

Review Article

Radiotherapy-Induced Skin Injuries (RISIs): Mechanisms and Therapeutic Approaches

Hamed Charkhian^{1,2} , Sule Karaman³ , Rabia Nergiz Dagoglu Sakin³ ,
Seref Bugra Tuncer^{2,*} 

¹Institute of Graduate Studies in Health Sciences, Istanbul University, Istanbul, Turkey

²Department of Cancer Genetics, Istanbul University, Istanbul, Turkey

³Department of Radiation Oncology, Istanbul University, Istanbul, Turkey

Abstract

Radiotherapy (RT) remains one of the most essential and effective modalities in cancer treatment, administered to more than half of all patients for both curative and palliative purposes. Despite remarkable technological advances in precision targeting and dose modulation, radiation-induced skin injuries (RISIs) remain among the most common and distressing side effects of RT, affecting approximately 85-95% of patients. These cutaneous toxicities—ranging from transient erythema and dry desquamation to severe ulceration, fibrosis, and necrosis—reflect complex cellular and molecular disruptions. The clinical management of RISIs remains inconsistent, with no universally accepted standard of care. While traditional topical agents and dressings provide symptomatic relief, their efficacy is limited by poor stability and insufficient antioxidant activity. Recent evidence underscores the promise of targeted molecular therapies—such as TGF- β /Smad3 and COX-2 inhibition—alongside regenerative approaches involving mesenchymal stem cells, biomaterials, and nanotechnology-based drug delivery systems. Furthermore, integrating predictive biomarkers may enable personalized prevention and treatment strategies. This review synthesizes current insights into the pathophysiological and molecular mechanisms of RISIs, highlighting both established and emerging therapeutic modalities. By bridging mechanistic understanding with translational innovation, it aims to inform the development of more effective, biologically guided interventions that mitigate toxicity, enhance tissue repair, and ultimately improve the quality of life and treatment outcomes for cancer patients.

Keywords

Radiotherapy, Skin Injuries, RISI, Molecular Mechanism, Cellular Senescence, Bystander Effect

1. Introduction

Cancer is rapidly emerging as the defining health crisis of our time. In 2022 alone, nearly 20 million new cases were reported, making it one of the leading causes of death and disability worldwide [1]. Despite significant advancements

and ongoing research in cancer therapy, radiotherapy (RT) continues to play a pivotal role in the management of nearly all cancer types across the disease spectrum [2-4], with over half of all cancer patients receiving it during the course of

*Corresponding author: seref.tuncer@istanbul.edu.tr (Seref Bugra Tuncer)

Received: 14 September 2025; **Accepted:** 25 October 2025; **Published:** 19 December 2025



Copyright: © The Author(s), 2025. Published by Science Publishing Group. This is an **Open Access** article, distributed under the terms of the Creative Commons Attribution 4.0 License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

their disease. It is extensively utilized for both curative and palliative purposes, particularly in the treatment of solid tumors such as those of the breast, head and neck, skin, and anogenital regions [5, 6].

The primary objective of radiotherapy is to maximize therapeutic efficacy while minimizing harm to healthy tissues [2]. While radiotherapy has evolved with advanced technologies and precision-targeting techniques, skin toxicity remains an almost inevitable side effect. Reports indicate that up to 95% of patients undergoing radiation therapy develop some form of skin reaction, often emerging within the first few weeks of treatment and potentially lingering for weeks post-therapy [7, 8]. These Radiotherapy-induced skin injuries (RISIs), ranging from mild erythema and dryness to painful blistering and tissue breakdown, are commonly assessed using grading systems such as the Common Terminology Criteria for Adverse Events (CTCAE) and the Radiation Therapy Oncology Group (RTOG) scale [7]. The severity of these reactions tends to escalate in cases involving concurrent chemotherapy or high-dose protocols, with breast cancer, lung cancer, sarcoma, head and neck cancer patients particularly at risk—where severe reactions can affect over a quarter of individuals [8, 9]. Beyond the physical discomfort—burning, swelling, scarring, and impaired wound healing—these visible changes in appearance can trigger emotional distress, body image concerns, and social withdrawal. More critically, late-onset skin complications may exert a lasting toll on quality of life, interfering with recovery, psychosocial well-being, and even long-term survival [5, 10].

