators can examine DNA damage repair proteins, reactive oxygen species, epithelial barrier function and gene expression changes in adult and pediatric human skin grafts following irradiation. Others have also sought to utilize skin-based assays for detection of radiation-induced gamma H2AX in hair follicles, to estimate absorbed radiation dose [136].

### 7.2 New methods to evaluate severity of CRI/LRI

For years, many cinical scoring paradigms have been established to assess degree of skin injury and healing. Most of these focus on attributes such as degree of erythema, desquamation, and ulceration [137, 138]. As discussed in detail above, there are many novel imaging technologies, including sonography and thermal imaging, with promise to understand the clinical presentation of severe radiation wounds more completely. In 2020, researchers in Korea used optical coherence tomography angiography (OCTA) [139], to detect subtle, non-observable (to the naked eye) changes in mouse skin after radiation exposure. With this method, skin changes such as thickness, and blood vessel alterations were observed, and could serve as early correlates to latent radiation effects. Earlier work with other optical techniques, such as reflectance confocal microscopy (RCM) and 2-photon microscopy (TPM) have also shown promise in predicting latent skin injuries following irradiation. Endpoints included changes in cellular structure and morphology of the epidermis and skin-resident glands [140]. In use since at least the early 2000’s, thermal imaging of skin to assess severity of burns has been a viable option and important tool available to physicians [49]. With availability of lower cost, infra-red imaging cameras, use of this this method for assessing radiation injuries in preclinical models has become more accessible, leading to an expansion of its use (discussed above). More recently, cheaper access to advanced imaging techniques like computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scans has meant that even small animal researchers can employ these modalities for preclinical studies. In addition, with advances in virtual reality imaging keeping pace, it is possible to combine these techniques to generate astounding images, and the ability to “step inside” a radiation wound (Figure 11). A minipig animal model for cutaneous radiation injury (CRI) has been developed to study the effects of radiation and test MCM through an interagency agreement between the National Institute of Allergy and Infectious Diseases (NIAID) and Armed Forces Radiobiology Research Institute (AFRRI). Working with the academic investigators, staff and scientists in the NIAID Office of Cyber Infrastructure and Computational Biology (OCICB) are using advanced technologies and minipig CT data to visualize radiation skin injuries, including proximity of soft tissue to bony structures, to understand how the

relationship between radiation dose, bone and tissue distribution affects the etiology of skin lesions, and provide objective measurements of wound area, volume and classification. This information helps researchers to better understand why wound severity can vary from one part of an animal to another (personal communication[7]).

### 7.3 Medical countermeasures for CRI/LRI

Aside from traditional approaches to address skin wounds that are part of the current practice of medicine for CRI discussed above, there are a number of emerging therapeutics under study that have shown promise in treating CRI/LRI. Some of these approaches have been described in detail above and in other chapters of this special issue (e.g., mesenchymal stromal cells derived from a variety of sources), so this section will focus on novel therapies that are at various stages of product development. These approaches range from nutraceuticals such as oral or topical curcumin [114, 141, 142] and drugs targeting the vasculature [143] to advanced wound care (Silverlon® dressings) and structural (KeraStat® cream) products. Detailed information about many of the approaches discussed here has been previously published [133].

Some drugs that have shown promise in other radiation injury models (e.g., hematopoietic or gastrointestinal ARS), have also been investigated for CRI/LRI. One such example is BP-C2 (Meabco A/S, Copenhagen, Denmark), a lignin-derived polymer with demonstrated effects in irradiated mice (29251085). More recently, BP-C2 has been studied in a protective/treatment mouse model as a CRI/LRI treatment in which animals were exposed to fractionated radiation prior to or after topical BP-C2 [144]. With BP-C2 treatment, skin dermatitis or ulcers were not observed in pre-treated animals, and post-irradiation treatment accelerated recovery. This product is being evaluated in a swine model, and wounds will be evaluated using 3-D imaging and scoring (personal communication[8]).

In addition to the approaches mentioned above, both BARDA and NIAID have supported contracts for other novel approaches to treat CRI/LRI. These have included investments in TP508 (Chrysalis Biotherapeutics), a thrombin peptide that targets the vasculature to provide mitigation of radiation injuries to the skin [143], Granexin gel, a product with an active ingredient consisting of the aCT1 peptide, which targets connexin 43 protein, downregulates inflammation, and is in late-stage human trials for a variety of indications (FirstString Research) [133], and Nor Leu 3-A(1–7) (US Biotest Inc.), an angiotensin analog that has shown promise in accelerating healing of severe radiation-induced lesions [122].

## 8. Conclusion

CRI/LRI is anticipated to occur following a large-scale, radiological or nuclear incident, although these complications are seen more commonly in small-scale incidents. Although much has been learned through the treatment of individuals exposed in industrial and medical accidents, there is still a lack of widespread understanding of the unique nature of these injuries. Great progress is being made in understanding the mechanisms underlying

[7]David Chen, OCICB, NIAID, NIH & Carmen Rios, RNCP, NIAID, NIH
[8]Sergei Pigarev, Meabco A/S, Denmark

this form of radiation damage, and in developing diagnostic and therapeutic modalities for management of skin and deeper tissue injuries.

