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Management of Radiation-induced Tissue Injuries: A Review of Current Treatment Strategies

Richard Simman, MD, FACS, FACCWS*†
Karen Bach, BS†
Fuad Abbas, BS‡
Kara Klomparens, BS‡
Bradley Joseph Brickman, BS†

Background: Although radiation therapy remains an integral component in cancer treatment, the sequela of tissue damage can result in long-term morbidity and mortality for patients. This article aimed to perform a comprehensive review of the current literature for both nonsurgical and surgical management strategies for radiation-induced injuries.

Methods: A literature search was performed on PubMed to review the current described management and treatment options for radiation-induced injuries. Patient demographics, medical diagnoses, complications, strategies of management care, and outcomes were reviewed.

Results: The most commonly described management options and reconstructive techniques of radiation wounds were analyzed and reported.

Conclusions: Consideration of current techniques and outcomes in the management of radiation-induced wounds demonstrates that impaired wound healing remains a major problem. This literature review provides a detailed overview of the most frequently used therapies with recommendations for surgeons. *(Plast Reconstr Surg Glob Open 2023; 11:e5043; doi: 10.1097/GOX.0000000000005043; Published online 16 June 2023.)*

INTRODUCTION

Radiation therapy remains a mainstay modality in cancer treatment, and it is estimated that 50% of all diagnosed cancer patients receive radiation as part of their treatment regimen.[1] Despite its efficacy in reducing and eradicating many types of cancer, radiation to overlying and surrounding tissue often leads to several clinical complications, including skin and subcutaneous impaired healing, soft tissue fibrosis, tendon and muscle damage, and osteoradionecrosis.[2] Effects of radiation therapy can present acutely, generally during the first 1–3 months, as radiation dermatitis (RD) involving erythema, dry or wet desquamation, or pigmentation changes, or chronically over a period of months to years as poor wound healing, fibrosis, or secondary malignancies.[3–6]

*From the *Department of Surgery, Jobst Vascular Institute, ProMedica Health Network, Toledo, Ohio; †Department of Surgery, University of Toledo College of Medicine, Toledo, Ohio; ‡Department of Surgery, Wayne State School of Medicine, Detroit, Mich.*

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Wound complication rates following radiation therapy have been reported in up to 67% of cases. Many patients will ultimately be referred to a plastic and reconstructive surgeon for management.[7] The purpose of this article is to review the current literature regarding various nonoperative and operative management of radiation-induced injuries.

METHODS

Literature Search

A literature review of works published between 1960 and 2022 was conducted in the PubMed database using search terms including "radiotherapy," "wound healing," and "management." After removal of duplicate entries, titles of articles and abstracts were reviewed for other relevant articles. References from each article were also reviewed for additional articles. Inclusion criteria included systematic reviews, meta-analyses, prospective studies, retrospective reviews, case series, case reports, clinical trials, and basic science papers. Exclusion criteria involved articles that were nonhuman studies and non-English publications.

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RESULTS

A total of 27 full-text articles of potentially relevant studies were identified and deemed to meet our inclusion criteria. The following is a comprehensive but not exhaustive report of all reported treatment modalities and options in the current literature. (**See table, Supplemental Digital Content 1**, which shows an overview of articles meeting inclusion criteria. Various treatment modalities for radiation wounds are detailed. Patient study demographics and outcomes are also reported, **http://links.lww.com/PRSGO/C597**.) Medical management starts with prevention through patient education about skin care and hygiene before, during, and after their radiation treatment. Subsequently, prompt recognition and intervention of any following radiation injuries can improve patients' quality of life and alleviate morbidity and mortality.

Takeaways

Question: What are the effects of radiation therapy damage and the management strategies available to optimize outcomes for patients?

Findings: A search of the current literature demonstrates that multiple conservative nonoperative and surgical modalities are available for the management of radiation-induced tissue injury.

Meaning: Radiation-induced injuries remain a major problem for many patients after therapy, and given the numerous available treatment options, the most appropriate management plan considers patient factors with the surgeon's expertise and resource availability.