Despite the high prevalence of RISIs, there is currently no universally accepted standard of care across radiotherapy centers for their prevention and management [8]. Clinical practices often rely on individual experience rather than robust scientific evidence [11]. While numerous topical agents, dressings, and ointments—targeting free radical damage—have been introduced, their clinical efficacy remains limited. Challenges such as poor solubility, low chemical stability, degradation during storage, limited antioxidant capacity, and adverse side effects hinder their effectiveness [12]. These limitations underscore an urgent need for innovative therapeutic strategies that enhance both radioprotection and the clinical management of RISIs.

This review aims to provide a comprehensive overview of RISIs by first outlining their cellular and molecular mechanisms, followed by an evaluation of current therapeutic strategies and emerging pharmaceutical approaches. By synthesizing existing literature and drawing connections between fragmented findings, this study seeks not only to promote a more unified understanding of RISIs but also to serve as a catalyst for future research. Ultimately, bridging the current gaps in knowledge may contribute to the development of more effective treatments and improve the overall quality of life for this vulnerable patient population.

2. Radiotherapy-induced Skin Injuries

Despite its therapeutic value, radiotherapy can induce complex tissue damage, especially when the balance between tumor control and normal tissue preservation is not adequately maintained [13]. Radiation-induced injury affects highly organized tissues, composed of diverse, interdependent cellular lineages and biologically active extracellular matrices. This complex tissue-level perspective stands in contrast to traditional reductionist models, which primarily focus on radiation effects at the single-cell level, often studied *in vitro* [14].

Normal tissue responses to radiotherapy are multifaceted and involve two interconnected components. The first mimics aspects of wound healing, including inflammation, cell recruitment, and tissue remodeling, but these processes are often disrupted or prolonged due to continuous radiation exposure. The second component involves distinct, radiation-specific insults to virtually all cellular and non-cellular elements within the irradiated field, which may initiate chronic damage and long-term tissue degeneration [15].

Unlike acute mechanical, thermal, or chemical injuries that cause immediate structural disruption, radiation injury unfolds more subtly and progressively. Ionizing radiation (IR) initiates a cascade of events by generating reactive oxygen species (ROS), which not only induce DNA strand breaks but also oxidatively modify lipids, proteins, carbohydrates, and other complex biomolecules. Although the total energy deposited is low, the biological impact of each exposure is significant, setting in motion both immediate and delayed tissue alterations that may persist for years [15].

Another notable characteristic of radiotherapy is its fractionated nature, wherein multiple small doses are administered over time rather than as a single exposure. Each fraction induces a subtle but cumulative insult to the tissue, contributing to a progressive cascade of biological disruptions. These repeated doses not only trigger direct cellular injury but also promote the recruitment and activation of inflammatory cells, exacerbating tissue stress and initiating complex pathophysiological processes [15].

As radiation accumulates across treatment sessions, the irradiated tissue is exposed to an evolving microenvironment—one already marked by ongoing repair mechanisms, active inflammation, oxidative stress (OS), and cellular dysfunction. This chronic exposure significantly amplifies or alters normal wound-healing responses, distinguishing radiation-induced injuries from those caused by acute trauma, burns, or chemical insults [15].

Clinically, the severity of radiation-induced skin damage is highly variable, ranging from mild erythema and dryness to desquamation, ulceration, and in extreme cases, necrosis. These effects are most commonly observed at the entry and exit points of the radiation beam. To facilitate objective clinical assessment, widely accepted classification systems such as the RTOG criteria and the National Cancer Institute's

Common Terminology Criteria for Adverse Events (NCI CTCAE) are employed. The latter categorizes radiation dermatitis into distinct grades based on the extent and characteristics of skin involvement [16, 17].

2.1. Molecular Mechanisms

The molecular mechanisms underlying RISIs are complex and multifactorial. A central contributor to RISI pathogenesis is chronic oxidative stress, which plays a pivotal role in both the early and late phases of tissue damage. The cellular redox system, in particular, is instrumental in modulating radiation-induced responses [12, 18].

IR is widely recognized for its capacity to induce both reversible and irreversible damage to DNA within biological tissues. Given that approximately 80% of cellular content is water, a significant portion of radiation-induced injury—particularly from low linear energy transfer (LET) radiation—stems from water radiolysis. This process generates reactive oxygen species (ROS), reactive nitrogen species (RNS), and highly reactive molecules such as hydroxyl radicals ($\text{OH}\cdot$), which are the principal mediators of normal tissue toxicity following IR exposure. These reactive species target and damage critical cellular components, including lipids, proteins, and DNA [6, 9].

