Management of Ionizing Radiation Injuries and Illnesses, Part 5: Local Radiation Injury

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This final article in the series on the medical management of ionizing radiation injuries and illnesses focuses on the effects of acute ionizing radiation exposure to one of the largest organ systems of the body—the skin. These injuries may extend beyond the skin into deeper tissues and cause local radiation injury. There are numerous causes of these injuries, ranging from industrial incidents to medical procedures. In the present article, the authors characterize the clinical course, pathophysiologic process, sources of injury, diagnosis, and management of local radiation injury and describe a clinical scenario. This information is important for primary care physicians, to whom patients are likely to initially present with such injuries.

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The skin is usually defined as the epidermis, dermis, and appendages (sebaceous, sweat, apocrine, mammary glands, and hair follicles).[1,2] Injury to the skin due to ionizing radiation (IR) can result in local radiation injury (LRI), which is not limited to the skin. Local radiation injury can be sustained from fluoroscopy, nuclear medicine, and computed tomography in disciplines such as radiology, nuclear medicine, interventional radiology, and interventional cardiology.[3] As noted by Shope,[4] the US Food and Drug Administration (FDA) first brought attention to fluoroscopy-induced cutaneous radiation injuries with the Safe Medical Devices Act of 1990. Since that time, much attention has been paid to LRI sustained from these injuries.[4] However, it is primary care physicians who order these tests and follow up with patients after testing and, therefore, primary care physicians should be a patient's primary source for information on the risks of medical imaging. All clinicians should be aware of the signs and symptoms of cutaneous and deeper-tissue injuries caused by IR. Many other sources of LRI exist, resulting in pain, disability, and death.[5] Industrial or commercial sources, medical sources, nuclear accidents, and, potentially, terrorist events can lead to cutaneous and deeper-tissue exposure to high doses of IR.

To increase physician awareness of LRI, we review the terminology, clinical presentation, sources of injury, and evaluation and management of LRI, and conclude with a clinical scenario to illustrate the major concepts. Although these are not common injuries, they are difficult to diagnose without a known history of IR exposure, and they are difficult to manage. Similar to chemical and thermal burns, the extent of dermatologic injury has been shown to be a strong prognosticator of patient survival.[6,7] However, these injuries have some significant caveats in management compared with chemical and thermal burns, which are discussed in the Management section.

Terminology

The terms used to describe IR injury to the skin and deeper tissues vary. Some authorities classify damage to the skin as a subsyndrome of acute radiation syndrome (ARS) and generally use the term *cutaneous radiation syndrome* (CRS) to refer to this injury. Cutaneous radiation syndrome is also used to describe the classic, clinical picture of IR injuries to skin without another organ system component of ARS.[6,8] *Local radiation injury* (LRI) is sometimes used to refer to injury to tissues or organs deeper than the skin,[9-12] and this term will be used henceforth in this article to describe IR injuries to the skin and deeper tissues. *Beta burns* refer to injury to the skin by beta particles and may cause a partial or even a full-thickness burn, depending on the beta energy of the radionuclide.[13] *Radiodermatitis* is often used to refer to radiotherapy-induced skin changes.[14]

Clinical Course

Acute LRI often occurs when an individual handles or comes into close contact with a high-dose rate, sealed radiation source. Many of these accidents are reported to the Radiation Emergency Assistance Center/Training Site (REAC/TS) and managed in consultation with patients' primary care physicians.

The 3 isotopes that cause the most concern for these injuries are ^{192}iridium, ^{60}cobalt, and ^{137}cesium. Local radiation injury is a deterministic effect, or an effect that varies with dose and for which a threshold is believed to exist.[15] The *Table* presents the clinical dose thresholds for LRI as used at REAC/TS. It is important to note that this information serves as a guideline and that there is some variation among sources for dose threshold and timing of appearance.[10,12,16]

Pathophysiology

A prodrome of erythema may occur transiently within a few hours of exposure and reappear weeks later as a manifestation of the injury. The mechanism causing erythema includes arteriolar constriction with capillary dilation and increased vascular permeability. Early erythema is highly variable, however, and may not occur at all, although the incidence increases with dose. With dry desquamation, there is diminished mitotic activity in the cells of the basal and parabasal layers, with thinning of the epidermis and desquamation of large macroscopic flakes of skin. Moist desquamation exhibits intracellular edema, coalescence of vesicles to form bullae, and a moist dermal surface. With doses greater than 25 Gy, overt radionecrosis may occur.