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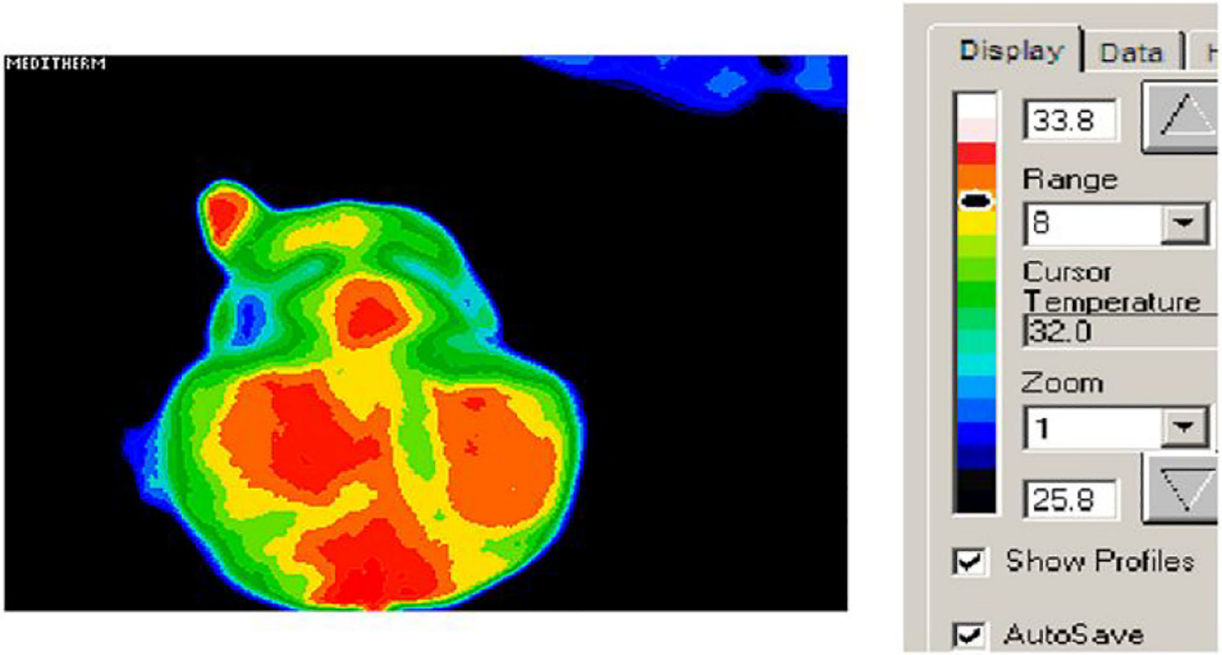



**Figure 1.**
Early transient erythema in a porcine model (15 Gy) at 15 minutes post-radiation exposure. The scale on the right shows the temperature scale. Red areas are hotter, blue and green areas cooler.