Free radicals produced by IR, in turn, upregulate the activity of key pro-oxidant enzymes such as cyclooxygenases (COXs), nitric oxide synthases (NOS), lipoxygenases (LOX), and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. This enzymatic activation contributes to mitochondrial dysfunction, marked by impaired electron transport chain function, ATP depletion, and structural mitochondrial damage [19]. The resulting accumulation of mitochondrial reactive oxygen species (mtROS) compromises membrane integrity and triggers the release of mitochondrial-derived danger signals, known as damage-associated molecular patterns (DAMPs), thereby amplifying oxidative stress and cellular injury [12, 20].

Additionally, oxidative stress initiates a cascade of intracellular signaling events, activating transcription factors and signal transduction pathways. These molecular alterations can result in DNA strand breaks, point mutations, and chromosomal aberrations, ultimately disrupting gene expression and protein synthesis [6, 9]. Such disruptions may culminate in cellular dysfunction, apoptosis, or necrosis [18].

Even after the first dose of radiotherapy, localized inflammatory responses can be observed immediately. This radiation-induced inflammation activates various signaling pathways and promotes the release of pro-inflammatory cytokines and chemokines, thereby exacerbating tissue injury.

The inflammatory response following IR is further amplified by the activation and nuclear translocation of nuclear factor- κB (NF- κB). Radiation-induced intracellular ROS activates the I κB kinase (IKK) complex, leading to the phosphorylation and subsequent degradation of the inhibitory

protein I κB . This process liberates NF- κB , allowing its migration into the nucleus, where it binds to promoter regions of target genes and stimulates the transcription of pro-inflammatory cytokines such as IL-1 β , IL-6, and TNF- α , along with various chemokines. Concurrently, ROS also activates the NLRP3 inflammasome, which promotes the activation of Caspase-1 and facilitates the extracellular release of additional inflammatory mediators like IL-1 β and IL-8. This signaling cascade collectively enhances inflammation and contributes to radiation-induced apoptosis [12, 21].

The early inflammatory response triggered by IR is predominantly mediated through a cascade of pro-inflammatory cytokines—including interleukins IL-1, IL-3, IL-5, IL-6, and tumor necrosis factor- α (TNF- α)—along with chemokines such as IL-8 and eotaxin, receptor tyrosine kinases, and adhesion molecules like intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin [6, 8]. These mediators collectively initiate the recruitment and activation of immune cells, particularly eosinophils and neutrophils, to the irradiated site, resulting in a localized inflammatory response [6, 22].

This infiltration not only contributes to sustained inflammation but also perpetuates tissue injury by compromising the skin's structural integrity and disrupting protective barriers. Furthermore, while cytokines such as TNF- α , IL-6, and IL-1 primarily orchestrate the inflammatory milieu, growth factors like transforming growth factor-beta (TGF- β) and platelet-derived growth factor (PDGF) play key roles in modulating fibroblast activity and stimulating the synthesis of extracellular matrix (ECM) components, thereby influencing tissue remodeling and fibrosis in the later stages of injury [8, 23].

The pathogenesis of chronic radiation dermatitis is closely linked to the activity of TGF- β , a multifunctional cytokine that regulates cell proliferation, differentiation, wound healing, and ECM synthesis during tissue responses to injury [6, 8]. Among its isoforms, TGF- β 1 is particularly implicated in the promotion of radiation-induced fibrosis [9]. IR drives the initiation and progression of post-radiation fibrosis primarily through the activation of myofibroblasts, key effector cells in fibrotic remodeling. This process is mediated by converging signaling cascades, most notably the TGF- β and Wnt/ β -catenin pathways [9, 24]. TGF- β 1 exerts its profibrotic effects by binding to type I and II serine/threonine kinase receptors, triggering downstream signaling through receptor-regulated Smad proteins—particularly Smad3 [8, 9, 25]. Once phosphorylated, Smad3 translocates to the nucleus and induces the transcription of genes involved in ECM production and fibroblast proliferation, a central axis driving late-stage fibrotic changes after radiation exposure [11, 12].