The classic presentation of LRI during the weeks to months after injury follows. Within the first week, the patient may present with a prodrome of transient erythema (which, as above, is highly variable), pruritis, and paresthesias of the skin. In subsequent weeks, true erythema develops along with progressive epilation, suppression of sweating, and diminished sebaceous gland secretion. As the injury evolves, the patient exhibits edema, pruritus, and blister formation, and he or she may have severe pain. There may be a spectrum of changes in

Table.
Clinical Dose Estimation for Local Radiation Injury

Radiation Dose, Gy	Clinical Sign	Exposure to Presentation, Time
3	Epilation (temporary)	14-17 d
6	Erythema	Minutes to weeks
10-15	Dry desquamation	2-3 wk
15-20	Moist desquamation	2-3 wk
>25	Deep ulceration/ radionecrosis	>21 d

Source: *The Medical Aspects of Radiation Incidents.* Oak Ridge, TN: The Radiation Emergency Assistance Center/Training Site; 2013:21-22. http://orise.orau.gov/files/reacts/medical-aspects-of-radiation-incidents.pdf. Accessed September 24, 2014.

pigmentation, ranging from redness to bronzing and blackening if necrosis develops. A higher dose leads to an earlier and more severe presentation.

Delayed effects of LRI, which may occur from months to years after injury, include telangiectasia formation, atrophy, and fibrosis. Telangiectasias occur as a result of damage to the microvasculature and subsequent distortion of capillary loops. Fibrosis, one of the most consistent delayed effects, may occur in tissues and vessels. Fibroblasts are the main producers of extracellular matrix, which is necessary for normal wound healing and scar formation. Local radiation injury causes the fibroblasts to become atypical and enlarged, often called *radiation fibroblasts*. These atypical and dysfunctional fibroblasts may be responsible for the delayed fibrosis.[17] This delayed and progressive fibrosis is 1 factor that makes LRI so different from chemical or thermal burns.[18]

The pathophysiology of LRI is still not fully understood and seems to be multifactoral. There is agreement that part of the reason LRI continues evolving is secondary to waves of various interrelated physiologic cascades.[12,19] Inflammation is a major component. Many mediators are involved with and feed back to prolong these processes. Damage to the microvasculature consists of damage to endothelial cells and subsequent activation of many proinflammatory and proclotting cascades. In addition, IR induces free radical species that may lead to oxidative stress.

It is important to recognize that patients may have a high dose of radiation to the skin with little to no dose to the whole body or to the bone marrow. As noted above, with deeper tissue injury, other organ systems may become involved in the area of injury and present different subsyndromes of ARS. There may be enough damage to deeper tissues over enough area or even a whole-body distribution to cause ARS. Therefore, a suspicion of ARS is warranted in any case of radiation exposure, even if only LRI is initially evident. Ionizing radiation injury to more than 50% of the body surface area is a poor prognosticator for survival.[6] Multiorgan failure and death may result.[5,18]

Sources of Injury

Many LRI incidents occur in industrial settings. In the United States, most of these cases are known to be IR-related early in their course. However, given that the injury may not manifest until weeks later, patients may delay seeking care. Internationally, a number of "orphaned" sources have been handled by persons who did not know the devices were radioactive. These injuries are often misdiagnosed. For further reading on many of these cases, full reports can be downloaded from the International Atomic Energy Agency at http://www-pub.iaea.org/mtcd/publications/.

The nuclear power plant accident at Chernobyl in 1986 is a well-known incident in which many of the victims had severe CRS caused by a mixture of beta particles and gamma-emitting radionuclides. Sixteen of the 28 acute deaths after the incident were attributed to CRS.[5]

Another source of LRI that has attracted much attention over the past 20 years is radiologic imaging techniques that deliver a large dose of IR. The average radiation dose received by patients in the United States has roughly doubled over the past 20 years, and the increase is primarily attributed to medical exposure (radiography, fluoroscopy, computed tomography, nuclear medicine, and external beam radiotherapy).[20,21]

Physician and patient education along with safety features on newer equipment have helped reduce the dose of radiation exposure. In the past, a lack of education resulted in patients not knowing that they were being exposed to radiation during their procedures or understanding the risk associated with exposure. A latent LRI presentation may not have been attributed to the procedure by patient or physician.[4,22-25] Educational efforts among physicians are improving and are including many different disciplines.[21,26] Discussing with patients the nature of a radiologic procedure, the radiation dose involved, and the risks and benefits of the procedure is necessary, especially if the procedure is potentially lifesaving. Radiotherapy-induced LRI should be suspected if the wound has a grid-like pattern (*Figure*), if there are 2 locations of injury that correspond to the angles used in

the procedure, or if the wound resembles a burn without a history of thermal or chemical burn.