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBOT) is an effective primary and adjunctive treatment for a wide spectrum of conditions. There are 14 approved use indications, including radiation injury.[8] HBOT utilizes high concentrations of oxygen at pressures greater than sea level to deliver more oxygen to areas of ischemia, such as that of chronic wounds from radiation treatment, to promote angiogenesis, reduce fibrosis, and recruit stem cells.[9] Removal of devascularized tissue before starting HBOT is key, as plasma oxygen levels do not penetrate dead tissues.

Although HBOT is one of the most studied and reported therapies for irradiated tissue damage, there is a lack of randomized control trials in the current literature. Regardless, numerous case studies, animal studies, and other published reports showed a positive trend for improved healing with HBOT.[10] Future investigations are needed to establish formal guidelines, but given that patients may benefit from this adjunctive therapy, they should be referred to an HBOT specialist for further consultation.

Herbal Treatments

Many herbal remedies, including calendula, catechins, aloe vera, chamomile, and beta-sitosterol, have been used for treatment of radiation-induced wounds, namely RD.[11] However, the efficacy of these compounds is highly debated. A recent meta-analysis of 16 randomized controlled trials found that no herbal treatments to date are effective in the treatment of RD, including the very commonly used aloe vera.[12]

While these treatments may not cure RD, they have been effective in alleviating some symptoms when used prophylactically. For example, use of epigallocatechin-3-gallate, a topical catechin, on breast cancer patients before chest wall radiation significantly decreased symptoms like burning, itching, and tenderness.[13] Beta-sitosterol, specifically Mebo, is another compound with promising results in clinical trials to decrease pain and pruritus in radiotherapy patients when used prophylactically.[14]

Topical Pharmaceuticals and Dressings

Topical pharmacological preparations, including ascorbic acid, pantothenic acid, triethanolamine cream, and corticosteroids, have been proposed for the prevention and/or treatment of radiation-induced injuries.[11] The benefit of ascorbic acid use stems from its properties as a powerful antioxidant but a review of antioxidant use concluded that there was no strong to support its use.[15]

Pantothenic acid promotes epithelial formation and regeneration, and it can be used topically at small concentrations.[16,17] It has a protective effect against irritation and pruritus of the skin; however, its efficacy in the treatment of radiation-induced injuries has not yet been fully elucidated. Pantothenic acid is one of the ingredients in Aquaphor cream along with mineral oil and ceresin. While it is frequently used as a moisturizer, this cream has been implemented in the protection of radiation wounds.

Triethanolamine, or trolamine, is an ingredient commonly used in skincare products, mainly as a way to stabilize the compound. It was previously investigated for the management of scars, with minimal convincing evidence.[18] A meta-analysis of trolamine trials found that although it is well tolerated and liked by patients, it fails to show significant efficacy in the prevention or treatment of RD.[19]

Silver is well known for its antimicrobial properties. Although some articles argue that silver sulfadiazine should be used prophylactically in the management of radiation injury, others recommend its use only in the presence of suspected infection.[20] Silver clear nylon dressings have been proposed for use in this setting; however, review of evidence has shown mixed results. Despite some studies demonstrating efficacy with prophylactic use of silver clear nylon dressings, others have inconsequential or even negative results with its use.[21]

Hydroactive colloid gels are composed of both hydrocolloids and hydrogels. This combination promotes healing through providing moisture via the hydrogel, and absorption of exudates to maintain hydration via the hydrocolloid. Hydroactive colloid gels have been shown to be superior in the treatment and prevention of RD when compared to pantothenic acid creams.[16,17]

Semipermeable silicone-based dressings have been recommended for the prevention of radiation-induced skin injury, including the feared radiation complication of wet desquamation. These dressings have very low inert toxicity and the ability to conform to the shape of wound beds while adhering to healthy tissue but avoiding wound

tissue.[21] A review found that silicone dressings increased patient comfort between radiation treatments and decreased local tissue trauma, thereby minimizing pain.[22]

As the basis of radiation injury is believed to lie in the chronic activation of inflammatory pathways, it is logical to presume that corticosteroids would be effective in the management of this condition. A meta-analysis of randomized controlled trials concerning topical steroids for RD found that this treatment is associated with decreased rates of wet desquamation.[23] Additionally, prophylactic topical corticosteroid treatment has been shown to decrease patient-perceived pain and pruritus.[24] The aforementioned review of current recommended guidelines also included only positive evidence toward the use of topical corticosteroids. As such, its use appears to be one of the only universally accepted methods of treatment for radiation skin injuries.[20]

Despite the frequent use of compounds and dressings, there is no clearly defined standard of treatment or recommended guidelines to support one therapy over the other.[25] Nonetheless, providers should be aware of the various options and cater treatment to their patients' specific needs.