In RISIs, TGF- β contributes to oxidative imbalance and vascular damage by modulating the expression of miR-21. Upon ligand-receptor interaction, TGF- β upregulates miR-21, which subsequently inhibits the expression of superoxide dismutase 2 (SOD2)—a critical mitochondrial antioxidant enzyme involved in scavenging ROS. The suppression of

SOD2 leads to excessive ROS accumulation, exacerbating oxidative stress within irradiated skin tissues. Simultaneously, miR-21 interferes with the apoptotic regulation of vascular endothelial cells by targeting the tumor suppressor gene PTEN, a key inhibitor of the PI3K/AKT signaling pathway. Through PTEN suppression, miR-21 disrupts the balance of this signaling cascade, impairing endothelial function and contributing to radiation-induced vascular injury [12, 26-28]. These interrelated pathways highlight the dual role of miR-21 in promoting oxidative stress while impairing vascular integrity, both of which are fundamental features in the molecular pathology of RISIs.

Moreover, IR can stimulate various cell types—including fibroblasts, endothelial cells, and vascular smooth muscle cells—to undergo phenotypic transition into myofibroblasts. One contributing mechanism involves the interaction between stromal cell-derived factor-1 α (SDF-1 α) and its receptor CXCR4, which activates TGF- β /Smad signaling via downstream mitogen-activated protein kinase (MAPK) pathways. These molecular events synergistically enhance fibrotic responses by promoting sustained fibroblast activation and excessive ECM deposition [9, 12, 29].

Experimental evidence further supports the essential role of TGF- β 1/Smad3 signaling in radiation-induced fibrosis [25]: Smad3-deficient mice exhibit significantly reduced cutaneous damage, diminished leukocyte infiltration, and improved epithelial regeneration following irradiation, underscoring the importance of this pathway in mediating chronic fibrotic remodeling in irradiated tissues.

2.2. Cellular Senescence and Bystander Effect

IR triggers profound cellular damage through both direct interaction with DNA molecules and indirect pathways involving ROS generation. These effects disrupt the structural integrity and chemical composition of DNA strands, leading to double-strand breaks, base modifications, and crosslinking. When cellular repair mechanisms fail to efficiently resolve this damage, it accumulates and contributes to critical cellular outcomes such as apoptosis, mutagenesis, and senescence—all of which compromise skin homeostasis and impair tissue regeneration [5, 12].

Radiation-induced senescence is characterized by permanent growth arrest, metabolic activity, and resistance to apoptosis. Senescent cells, though non-proliferative, remain highly active in secreting a wide array of pro-inflammatory and pro-fibrotic factors, collectively termed the senescence-associated secretory phenotype (SASP). These factors alter the surrounding microenvironment, promoting chronic inflammation and fibrotic remodeling, both hallmarks of late-stage radiation-induced skin injury [13, 30].

A notable mechanism of IR-induced senescence propagation is the bystander effect, wherein neighboring, non-irradiated cells adopt senescence-like phenotypes due to signals—especially exosomes and microRNAs (miR-

NAs)—emitted by damaged cells. These exosomes are enriched with inflammatory cytokines such as IL-6, IL-8, and TNF- α , which activate inflammatory pathways in adjacent healthy cells, fostering a sustained pro-aging and pro-inflammatory milieu [12, 31].

MicroRNAs play pivotal roles in mediating DNA damage responses and promoting senescence in irradiated tissues. For instance, miR-34a enhances senescence by suppressing SIRT1 expression, leading to p53 activation and the accumulation of DNA damage markers such as γ H2AX. Similarly, miR-21 reduces the replicative capacity of human umbilical vein endothelial cells (HUVECs), while miR-22 facilitates senescence in fibroblasts and epithelial cells through the downregulation of CDK6, Sp1, and SIRT1 [32-34]. These molecular changes collectively increase oxidative stress, exacerbate mitochondrial dysfunction, and ultimately accelerate skin aging.

Key signaling axes, including p53-p21 and p16-pRB, are central to the enforcement of radiation-induced growth arrest and senescence. Moreover, mitochondrial abnormalities, ferritin autophagy failure, and activation of the cyclic GMP-AMP synthase (cGAS)-STING inflammatory pathway further amplify the senescence response [12, 33]. Notably, Chen et al. [35] has identified the accumulation of human positive cofactor 4 (PC4) as a novel contributor to radiation-induced aging, wherein PC4 accelerates senescence by disrupting mTOR-regulated proteostasis.