Diagnosis and Evaluation

The diagnosis of LRI depends on a detailed recent history and a complete physical examination. Physicians should collect incident histories, including what the patients were doing at the time of injury and for how long; whether they touched the source and if so with which fingers/hands; whether they held the source to their face to examine it closely (eye exposure); whether anyone else handled it or was exposed; whether the source was intact (some radiotherapy sources may be broken open); and whether they put it in a clothing pocket. Obviously, these questions will vary depending on the incident. A health or medical physicist should be enlisted to fully elucidate the details of an incident to estimate the dose. The health physicist may also recreate the incident to assist in dose estimation. For the physician, it is important to ask patients about their symptoms and the timeline of the onset, severity, and disappearance of symptoms. These symptoms may include erythema, hair loss, peeling, blistering, itching, tingling, burning, and pain.

Because ARS should be considered in any case of radiation exposure, blood chemistry should be analyzed as appropriate. Baseline and serial complete blood cell (CBC) counts with differentials should be obtained (ideally, every 8 hours) to assess for a decline in absolute lymphocyte count during the first 12 to 48 hours after LRI.[27,28] If it is determined that the patient has a severe local injury that could result in ARS, CBC counts with differentials will be needed to monitor for bone marrow suppression.[9,27,28] Other laboratory tests to consider include serum amylase (for head or neck exposure) and C-reactive protein (CRP), because CRP will be elevated in cases of significant partial body or total body irradiation. More information about the laboratory evaluation of ARS can be found in Christensen et al.[29]

Imaging studies should be performed as indicated and to detect the degree of tissue and microvascular damage. Magnetic resonance imaging and magnetic resonance angiography are helpful in determining the extent of tissue damage. There has been much research and some historical use of ultrasound with Doppler and thermography to evaluate the extent of tissue damage, but these modalities are not in widespread use for the evaluation of LRI.[30-32] Some additional studies to determine the margin of damage to the microvasculature include laser Doppler, blood perfusion imaging, radioisotope clearance, transcutaneous oxygen pressure, spectrophotometry, and photoplethysomography.[33-40]

Electron spin or electron paramagnetic resonance (EPR) may be a helpful tool for dose estimation in conjunction with other methods of dose estimation (eg, incident recreation and cytogenetic biodosimetry).[41-43] Electron paramagnetic resonance, which measures the radiation-induced free radical formation, can be performed on tissue, bone, teeth or tooth enamel, nails, and textiles. This specialized test is still considered primarily a research tool; it is not widely or commercially available. In the United States, EPR for radiation dose assessment is currently used in research activities at the National Institute of Standards and Technology, the US Naval Dosimetry Center, and the EPR Center for the Study of Viable Systems at the Geisel School of Medicine at Dartmouth.[41,42,44] The *Institut de Radioprotection et de Surete Nucleaire* (the French Institute for Radiological Protection and Nuclear Safety) and other institutions around the world are also actively performing research in EPR dosimetry.[41,42] An important clinical consideration for using this biodosimetry tool is that all tissue (from debridement, amputation, etc) must be preserved for study, as it may provide important dose information.

One of the best tools for evaluating LRI is serial, digital color photography. This format is ideal for electronic submission of photographs to subject matter experts for consultation and evaluation. These wounds do evolve over time, and keeping a photographic timeline captures the progression. As with any medical condition that changes with time, it is advantageous to show disease course, treatment response, and treatment progression or

regression. Many dermatologists use photo-mapping for skin surveillance of atypical nevi and in microscopically controlled surgery.[45]

Management

Most treatment regimens for patients with LRI have been derived from radiation oncology, traditional burn care, and past experiences with acute LRI. Acute LRI may differ dramatically from radiotherapy-induced injuries, because radiotherapy-induced skin injuries are the result of fractionated doses, not acute doses. Fractionation of a radiation dose allows for some tissue healing and repair to occur between treatments. Many of the incidents of accidental LRI are delivered much more rapidly or at high doses with little or no fractionation.

Local radiation injury is managed similarly to thermal burns—with a few important caveats. One is that LRI needs to be protected from temperature extremes and trauma from the moment of injury indefinitely, even after apparent healing. These injuries are prone to reactivation with even the mildest of trauma for years after the initial injury. As soon as the injury is known to be IR-induced, the patient needs to be counseled about ways to protect the area, including work restrictions. In the case of an occupational LRI, patient and employer need to understand the health risks involved. Like thermal burns, IR wounds are very painful. The difference is that the pain may continue, perhaps for years, until successful wound healing has occurred. Often, wound healing is achieved with skin grafting or amputation. Another caveat is the damage to the microvasculature, which may be too extensive for the skin grafting techniques used in burn surgery. There must be a well-vascularized flap for these wounds to heal.[41]

Inflammation plays a large role in LRI, and methods to reduce inflammation are beneficial. There is consensus for topical steroidal treatment; class II and III topical steroids have been used historically.[8,47,48] Some radiation oncologists have had success with intralesional steroids (A.L. Wiley, personal communication, September 2013). The World Health Organization consultancy was strongly against use of systemic steroids in the absence of a specific indication.[8] Nonsteroidal anti-inflammatory drugs may also be indicated, but their use for LRI has not been addressed by the World Health Organization consultancy. Further, they should only be used if no contraindication is present (eg, gastrointestinal ulcer or bleeding, thrombocytopenia, coagulopathy, or aspirin allergy).