Biologic Preparations and Agents

Various growth factors have also been investigated for efficacy in the treatment of radiation-induced wounds. At the cellular level, basic fibroblast growth factor and transforming growth factor beta have been shown to decrease after being exposed to radiation, thereby reducing the tissues' ability to heal.[26] It has been posited that adding these depleted growth factors to the tissue would then be able to mitigate this deficit. Growth factors, such as epidermal growth factor, platelet-derived growth factor, and granulocyte macrophage colony-stimulating factor, are commonly used. The use of platelet-derived growth factor dates back to at least the 1980s, as it promotes healing by stimulating granulation tissue formation and recruiting macrophages at the wound site.[27,28] In the treatment of osteoradionecrosis, clinicians have found great results in the use of plasma rich in growth factors when combined with surgical resection.[29] Additionally, authors have found a clinical benefit with the use of recombinant human epidermal growth factor for the treatment of RD in patients with anorectal cancer[30] and head and neck cancer[31] based on small-scale studies. Larger randomized clinical trials are necessary to confirm the benefits of recombinant human epidermal growth factor.

Collagenases have also been investigated in the treatment of nonhealing wounds. Case reports have shown high rates of reduction of the wound area when treated with Santyl collagenase ointment.[32] Collagenases efficacy lies in enzymatic debridement of necrotic tissue, making it ideal for highly fibrous wounds.

Surgical Interventions

When conservative therapies fail, surgical reconstruction of the radiation-affected areas serve as the next best option. Surgical reconstruction of radiation injuries follows the core principles of the reconstructive ladder—that is, selection of closure technique relies on the wound's own complexity and requirement. The simplest technique, such as direct reapproximation of wound edges, should be attempted before advancing to a more aggressive option.

Before any surgical intervention, workup and evaluation of the previously irradiated area should include a biopsy to rule out any recurrent malignancies. Tissue that has been treated with radiation has a high possibility of developing subsequent malignancies.[33,34] After ruling out recurrent tumors, surgeons may proceed with radical excision of any nonviable tissue. Skin grafts may be considered for reconstruction depending on the patients' preferences and situational circumstances, like availability of donor site. However, the present literature demonstrates that reconstruction of radiation-damaged tissues with skin grafts has a failure of almost 100% as the prior irradiated wound bed lacks sufficient nutrients, vessels, and oxygen to allow for graft uptake.[35] Thus, some authors advocate that at a minimum, flaps are required to treat radiation wounds.[36,37]

Early debridement paired with immediate flap reconstruction has lower wound complication rates compared to delayed flap reconstruction.[38,39] Axial musculocutaneous flaps, microvascular free flap transfer, and perforator flaps are examples of flap options that have all been recommended due to their availability to cover large and well-vascularized tissues.[36] For radiation injury that involves deeper structures, like bone, the use of single or double free flaps is widely used.[40–42] Considerations during surgery should include discerning the extent of disease on bone and resecting this affected bone and surrounding tissue as well as removing bone that no longer has adequate vascular supply. A recent case series highlighted the potential use of a double free flap reconstruction with a vascularized free fibula graft protected by a fascia-sparing vertical rectus abdominis musculocutaneous flap.[42] Their series of four patients showed successful results and concluded that this may be an optimal approach to free flaps in radiation bone injuries, but will require further research to confirm. In general, the choice of flap depends on the extent and location of the injury, as well as general health and condition of the patient.

DISCUSSION

Wound Healing and Pathophysiology of Radiation Damage

Normal acute wound healing takes place across four stages: hemostasis, inflammation, proliferation, and remodeling or maturation.[2] These stages and their biophysiological functions must occur in the normal timely sequence in order to prevent chronic wound formation. There are several factors that can disrupt this process, including infection, chronic inflammation, and vascular insufficiency.