Although these findings offer important insights, the intricate network of molecular events underpinning IR-induced cellular senescence and its role in RISIs remains incompletely understood and requires further exploration.

2.3. Pathophysiology

RISIs result from a complex interplay of cellular, molecular, and tissue-level alterations triggered by IR. These changes occur in both acute and chronic phases, leading to significant disruption of skin structure and function.

The epidermis, particularly its basal layer, is highly susceptible to radiation due to its high cellular turnover. Basal keratinocytes, melanocytes, and hair follicle stem cells are primary targets, and radiation exposure impairs their proliferation and differentiation [36, 37]. This interference compromises the skin's regenerative capacity and disrupts the integrity of the epidermal barrier. Repeated exposures, especially in fractionated radiotherapy, prevent complete cellular repair, leading to cumulative injury and persistent epithelial dysfunction [13, 38].

At the tissue level, radiation-induced oxidative stress and inflammation, as detailed in the molecular mechanisms section, compromise vascular integrity by disrupting endothelial junctions. This vascular injury increases permeability, impairs barrier function, and promotes hypoxia and necrosis [28]. During the chronic phase of radiation injury, fibroblasts and endothelial cells in the dermis become highly vulnerable.

Persistent damage and pro-fibrotic signals drive fibroblasts to transdifferentiate into myofibroblast-like cells, which secrete abundant ECM proteins (collagen I, III, IV) and express α -SMA. The α -SMA fibers form contractile stress structures that, through integrin-collagen interactions, generate mechanical tension within the dermis. This tension promotes matrix stiffening, structural disorganization, and progressive fibrosis, ultimately resulting in dermal sclerosis and impaired skin function—key features of late radiation injury [12, 39, 40].

Radiation-induced endothelial injury leads to vascular rarefaction and impaired angiogenesis, which exacerbate tissue hypoxia and hinder reparative processes [8, 9, 25, 41]. This vascular dysfunction is compounded by the exposure of subendothelial ECM, triggering platelet activation and the release of pro-thrombotic mediators such as von Willebrand factor (vWF) and platelet-activating factor (PAF). Concurrently, diminished levels of nitric oxide (NO), prostacyclin, thrombomodulin (TM), and reduced fibrinolytic activity drive a pro-coagulant and anti-fibrinolytic state, culminating in microvascular thrombosis and occlusion [42]. These changes accelerate tissue ischemia and fibrosis, thereby amplifying the severity of radiotherapy-induced skin injury [43].

Clinically, this chronic vascular and fibro-inflammatory imbalance manifests as skin atrophy, telangiectasia, induration, and, in severe cases, non-healing ulcers [8, 12]. The compromised vasculature also impairs immune surveillance, increasing susceptibility to infections. Moreover, radiation disrupts Langerhans cell function and antigen presentation, further compromising local immune regulation and perpetuating chronic inflammation.

2.4. Therapeutic Strategies

2.4.1. Mechanism-Based Therapeutic Strategies for RISRs

The development of therapeutic interventions for RISRs has been largely guided by elucidating the underlying molecular and cellular mechanisms of injury. The following strategies highlight how mechanistic insights have been translated into clinical and experimental treatments:

1) Targeting Inflammation via Corticosteroids

Corticosteroids exert anti-inflammatory, immunosuppressive, vasoconstrictive, and anti-proliferative effects by inhibiting cytokines such as IL-1, IL-6, IFN- γ , and TNF- α . They also reduce histamine release, thereby attenuating erythema and edema. These mechanisms make corticosteroids (e.g., mometasone furoate, methylprednisolone, betamethasone) superior to moisturizers in reducing acute radiation-induced toxicity, positioning them as strong candidates for preventive therapy [6, 44, 45].

2) Modulating Immune Response and ECM Remodeling via Trolamine-Based Creams

Trolamine-containing emulsions (e.g., biafine) promote macrophage recruitment, fibroblast proliferation, collagen

synthesis, and vascular protection. By regulating IL-1 and IL-6 signaling, they accelerate re-epithelialization and granulation tissue formation. Their wound-healing properties provide both protective and reparative benefits during acute RISRs [11, 46].