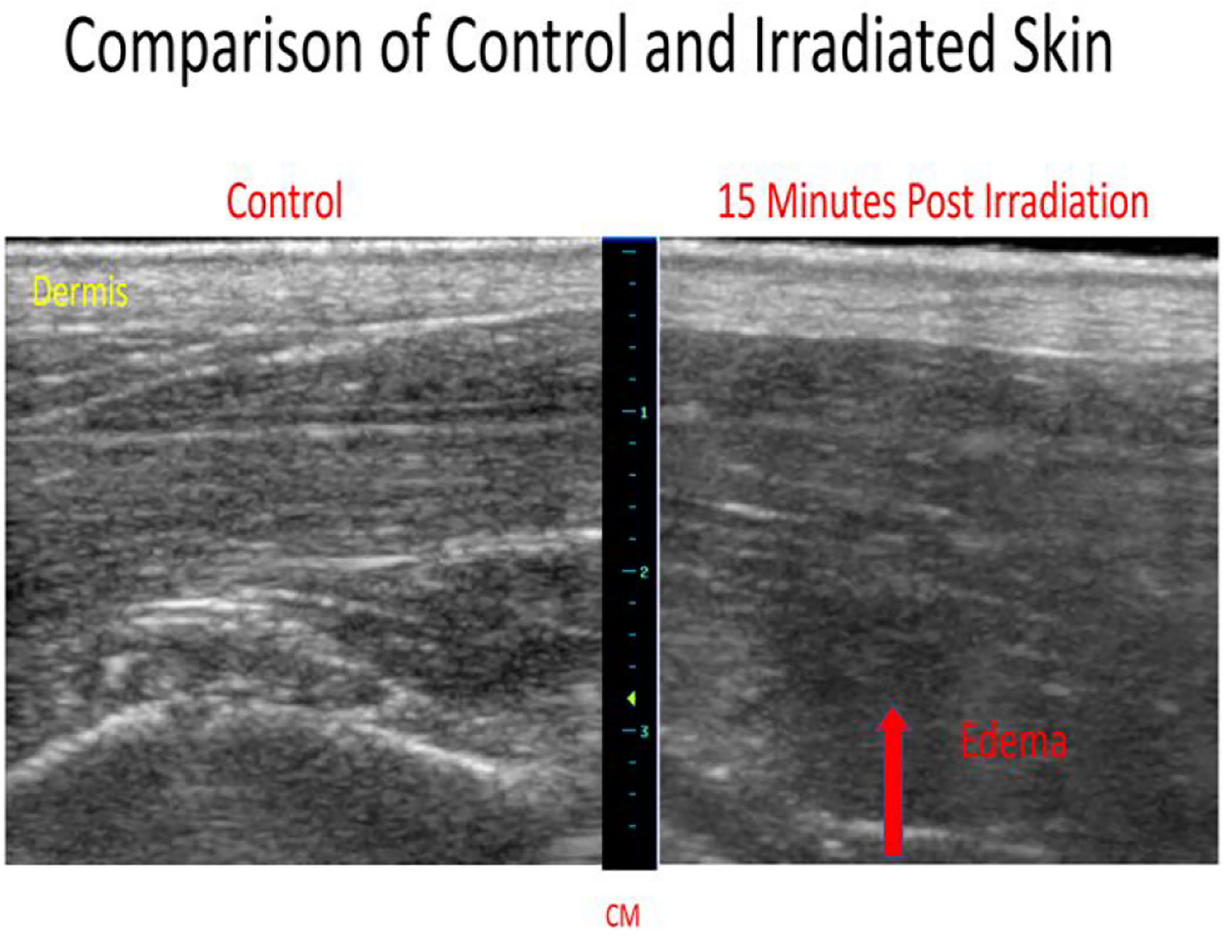



**Figure 2.**
Gray scale ultrasound image of control (L) and irradiated tissue (R).

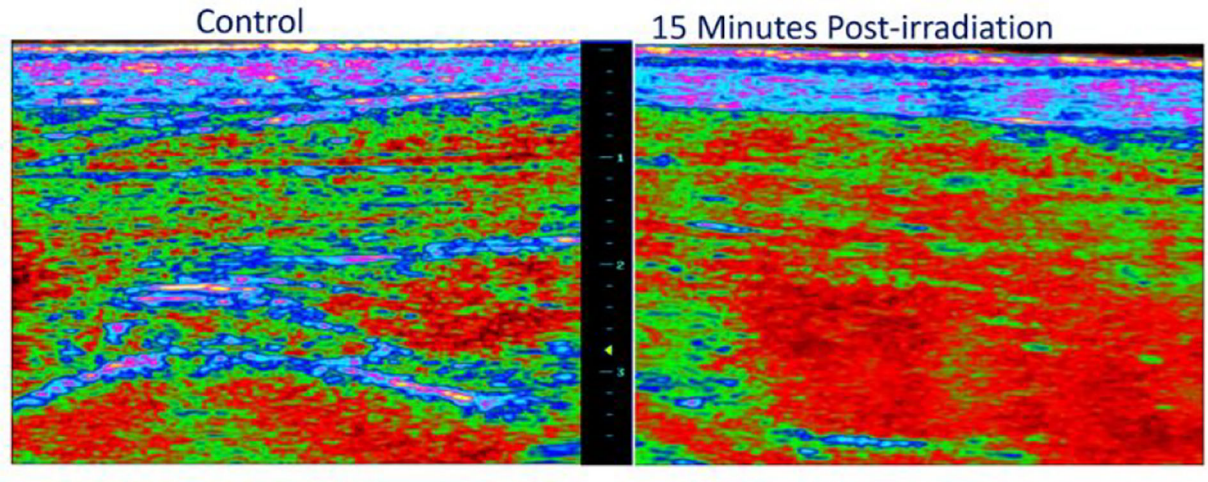



**Figure 3.**
Colorized version of Figure 2, illustrating edema fluid density in red.

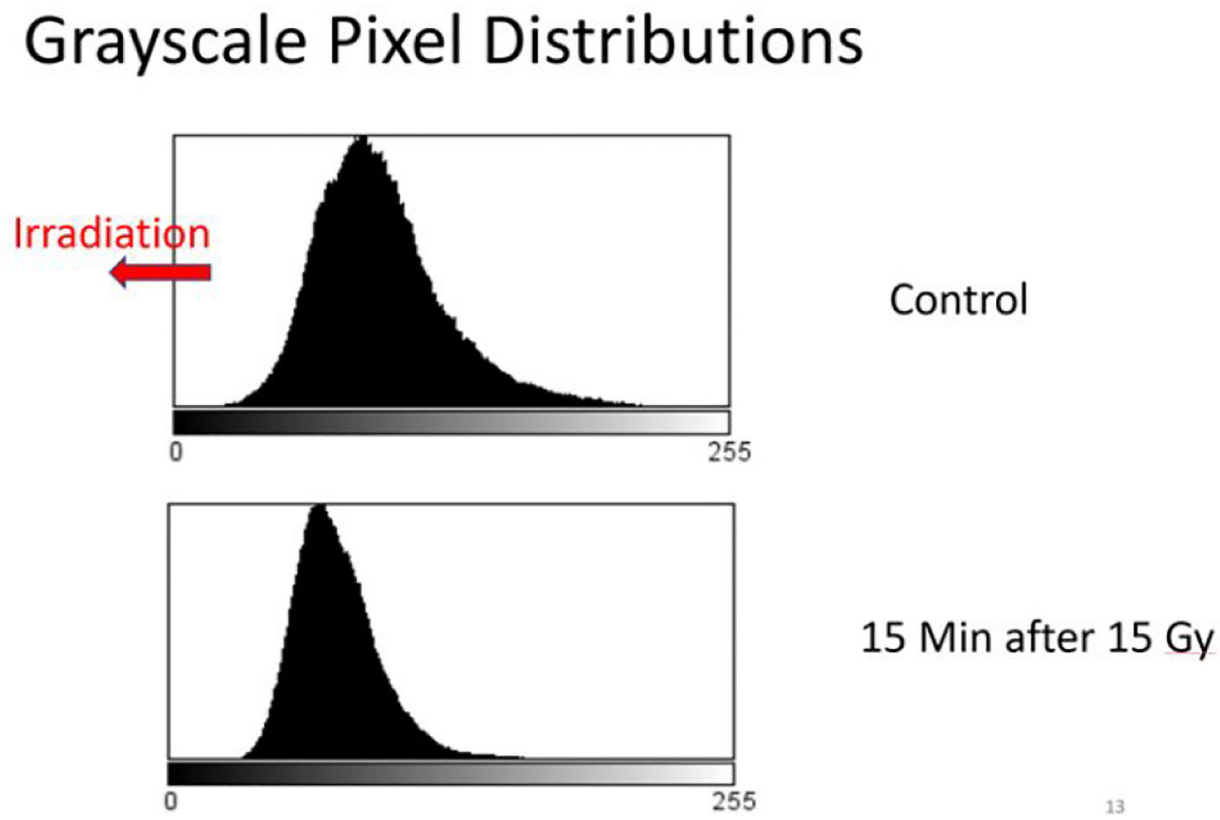



**Figure 4.**

Pixel distribution in control tissue and in tissue after irradiation. The distribution in irradiated tissue is narrower and with a lower mean value, due to edema fluid making the medium more uniform. This shifts the distribution to the left. The x-axis is the pixel number (256 pixel gray scale) and the y-axis is the number of pixels with each gray scale value.