Recommendations have been fairly consistent on the use of topical antibiotics for LRI.[9] The use of systemic antibiotics should be based on the clinical picture. Physicians should consider consulting with infectious disease specialists if there is suspicion of a high dose to deep tissues, a large percentage of affected body surface area, or another organ system is involved. The use of silver sulfadiazine and dressings may be helpful, as indicated. "Skin substitutes" and other dressing constructs should be used as indicated for thermal burns.

Combination treatment with 400 mg of pentoxifylline (not FDA-approved for this use) 3 times per day and α-tocopherol (a form of vitamin E) has shown success in decreasing radiofibrosis.[49-51] Pentoxifylline alone may also help to decrease pulmonary damage due to lung and breast radiotherapy.[52] Other antioxidants or antioxidant enzymes such as superoxide dismutase have been used to manage these injuries and are still areas with active research for further development.[53-55] Topical aloe vera seems to shorten healing time, has anti-inflammatory and antihistaminic properties, and is an excellent moisturizer.[56] Aloe vera is often recommended to patients undergoing radiotherapy; however, the literature about its efficacy is mixed.[57,58]

Reports have provided evidence that mast cells may play a role in LRI. Mast cells store 98% of our body's histamine.[59] They become activated and degranulate, releasing histamine and many other proinflammatory mediators. Historically, antihistamines have been used for symptomatic relief of pruritus and erythema.[8,59-62] Some animal studies support a treatment role for these medications.[62-64] Nonsedating antihistamines (fexofenadine or loratadine) have worked well in REAC/TS' experience.

Another treatment modality that may be helpful is hyperbaric oxygen therapy. This modality has been effective for delayed radiotherapy injuries, particularly osteoradionecrosis.[65] Hyperbaric oxygen therapy may result in improved quality of life, as exhibited in gynecologic oncology patients with delayed manifestation of radiotherapy-induced injuries, such as tissue necrosis and osteoradionecrosis.[66] The benefits of hyperbaric oxygen may include vasculoneogenesis, increased oxygenation of the tissues, and, possibly, increased production of various growth factors.[65]

Traditional surgical management of LRI may be indicated, but surgeons must be aware that the margin of injury and nonviable tissue will not be grossly visible or evident. Imaging modalities or radiation dose mapping should be used to delineate the margin of the damage to the microvasculature or margin for necrosis before surgical intervention. If the microvasculature and infrastructure are adequate, and the dose is below the threshold for necrosis, successful skin-grafting may be achieved. Consultation with experts in radiation-induced injuries should be done before definitive surgical therapy.

A newer treatment approach that shows promise is mesenchymal stem cell therapy or adipose-derived stem cells. Japanese investigators,[67] using adipose-derived stem cells injected into the wound and surgical debridement, showed good wound healing in a gynecologic oncology patient with late tissue and bone necrosis. French investigators[10] successfully used bone marrow mesenchymal stem cell wound injections, with and without skin grafting, in a small series of patients. They used dose mapping techniques to determine the margins for excision of all of the necrotic or potentially necrotic tissue and then injected the area with the mesenchymal stem cells.[10] Both aforementioned investigation teams are engaged in ongoing clinical trials of these methods, with continued success. Appropriate controlled studies need to be performed with long-term follow-up before these techniques can be recommended unequivocally. However, such results may be difficult to achieve with the relatively low incidence rate of LRI.