3) Restoring Skin Microenvironment with Hydrogel and Hydrocolloid Dressings

These dressings establish a moist wound environment, which stimulates keratinocyte migration, angiogenesis, and granulation tissue formation. Hydrocolloids additionally promote autolytic debridement, while hydrogels reduce infection risk and pain. Clinically, they significantly shorten wound healing time in moist desquamation and necrotic ulcers [47, 48].

4) Harnessing Mesenchymal Stem Cells (MSCs) for Regeneration

MSCs mediate therapeutic effects via paracrine signaling, immunomodulation, and multilineage differentiation. They downregulate pro-inflammatory (TNF- α , ICAM-1) and pro-fibrotic mediators (TGF- β , CTGF), while upregulating antioxidant enzymes. MSCs also enhance angiogenesis and oxygen delivery, reducing oxidative stress and chronic fibrosis. Importantly, MSCs modulate macrophage polarization ($\downarrow$ IL-1 β , $\uparrow$ IL-10), thereby controlling inflammation and promoting tissue regeneration [49, 50].

5) Reversing Hypoxia with Hyperbaric Oxygen Therapy (HBOT)

HBOT enhances tissue oxygenation, angiogenesis, and vascular density in irradiated skin. By reducing hypoxia and edema, it supports reparative processes in chronic radiation ulcers. Its efficacy in necrotic tissue healing and delayed radiation injury highlights oxygen signaling as a critical therapeutic axis [51, 52].

6) Counteracting Oxidative Stress with Superoxide Dismutase (SOD)

As a key antioxidant enzyme, SOD neutralizes ROS and prevents oxidative-stress-driven fibrosis. Liposomal and synthetic SOD analogs (e.g., EUK-207) inhibit TGF- β -mediated myofibroblast activation, accelerating wound healing and reducing desquamation. Clinical studies further confirm fibrosis regression after SOD administration, underlining its promise as a redox-modulating therapy [53-55].

7) Enhancing Mitochondrial Bioenergetics with Low-Intensity Laser Therapy (LILT)

LILT activates mitochondrial cytochromes, increasing ATP production, protein synthesis, and cell proliferation. By stimulating tissue repair, reducing edema, and relieving pain, LILT shows potential in mitigating chronic RISRs through cellular bioenergetic restoration [56-58].

2.4.2. Innovative Drug Development Strategies

Understanding the mechanisms of chronic oxidative damage and injury of affected cells, tissues, and organs after exposure to IR may contribute to the development of treat-

ment and management strategies of the complications associated with RT [6].

Janko et al ascertained that IL-1 had an important role in the development of RISRs. They found that mice that lack either IL-1 or the IL-1 receptor developed less inflammation and less severe pathological changes in their skin, especially at later time points. This study provided a potential therapeutic targeting of IL-1 for the remission of RISRs. The production of IL-1 in skin is mainly regulated by monocytes, macrophages, fibroblasts, keratinocytes, and many other immune mediators. In the acute phase, all resident cells, including keratinocytes, fibroblasts, and endothelial cells, respond to IR by the activation of the early response genes and proteins, which include a lot of growth factors, chemokines, and cytokines. These various growth factors then attract inflammatory cells that participate in the second phase of RISRs [6].

The TGF- β is a regulatory protein that controls wound healing, proliferation, and differentiation of multiple cell types and synthesis of ECM proteins in the normal tissue inflammatory response, and is known as a central player in the fibrotic process. Its main function on connective tissues *in vivo* is to promote growth. The proliferation of endothelial cell is also stimulated, but the growth of epithelial cell is inhibited. Mice lacking a downstream mediator of TGF- β , Smad3, demonstrated reduced tissue damage and fibrosis after irradiation and accelerated healing [6].

Inhibition of pro-inflammatory cytokines such as MCP-1 and COX-2 can improve skin tolerance to RT. Some studies have also reported COX-2 to be an important gene mediating the subsequent inflammation. The study by Cheki et al showed that inhibition of COX-2 by celecoxib can reduce inflammation of the dermis, MCP-1 mRNA expression, and RISRs [6].

Given the significant role of oxidative stress and ROS/RNS in radiation-induced tissue damage, targeting these pathways could provide a therapeutic approach to mitigate the side effects of radiotherapy. Developing inhibitors or scavengers of ROS and RNS, as well as redox system modulators, could help protect normal tissues, reduce inflammation, and enhance skin recovery in cancer patients undergoing radiation treatment [6, 9].