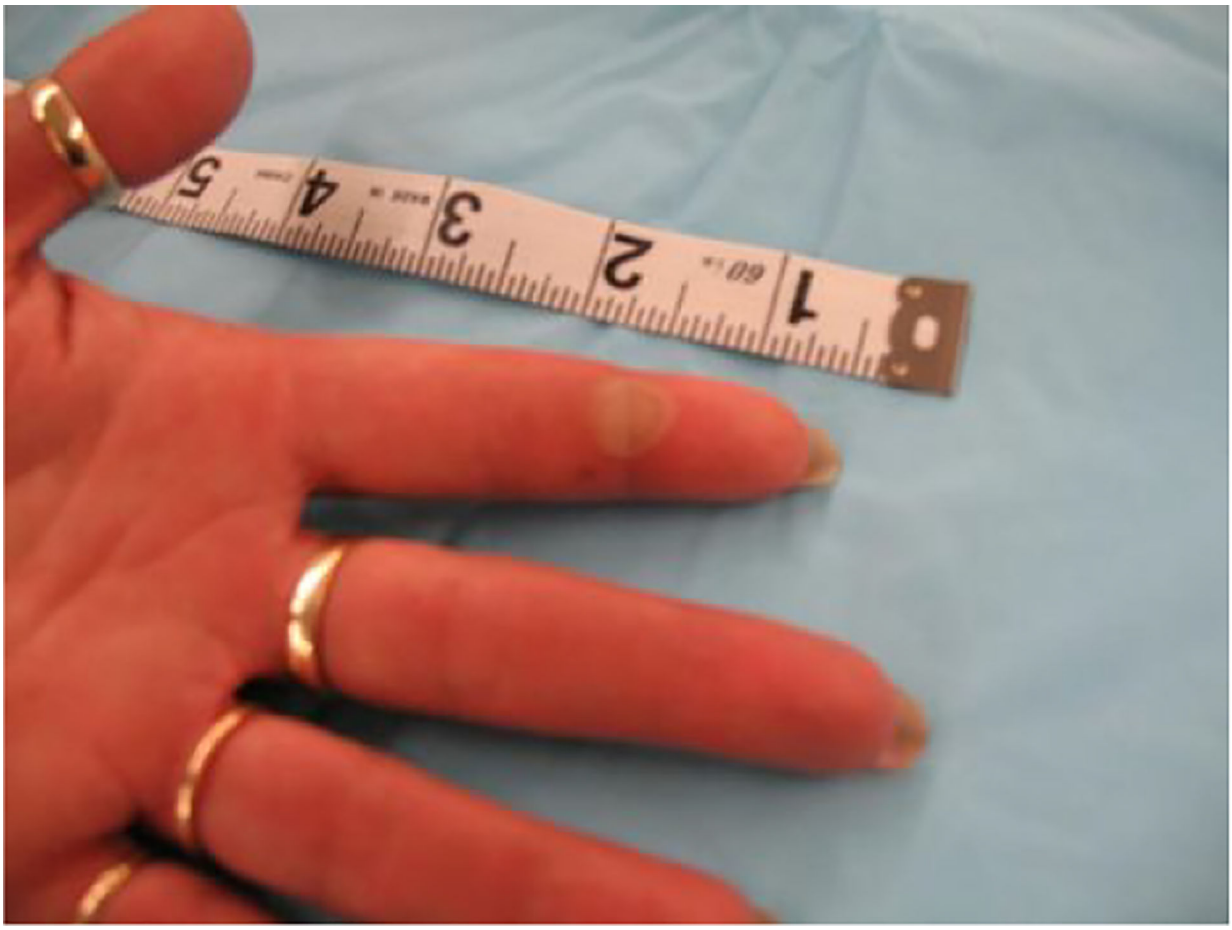



**Figure 5.**
Patient S on Day 27 after an accident with a 22-Ci Ir-192 source. Note blister on left