Clinical Scenario

A 62-year-old man had chest pain while traveling alone overseas. His medical history included diabetes, coronary artery disease, and 2 previous percutaneous coronary interventions, with 1 stent placed each time. In addition, he had a 40 pack-per-year history of tobacco abuse and was obese (height, 5'9"; weight, 240 lb). He was rushed into the interventional cardiology suite of a large metropolitan hospital and, after several hours, a successful percutaneous coronary intervention was accomplished. The patient returned home from his travels without further incident. Twelve days later, he experienced itching in his back, but it stopped. Twenty-five days after his return home, he began to have more itching, burning, and pain in his back. His primary care physician noted some erythema and desquamation on his left, lower scapular area and his right subscapular area (laterally) but was more concerned with establishing follow-up with his cardiologist. A month after the follow-up, his physician noted some blister formation in the left, lower scapular area and the right, subscapular area (laterally) (*Figure*). His primary care physician requested a consultation with a dermatologist, who tried conservative topical treatment without success. The dermatologist performed a punch biopsy, and the specimen showed morphea consistent with sclerosis or radiation injury. At that point, the primary care physician consulted REAC/TS. The patient was evaluated and started on a treatment protocol similar to the management recommendations outlined in the Management section in the current article. He received more than the standard recommended hyperbaric oxygen therapy (100 treatments). His wound care continued for 4 years, and then he underwent wide local excision of the nonhealing area of the lesion, with aggressive postoperative wound care (months of wound vacuum dressings, dressing changes, etc). He also had successful excision and skin grafting of the lesion on the left. One year after his surgical procedures and aggressive wound care, his wounds healed completely.

Discussion

Local radiation injury has a classic presentation with a somewhat predictable course. Presenting signs include transient erythema, itching, and edema, resulting in a nonhealing wound, possibly with a grid-like pattern, that may progress to necrosis. The additional presence of nausea, emesis, and diarrhea should put the physician on alert that such a patient may have ARS. Furthermore, immunologic compromise may result in a complex and potentially life-threatening situation that requires intensive therapy. Many cases of occupational LRI involve the hands. While not necessarily life-threatening, LRI can cause significant disability and psychosocial problems. On-the-job LRI is further complicated by the unapproved, "experimental" therapies that may be required in these cases but are not covered by worker's compensation insurance carriers. Mesenchymal stem cell wound injections are not approved by the FDA.

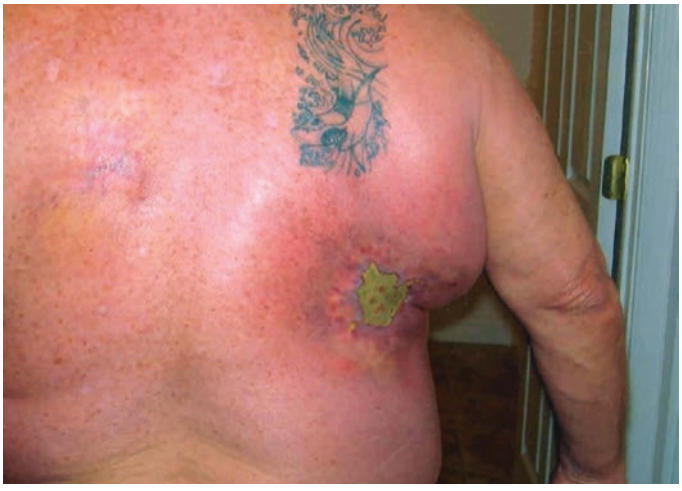

Figure.
Blister formation in the left lower scapular and right subscapular regions of a patient who underwent percutaneous coronary intervention a month earlier. The grid-like pattern is associated with ionizing radiation injury.

Conclusion

Although uncommon, LRI is difficult to diagnose without a known history of radiation exposure. These injuries often have a delayed presentation that may make the history and dose estimation difficult to impossible. They may initially present as minor but evolve into a critical stage and are often associated with a high degree of disability and morbidity. An evolving wound resembling a burn in the absence of a history of thermal or chemical exposure should alert physicians to the possibility of LRI. As with most complex medical cases, specialty consultation should be obtained when dealing with IR-induced injuries of all types. Specialties that may be helpful include radiation oncology, nuclear medicine/radiology, hematologic oncology, surgical oncology, dermatology, burn surgery, and infectious diseases. Other resources available for assistance are REAC/TS (emergency number, 865-576-1005; http://orise.orau.gov/reacts/), the Armed Forces Radiobiology Research Institute (301-295-0530; http://www.usuhs.mil/afrri/), the Radiation Treatment Injury Network (http://ritn.net), and public radiologic health departments.