DNA repair system plays a key role in normal tissue tolerance to RT. There is a predictable increase in regulation of DNA repair genes after radiation exposure. Inflammation and Oxidative stress may inhibit DNA damage repair. There is evidence that chronic inflammation lead to suppression of DNA repair response and mutations in tumor suppressor genes and oncogenes. NO produced by immune cells including macrophages and neutrophils can inhibit DNA repair and alter the expression of certain genes. Understanding radiation-induced DNA damage and DNA repair system may contribute to the development of adjuncts to RT [6].

Targeting the TGF- β /Smad3 signaling pathway offers a promising strategy for treating RISRs. TGF- β 1 plays a central role in fibrosis by promoting ECM production. Its activation,

especially through Smad3, leads to chronic tissue damage. Studies show that inhibiting Smad3 reduces inflammation, fibrosis, and skin injury. Smad3 knockout models demonstrate faster healing and less damage. Thus, blocking this pathway can effectively limit radiation-induced skin toxicity [9].

Notably, the AIM2 inflammasome has been identified as a key mediator of caspase-1-driven cell death in epithelial and bone marrow cells following exposure to IR. Inhibiting the AIM2 pathway could therefore offer a protective strategy against gastrointestinal and hematopoietic toxicity. Additionally, the cGAS-STING signaling axis plays a critical role in radiation-induced cellular senescence and inflammation, particularly in hepatocytes. Cytosolic chromatin fragments derived from irradiated nuclei activate cGAS, which subsequently stimulates STING and promotes the expression of pro-inflammatory cytokines via NF- κ B signaling. These findings suggest that selective inhibition of the AIM2 and cGAS-STING pathways may reduce inflammatory damage in normal tissues post-radiotherapy, offering a promising therapeutic avenue for conditions such as RISRs [5].

3. Discussion and Conclusion

The evidence synthesized in this review highlights that RISIs result from a complex interplay of oxidative stress, inflammatory signaling, fibroblast activation, and aberrant tissue remodeling. Acute manifestations such as erythema, desquamation, and ulceration are largely driven by reactive oxygen and nitrogen species (ROS/RNS) and subsequent inflammatory cascades [11], while chronic injuries—including fibrosis, atrophy, and necrosis—are perpetuated by dysregulated TGF- β /Smad signaling, cellular senescence, and vascular dysfunction. These insights emphasize that RISIs are not simply localized toxicities but represent systemic biological disruptions with long-term implications for patient quality of life and treatment adherence [39].

Emerging therapies targeting molecular pathways—particularly TGF- β /Smad3 inhibition, IL-1 blockade, and COX-2 inhibition—represent promising avenues for reducing fibrosis and chronic inflammation [20]. Preclinical evidence also highlights the therapeutic potential of MSCs, which exert reparative effects through paracrine signaling, immune modulation, and angiogenic stimulation [11, 59]. In parallel, novel strategies targeting innate immune sensors such as the AIM2 inflammasome and the cGAS-STING pathway may offer opportunities to curb radiation-induced senescence and bystander effects [60-62]. These approaches align with a broader shift in oncology toward mechanism-based interventions that not only address acute toxicity but also prevent late-stage sequelae.

The integration of advanced biomaterials and nanotechnology may further revolutionize RISI management. Smart dressings capable of controlled drug release, nanocarriers enhancing antioxidant and anti-inflammatory delivery, and

bioengineered scaffolds promoting angiogenesis represent exciting translational opportunities. Furthermore, advances in radiotherapy itself—such as intensity-modulated radiotherapy (IMRT), proton therapy, and FLASH radiotherapy—hold promise in reducing normal tissue toxicity by minimizing collateral exposure. However, these technological advancements must be complemented by biologically informed therapeutic strategies to achieve meaningful reductions in RISIs.

Another key consideration is the role of predictive biomarkers in identifying patients at high risk for severe RISIs. Genetic variants in DNA repair pathways, redox regulators, and inflammatory cytokines, as well as circulating markers of oxidative stress and senescence, could provide valuable tools for stratifying patients and guiding personalized prevention strategies. Incorporating biomarker-driven approaches may help bridge the variability observed in current clinical management and pave the way toward precision supportive care in radiation oncology.