index finger and generalized edema throughout the finger.

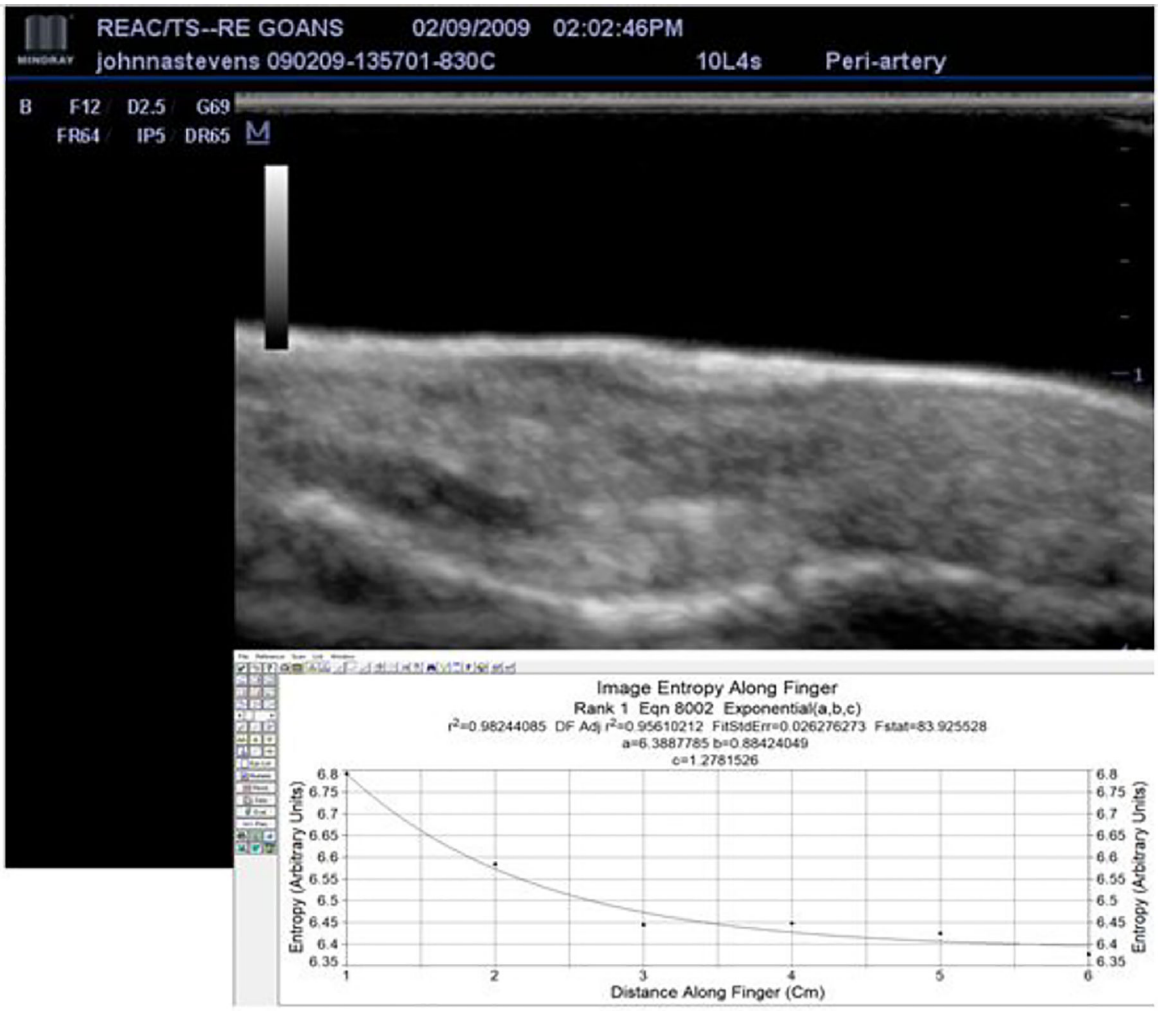
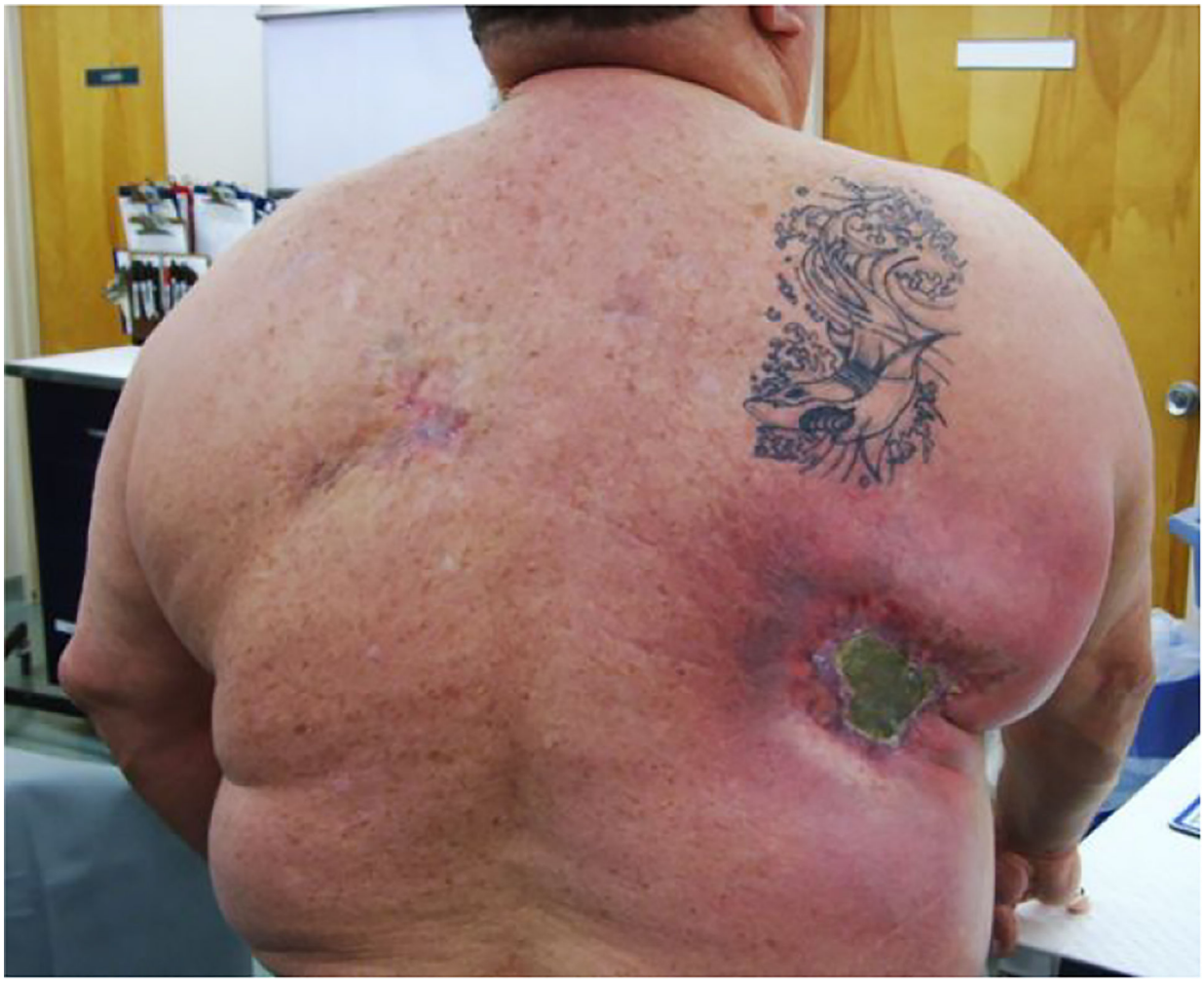