References

1. MacKie RM. *Clinical Dermatology (Oxford Core Texts)*. 5th ed. New York, NY: Oxford University Press; 2003:19.
2. Marks JG Jr, Miller JJ. *Lookingbill and Marks' Principles of Dermatology*. 5th ed. Philadelphia, PA: Saunders; 2013:2.
3. Koenig TR, Mettler FA, Wagner LK. Skin injuries from fluoroscopically guided procedures: part 2, review of 73 cases and recommendations for minimizing dose delivered to patient. *AJR Am J Roentgenol*. 2001;177(1):3-20.
4. Shope TB. Radiation-induced skin injuries from fluoroscopy. *Radiographics*. 1996;16(5):1195-1199.
5. Gottlober P, Steinert M, Weiss M, et al. The outcome of local radiation injuries: 14 years of follow-up after the Chernobyl accident. *Radiat Res*. 2001;155(3):409-416.
6. Meineke V, van Bueningen D, Sohns T, Fliedner TM. Medical management principles for radiation accidents [review]. *Mil Med*. 2003;168(3):219-222.
7. Fliedner TM, Dörr HD, Meineke V. Multi-organ involvement as a pathogenetic principle of the radiation syndromes: a study involving 110 case histories documented in SEARCH and classified as the bases of haematopoietic indicators of effect. *BJR Suppl*. 2005;27:1-8.

8. Dainiak N, Gent RN, Carr Z, et al. Literature review and global consensus on management of acute radiation syndrome affecting nonhematopoietic organ systems. *Disaster Med Public Health Prep*. 2011;5(3):183-201. doi:10.1001/dmp.2011.73.

9. Oak Ridge Institute for Science and Education website. Guidance for Radiation Accident Management. Managing radiation emergencies: guidance for hospital medical management. http://www.orise.orau.gov/reacts/guide/syndrome.htm. Accessed July 8, 2014.

10. Benderitter M, Gourmelon P, Bey E, et al. New emerging concepts in the medical management of local radiation injury. *Health Phys*. 2010;98(6):851-857. doi:10.1097/HP.0b013e3181c9f79a.

11. Radiation Emergency Assistance Center/Training Site. *The Medical Aspects of Radiation Incidents*. Oak Ridge, Tennessee: Oak Ridge Institute for Science and Education; 2011. http://orise.orau.gov/files/reacts/medical-aspects-of-radiation-incidents.pdf. Accessed July 8, 2014.

12. Muller K, Meineke V. Advances in the management of localized radiation injuries. *Health Phys*. 2010;98(6):843-850. doi:10.1097/HP.0b013e3181adcba7.

13. Ansari A. *Radiation Threats and Your Safety: A Guide to Preparation and Response for Professionals and Community*. Boca Raton, FL: Chapman & Hall/CRC; 2009.

14. Dini D, Macchia R, Gozza A, et al. Management of acute radiodermatitis: pharmacological or nonpharmacological remedies? *Cancer Nurs*. 1993;16(5):366-370.

15. Radiation terms and definitions. Health Physics Society website. http://hps.org/publicinformation/radterms/. Accessed July 8, 2014.

16. National Council on Radiation Protection & Measurements. *NCRP Report No. 161, Management of Persons Contaminated With Radionuclides*. Bethesda, MD: NRCP; 2008:131.

17. Fajardo LF, Berthrong M, Anderson RE. *Radiation Pathology*. New York: Oxford University Press Inc; 2001:159.

18. Peter RU. Cutaneous radiation syndrome in multi-organ failure. *BJR Suppl*. 2005;27:180-184.

19. Benderitter M, Gourmelon P, Bey E, et al. New emerging concepts in the medical management of local radiation injury. *Health Phys*. 2010;98(6):851-857. doi:10.1097/HP.0b013e3181c9f79a.

20. National Council on Radiation Protection & Measurments. *NCRP Report No.160, Ionizing Radiation Exposure of the Population of the United States, National Council on Radiation Protection and Measurements*. Bethesda, MD: NCRP; 2009:4-5.

21. Balter S, Miller DL. Patient skin reactions from interventional fluoroscopy procedures [review]. *AJR Am J Roentgenol*. 2014;202(4):335-342. doi:10.2214/AJR.13.12029.

22. Frazier TH, Richardson JB, Fabre VC, Callen JP. Fluoroscopy-induced chronic radiation skin injury: a disease perhaps often overlooked. *Arch Dermatol*. 2007;143(5):637-640.

23. Otterburn D, Losken A. Iatrogenic fluoroscopy injury to the skin. *Ann Plast Surg*. 2010;65(5):462-465. doi:10.1097/SAP.0b013e3181d6e2d3.

24. Valentin J. Avoidance of radiation injuries from medical interventional procedures [review]. *Ann ICRP*. 2000;30(2):7-67.

25. Henry MF, Maender JL, Shen Y, et al. Fluoroscopy-induced chronic radiation dermatitis: a report of three cases. *Dermatol Online J*. 2009;15(1):3.

26. Boncher J, Bergfeld WF. Fluoroscopy-induced chronic radiation dermatitis: a report of two additional cases and a brief review of the literature. *J Cutan Pathol*. 2012;39(1):63-67. doi:10.1111/j.1600-0560.2011.01754.x.