Radiation therapy uses an external beam to deliver high-energy photons to the site of malignancy. The ionization of electrons breaks DNA strands of cancerous

cells to prevent replication and division. Although effective at halting malignant growths, radiation also generates reactive oxygen species and free radicals during this process, resulting in a persistent proinflammatory state with upregulation of certain cytokines, such as TNF-alpha, IFN-gamma, IL-1, and IL-6, and down regulation of other mediators and growth factors, including nitric oxide, vascular endothelial growth factors, basic fibroblast growth factor, and transforming growth factor beta 1.[43–45] Other concurrent disruptions in the wound healing process include cellular depletion as ionizing radiation targets cells in the G2 and M phases,[46] extracellular matrix alteration with increases in matrix metalloproteinases[47] and abnormal collagen synthesis,[48] and microvascular changes from decreased angiogenesis and increased fibrosis of vessels.[49,50] Over time, the cumulative effects of the progressive microvascular obliteration and fibrosis result in hypoxia that impairs wound healing.

Level of Injury

Skin and Subcutaneous Tissue Injury

The most common site of radiation injury is the skin and underlying soft tissue, with nearly 85%–95% of cancer patients having developed some degree of skin damage following therapy.[11] The consequences of radiation can lead to acute side effects, such as erythema, dry or wet desquamation, pigmentation changes, and hair loss. If these effects persist, it can lead to chronic complications, like unhealed ulcers, vascular fibrosis, or secondary skin malignancies.

Tendon and Muscle Injury

Radiation fibrosis syndrome is a common complication of radiation therapy that can affect any tissue type, including muscles, ligaments, and tendons. When muscles or tendons are involved, it can cause weakness, muscle spasms, tendon contractions, and loss of elasticity and mobility.[51,52] Early prevention, such as with physical therapy during radiation treatment, can help to mitigate subsequent morbidity.[51]

Bone Injury

Radiation injury to bone, commonly termed osteoradionecrosis, usually presents with pain, bleeding, and a malodorous exposed bone. This most likely occurs in patients with cancers of the head and neck, as the poorly vascularized bone in this area is susceptible to hypoxia and necrosis.[53] Treatment can either be conservative, with saline irrigation and antibiotics, or surgical, with resection and/or reconstruction.

Limitations

This literature review was mainly limited by the large scope of the primary research question. As there are no well-defined treatment guidelines for radiation-induced injuries, selecting the best modality may be difficult given the vast array of options. While an exhaustive list of these modalities was not feasible to create, the most utilized and recent recommendations were included to assist physicians in their care of this patient population.

The other main limitation encountered during this project was wide discrepancies in research design. Investigations of radiation-induced injuries in the literature encompassed everything from case reports to randomized clinical trials with varying methodology and outcome measures. This made a meta-analysis for comparison of treatments difficult.

Furthermore, larger-based research needs to be conducted to evaluate various treatment modalities with specific measurable outcomes and controlled groups. Several other systematic reviews and meta-analyses surrounding this topic have encountered the aforementioned limitations as well and have also concluded that there is a lack of randomized controlled trials on these treatments.[54–58] In this way, we can move toward a defined standard of treatment and prevention for radiation-induced injuries.

CONCLUSIONS

Radiation-induced injuries can have debilitating consequences on patients' morbidity and mortality. Clinical complications of radiation range from superficial skin and subcutaneous wounds to deeper injury to the bone. Our study is not without limitations given the broad scope of management options. However, as the sequelae of complex wound healing continue to pose a challenge to many plastic surgeons, we highlight the current nonsurgical and surgical practices for radiation-induced injury. Ultimately, the best option for reconstruction will depend on the patient's presentation and preferences, surgeon's expertise, and resource availability.

Richard Simman, MD, FACS, FACCWS
Department of Surgery
Jobst Vascular Institute
ProMedica Health Network
2109 Hughes Dr., CJT Suite 400
Toledo, OH
E-mail: richard.simmanmd@promedica.org

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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