**Figure 6.**

A 12-MHz ultrasound view of the irradiated Patient S finger (proximal to distal, left to right). From the top, there is a black water density stand-off pad so that that the epidermis and dermis can be separated from the initial ultrasound pulse. From the stand-off pad downward, there is a thin epidermis, dermis, and then bone. Note the blister, necrotic base, and fluid density exudates in the substance of the bone. Inset: Graph of exponentially decreasing image entropy along the finger.



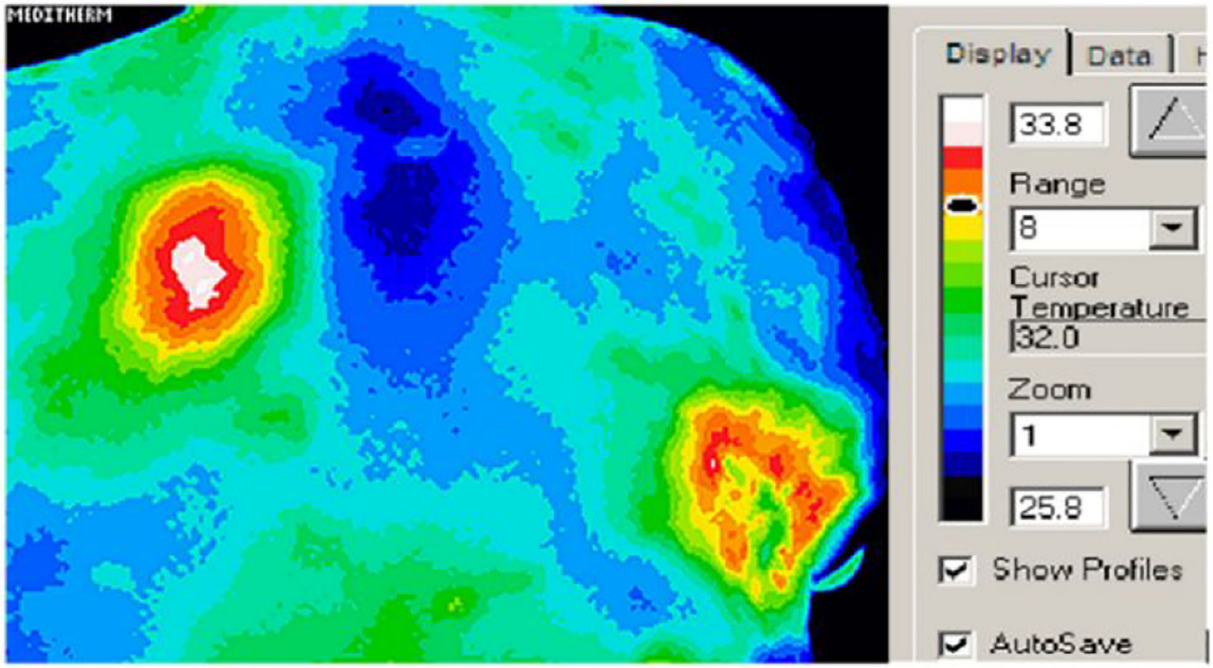



**Figure 7.**

(a) Fluoroscopically-induced necrotic lesions on patient D's back; (b) Thermography image of patient D. Red and white areas indicate increased temperature and perfusion; green and blue areas are indicative of decreased perfusion.