27. Goans RE, Holloway EC, Berger ME, Ricks RC. Early dose assessment following severe radiation accidents. *Health Phys*. 1997;72(4):513-518.

28. Goans RE, Holloway EC, Berger ME, Ricks RC. Early dose assessment in criticality accidents. *Health Phys*. 2001;81(4):446-449.

29. Christensen DM, Iddins CJ, Parrillo SJ, Glassman ES, Goans RE. Management of ionizing radiation injuries and illnesses, part 4: acute radiation syndrome. *J Am Osteopath Assoc*. 2014;114(9):702-711. doi:10.7556/jaoa.2014.138.

30. Goans RE, Iddins CJ, Christensen DM. Ultrasound and thermography for diagnosis of extent and magnitude of acute local radiation injury (LRI). *Proceedings of the 5th International REAC/TS Symposium: The Medical Basis for Radiation Accident Preparedness and the Biodosimetry Workshop*. Oak Ridge, TN: Oak Ridge Associated Universities; 2013.

31. Jammet H, Gongora R, Jockey P, Zucker JM. The 1978 Algerian accident: acute local exposures of two children. In: Hubner KF, Fry SA. *The Medical Basis for Radiation Accident Preparedness*. Amsterdam, The Netherlands: Elsevier; 1980:229-245.

32. Goans RE, Goans RH, Goans RE Jr, Christensen DM. Ultrasonic analysis of acute thermal and radiation injury—a pilot study. *Radiat Meas*. 2007;42(6-7):1261-1264.

33. Allen J. Photoplethysmography and its application in clinical physiological measurement. *Physiol Meas*. 2007;28:R1-R39.

34. Swain ID, Grant LJ. Methods of measuring skin blood flow [review]. *Phys Med Biol*. 1989;34(2):151-175.

35. Schultz-Ehrenburg U, Blazek V. Value of quantitative photoplethysmography for functional vascular diagnostics: current status and prospects. *Skin Pharmacol Appl Skin Physiol*. 2001;14(5):316-323.

36. Malvezzi L, Castronuovo JJ Jr, Swayne LC, Cone D, Trivino JZ. The correlation between three methods of skin perfusion pressure measurement: radionuclide washout, laser Doppler flow, and photoplethysmography. *J Vasc Surg*. 1992;15(5):823-829.

37. Almond NE, Cooke ED. Observations on the photoplethysmograph pulse derived from a laser Doppler flowmeter. *Clin Phys Physiol Meas*. 1989;10(2):137-145.

38. Huelsbusch M, Blazek V. Contactless mapping of rhythmical phenomena in tissue perfusion using PPGI. In: Clough AV, Chen CT. *Medical Imaging 2002: Physiology and Function From Multidimensional Images*. Society of Photo Optical; 2002. doi:10.1117/12.463573. *Proceedings of Spie*; vol 4683.

39. Brumen V, Horvat D, Bonic I. Evaluation of serial application of capillaroscopy, photoplethysmography, and dermatothermometry in diagnosis and prevention of radiolesions of peripheral microvessles. *Microvasc Res*. 1994;47(2):270-278.

(continued)

40. Levitskaia TG, Bryan SA, Creim JA, et al. Optical spectroscopy and multivariate analysis for biodosimetry and monitoring of radiation injury to the skin. *Drug Develop Res*. 2012;73:252-273. doi:10.1002/ddr.21021.

41. Romanyukha A, Mitchell CA, Schauer DA, Romanyukha L, Swartz HM. Q-band EPR biodosimetry in tooth enamel microsamples: feasibility test and comparison with x-band. *Health Phys*. 2007;93(6):631-635.

42. Wieser A, Debuyst R, Fattibene P, et al. The 3rd international intercomparison on EPR tooth dosimetry: part 1, general analysis. *Appl Radiat Isot*. 2005;62(2):163-171.

43. Romanyukha A, Trompier F. Electron paramagnetic resonance retrospective dosimetry. *AIP Conf Proc*. 2011;1345(1):120-128.

44. Desrosiers M, Schauer DA. Electron paramagnetic resonance biodosimetry. *Nucl Instrum Methods Phys Res B*. 2001;184:219-228.

45. Koranda FC, Heffron ET, Modert CW, Perkins LL. Photo-mapping for microscopically controlled surgery. *J Dermatol Surg Oncol*. 1982;8(6):463-465.

46. Nenot JC. Medical and surgical management for localized radiation injuries [review]. *Int J Radiat Biol*. 1990;57(4):783-795.

47. Flynn DF, Goans RE. Nuclear terrorism: triage and medical management of radiation and combined-injury casualties. *Surg Clin N Am*. 2006;86(3):601-636.