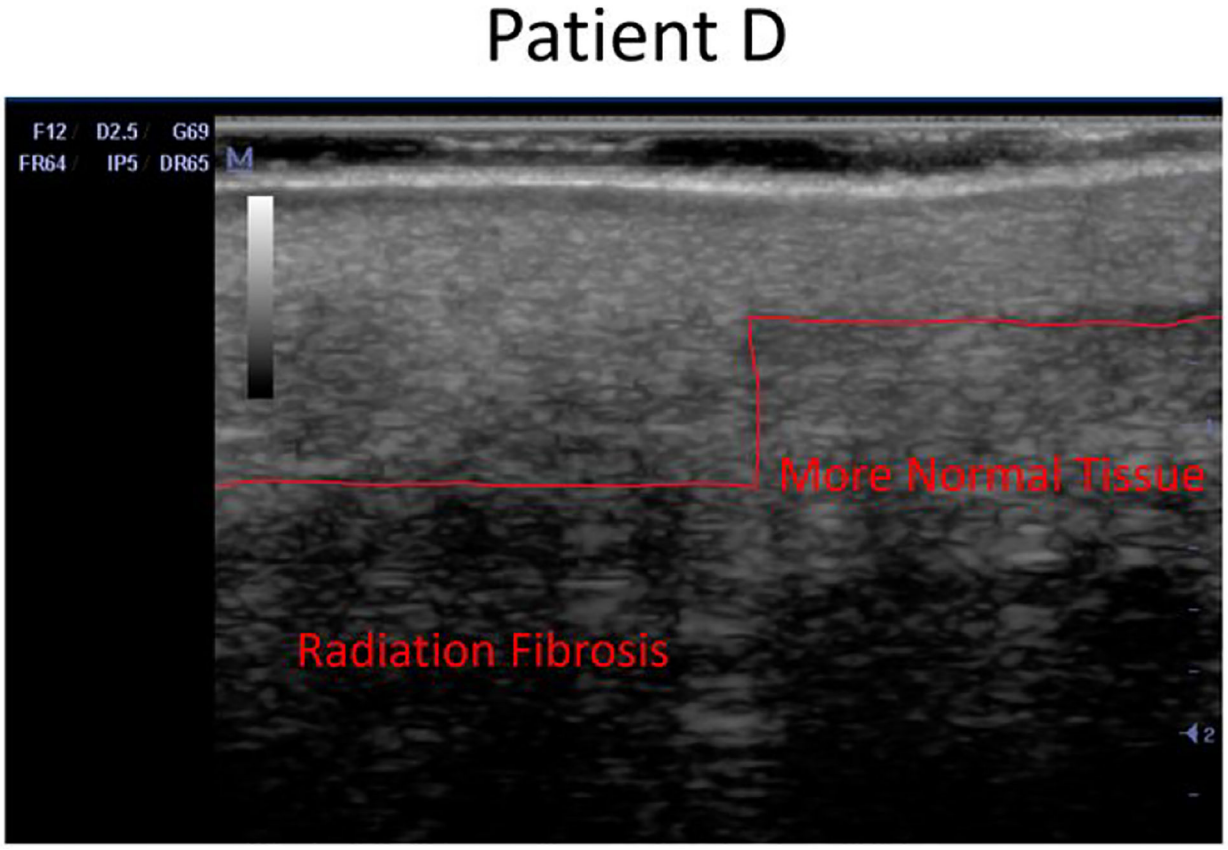



**Figure 8.**
Ultrasound image showing radiation fibrosis on patient D’s back.

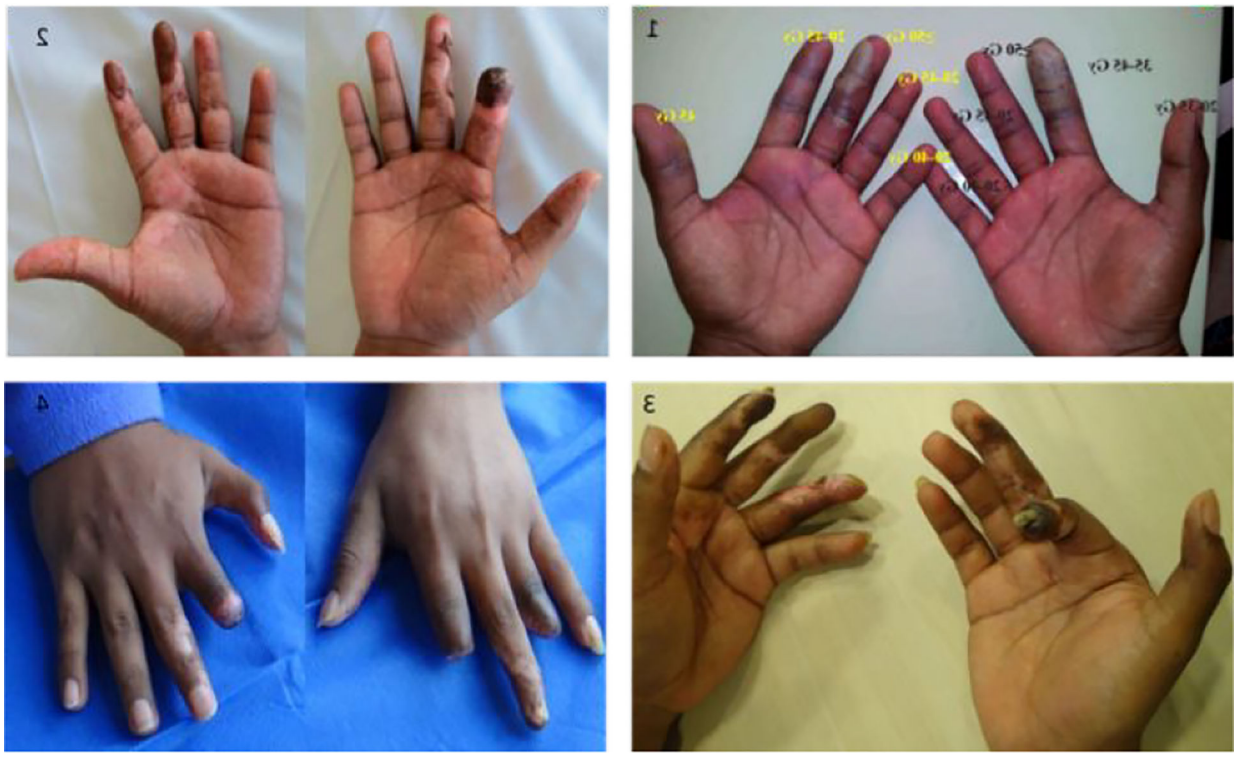


**Figure 9.**

The affected worker from a radiological accident in Chilca in 2012 [26]. Progression of an LRI in a worker exposed to an Ir-192 source, gamma emitter. Picture 1: Hands of the patient 10 days after exposure, absorbed doses assigned to each finger, estimated by EPR from fingernails. Picture 2: Day 124 after exposure, the patient returned home with no symptoms. Picture 3: Day 572 after exposure, the patient presented a recurrence of the LRI, starting a year after the accident. Picture 4: Day 604 after exposure, due to the severe LRI and joint ankylosis, administration of MSC and surgery were applied (Pictures courtesy of Percy–IRSN and IAEA).

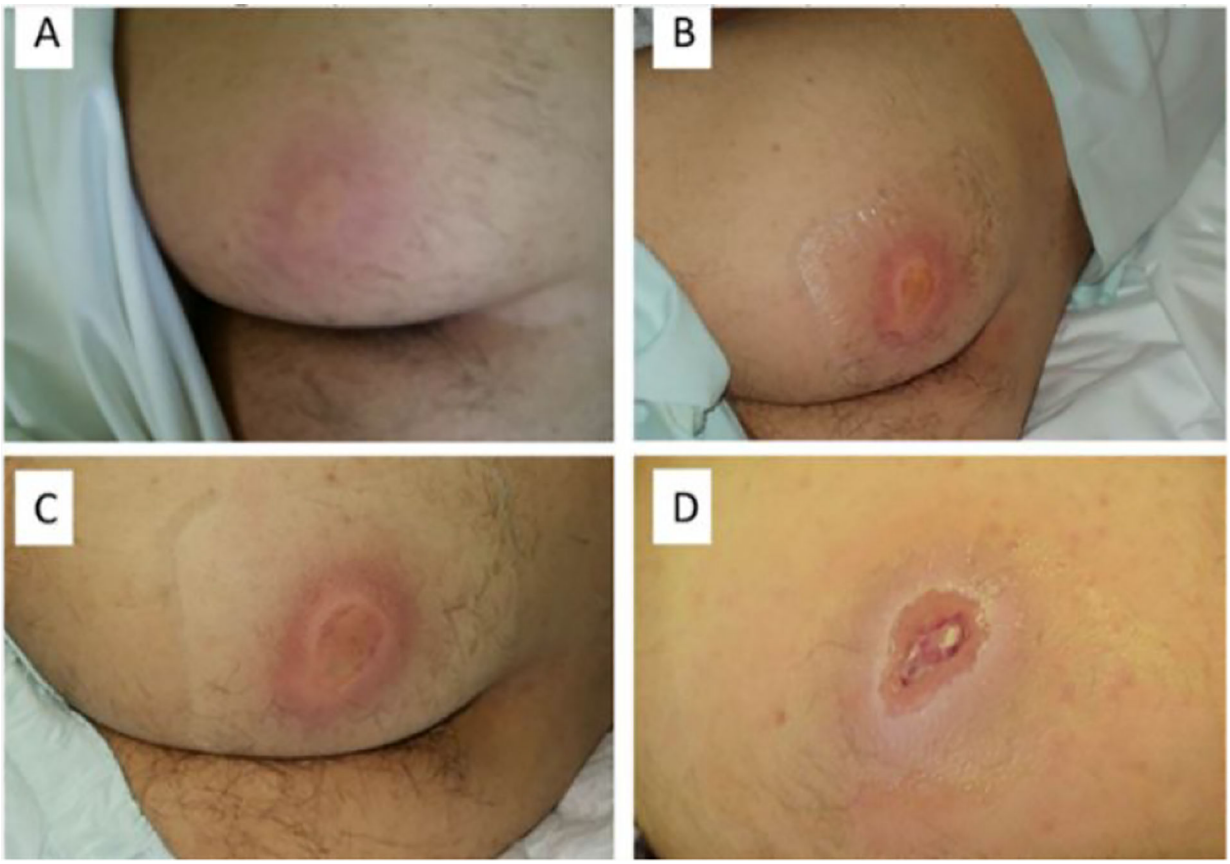



**Figure 10.**
Images of the local radiation injury in the left gluteus of the patient, and evolution of the lesion over ten days (Nueva Aldea Radiological Accident). (a) Image taken two days after exposure (16 December 2005). (b) Image taken five days after the exposure (19 December 2005). (c) Image taken six days after the exposure (20 December 2005). (d) Image taken 12 days after the exposure (26 December 2005) [97].

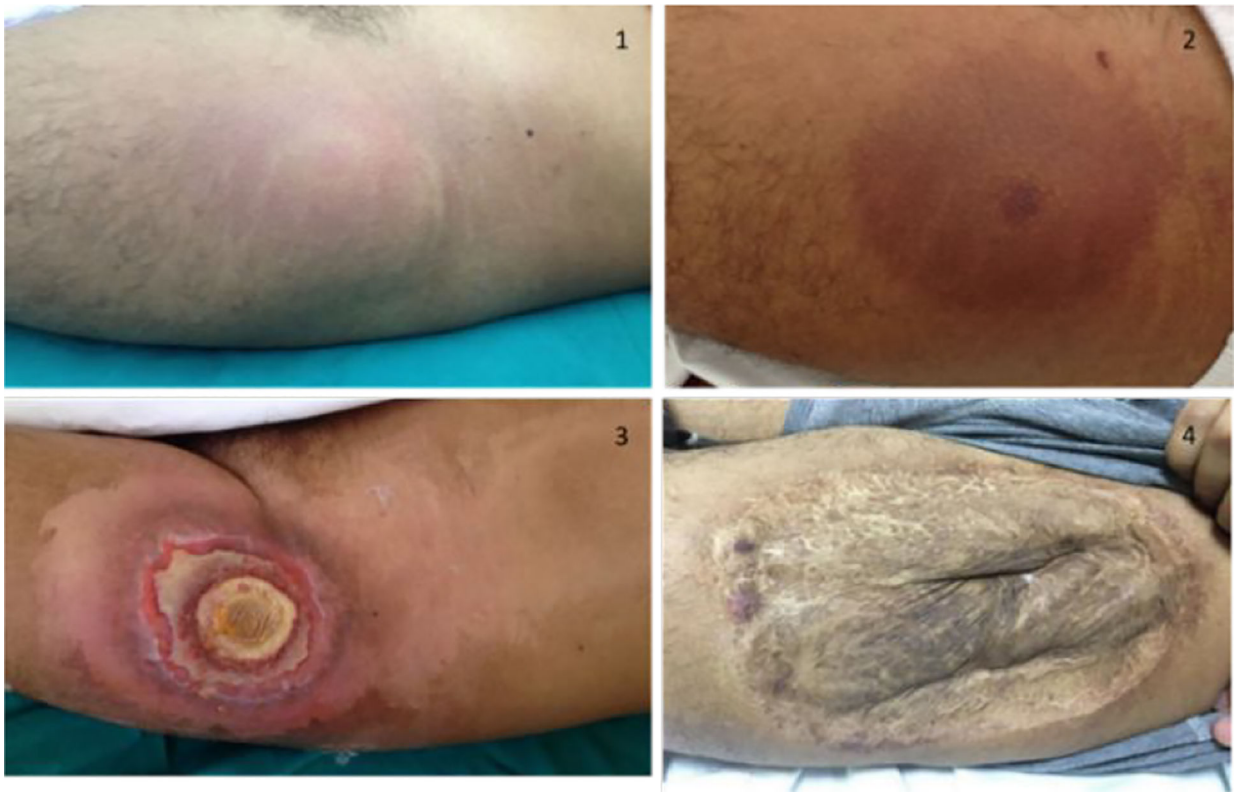



**Figure 11.**

An affected individual from a radiological accident in Ventanilla [102]. Progression of CRI/LRI in a worker exposed to an Ir-192 source (gamma emitter). Picture 1: Day 3 after exposure. Picture 2: Day 12 after exposure. Picture 3: Day 76 after exposure; Picture 4: Follow-up of the patient, day 1476 after exposure, after the dosimetry guided surgery (day 120 post exposure) and administration of MSC (Pictures courtesy of Dr. Alberto Lachos, Dr. German Mendoza and IAEA) [26].

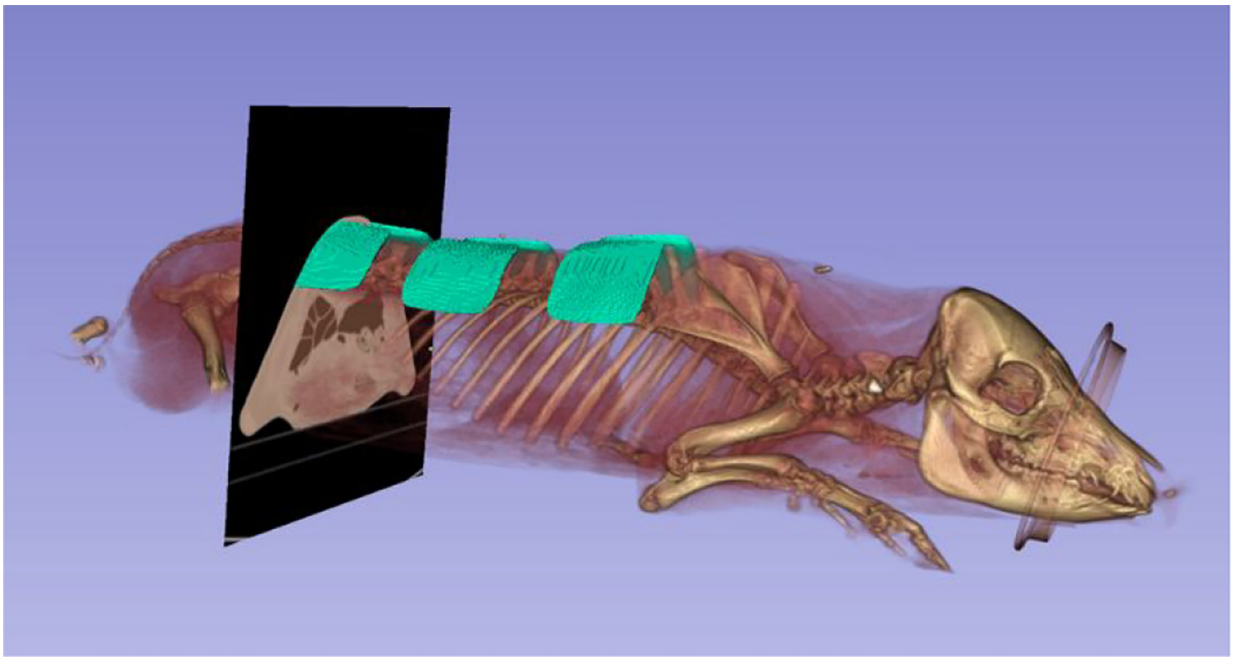


**Figure 12.**

3-Dimensional visualization of a porcine CRI model: Combining CT imaging with radiation dosimetry data in an immersive environment creates a visual representation of underlying tissue topology, allowing for more accurate analysis to refine current modeling systems.

**Table 1.**

Threshold doses for different manifestations of local radiation injuries [11].

| Skin Clinical Manifestation | Absorbed Dose Threshold |
|---|---|
| Second phase erythema | 3 Gy |
| Temporary epilation | 3 Gy |
| Definitive epilation | 7 Gy |
| Dry desquamation | 10 Gy |
| Moist desquamation | 15 Gy |
| Necrosis | ≥25 Gy (Skin) |