48. Berger ME, Christensen DM, Lowry PC, Jones OW, Wiley AL. Medical management of radiation injuries: current approaches. *Occup Med (Lond)*. 2006;56(3):162-172.

49. Delanian S, Porcher R, Balla-Mekias S, Lefaix J. Randomized, placebo-controlled trial of combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis. *J Clin Oncol*. 2003;21(13):2545-2550.

50. Delanian S, Porcher R, Rudant J, Lefaix JL. Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis. *J Clin Oncol*. 2005;23(34):8570-8579.

51. Magnusson M, Hoglund P, Johansson K, et al. Pentoxifylline and vitamin E treatment for prevention of radiation-induced side-effects in women with breast cancer: a phase two, double-blind, placebo-controlled randomised clinical trial (Ptx-5). *Eur J Cancer*. 2009;45(14):2488-2495. doi:10.1016/j.ejca.2009.05.015.

52. Ozturk B, Egehan I, Atavci S, Kitapci M. Pentoxifylline in prevention of radiation-induced lung toxicity in patients with breast and lung cancer: a double-blind randomized trial. *Int Rad Onc Biol Phys*. 2004;58(1):213-219.

53. Campana F, Zervoudis S, Perdereau B, et al. Topical superoxide dismutase reduces post-irradiation breast cancer fibrosis. *J Cell Mol Med*. 2004;8;(1):109-116.

54. Delanian S, Baillet F, Huart J, Lefaix JL, Maulard C, Housset M. Successful treatment of radiation-induced fibrosis using liposomal Cu/Zn superoxide dismutase: clinical trial. *Radiother Oncol*. 1994;32(1):12-20.

55. Esco R, Valencia J, Coronel P, Carceller JA, Gimeno M, Bascón N. Efficacy of orgotein in prevention of late side effects of pelvic irradiation: a randomized study. *Int J Radiat Oncol Biol Phys*. 2004;60:(4):1211-1219.

56. Maenthaisong R, Chaiyakunapruk N, Niruntraporn S, Kongkaew C. The efficacy of aloe vera used for burn wound healing: a systematic review. *Burns*. 2007;33(6):713-718.

57. Richardson J, Smith JE, McIntyre M, Thomas R, Pilkington K. Aloe vera for preventing radiation-induced skin reactions: a systematic literature review. *Clin Oncol (R Coll Radiol)*. 2005;17(6):478-484.

58. Ahmadi A. Potential prevention: aloe vera mouthwash may reduce radiation-induced oral mucositis in head and neck cancer patients. *Chin J Integr Med*. 2012;18(8):635-640. doi:10.1007/s11655-012-1183-y.

59. Donlon MA. Role of mast cell mediators in radiation injury and protection. *Pharmacol Ther*. 1988;39(1-3):373-377.

60. Denham JW, Hauer-Jensen M. The radiotherapeutic injury—a complex 'wound.' *Radiother Oncol*. 2002;63(2):129-145.

61. Albrecht M, Muller K, Kohn FM, Meineke V, Mayerhofer A. Ionizing radiation induces degranulation of human mast cells and release of tryptase. *Int J Radiat Biol*. 2007;83(8):535-541.

62. Moriyasu S, Yamamoto K, Kureyama N, Okamura K, Ikeda T, Yamatodani A. Involvement of histamine released from mast cells in acute radiation dermatitis in mice. *J Pharmacol Sci*. 2007;104(2):187-190.

63. Doyle TF, Turns JE, Strike TA. Effect of antihistamine on early transient incapacitation of monkeys subjected to 4000 rads of mixed gamma-neutron radiation. *Aerosp Med*. 1971;42(4):400-403.

64. Alter WA, Hawkins RN, Catravas GN, Doyle T, Takenaga JK. Possible role of histamine in radiation-induced hypotension in the Rhesus monkey. *Radiat Res*. 1983;94:654.

65. Feldmeier JJ, Packard MW. Delayed radiation injuries (soft tissue and bony necrosis). In: Gesel LB, ed. *Hyaperbaric Oxygen Therapy Indications*. 12th ed. Durham, NC: Undersea and Hyperbaric Medical Society; 2008.

66. Craighead P, Shea-Budgell MA, Nation J, et al. Hyperbaric oxygen therapy for late radiation tissue injury in gynecologic malignancies. *Curr Oncol*. 2011;18(5):220-227.

67. Akita S, Akino K, Hirano A, Ohtsuru A, Yamashita S. Noncultured autologous adipose-derived stem cells therapy for chronic radiation injury. *Stem Cells Int*. 2010;532704. doi:10.4061/2010/532704.