In conclusion, RISIs remain a critical challenge in cancer therapy, reflecting the dual-edged nature of radiotherapy as both a life-saving and tissue-damaging intervention. While conventional wound care and symptomatic management continue to dominate clinical practice, advances in molecular oncology, regenerative medicine, and nanotechnology are reshaping the therapeutic landscape. Future progress will depend on integrating mechanistic insights with translational research, developing standardized protocols, and validating innovative therapies through robust clinical trials. Ultimately, reducing the burden of RISIs is essential not only for improving patient comfort and quality of life but also for ensuring optimal adherence and outcomes in cancer treatment.

Abbreviations

RT	Radiotherapy
RISI	Radiation-induced Skin Injury
RTOG	Radiation Therapy Oncology Group
IR	Ionizing Radiation
ROS	Reactive Oxygen Species
NCI	National Cancer Institute's Common
CTCAE	Terminology Criteria for Adverse Events
OS	Oxidative Stress
LET	Linear Energy Transfer
OH	Hydroxyl Radicals
COX	Cyclooxygenase
NOS	Nitric Oxide Synthases
LOX	Lipoxygenases
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
mtROS	Mitochondrial Reactive Oxygen Species
DAMP	Damage-associated Molecular Pattern
IKK	I κ B Kinase
TNF- α	Tumor Necrosis Factor-alpha
ICAM-1	Intercellular Adhesion Molecule-1

VCAM-1	Vascular Cell Adhesion Molecule-1
TGF- β	Transforming Growth Factor-beta
PDGF	Platelet-derived Growth Factor
SDF-1 α	Stromal Cell-derived Factor-1 α
MAPK	Mitogen-activated Protein Kinase
SASP	Senescence-associated Secretory Phenotype
miRNA	microRNA
HUVEC	Human Umbilical Vein Endothelial Cell
PC4	Positive Cofactor 4
vWF	Von Willebrand Factor
NO	Nitric Oxide
TM	Thrombomodulin
MSC	Mesenchymal Stem Cell
HBOT	Hyperbaric Oxygen Therapy
SOD	Superoxide Dismutase
LILT	Low-Intensity Laser Therapy
IMRT	Intensity-modulated Radiotherapy

Author Contributions

Hamed Charkhian: Conceptualization, Resources, Project administration, Writing - original draft

Sule Karaman: Data curation, Methodology, Validation, Supervision, Writing - review & editing

Rabia Nergiz Dagoglu Sakin: Data curation, Methodology, Validation, Supervision, Writing - review & editing

Seref Bugra Tuncer: Conceptualization, Formal analysis, Supervision, Writing - review & editing

Funding

There was no Funding.

Conflicts of Interest

The authors declare no competing interests.

References

- [1] WHO. WHO. 2025. Global Cancer Observatory.
- [2] Almeida, V., Pires, D., Silva, M., Teixeira, M., Teixeira, R. J., Louro, A., Dinis, M. A. P., Ferreira, M., Teixeira, A.: Dermatological side effects of cancer treatment: psychosocial implications—a systematic review of the literature. In: Healthcare. p. 2621. MDPI (2023)
- [3] Chandra, R. A., Keane, F. K., Voncken, F. E. M., Thomas, C. R.: Contemporary radiotherapy: present and future. The Lancet. 398, 171-184 (2021).
- [4] Charkhian, H., Tuncer, S. B., Karaman, S., Dağoglu Sakin, R. N., Hallaj-Salahipour, M.: Clinical applications and recent advances in radiotherapy for the management of neoplasia in companion animals. Avicenna Veterinary Research. (2025). <https://doi.org/10.22084/avr.2025.31489.1016>

- [5] De Ruyscher, D., Niedermann, G., Burnet, N. G., Siva, S., Lee, A. W. M., Hegi-Johnson, F.: Radiotherapy toxicity. *Nat Rev Dis Primers*. 5, 13 (2019).
- [6] Wei, J., Meng, L., Hou, X., Qu, C., Wang, B., Xin, Y., Jiang, X.: Radiation-induced skin reactions: mechanism and treatment. *Cancer Manag Res*. 167-177 (2018).
- [7] Burke, G., Faithfull, S., Probst, H.: Radiation induced skin reactions during and following radiotherapy: A systematic review of interventions. *Radiography*. 28, 232-239 (2022).
- [8] Bray, F. N., Simmons, B. J., Wolfson, A. H., Nouri, K.: Acute and chronic cutaneous reactions to ionizing radiation therapy. *Dermatol Ther (Heidelb)*. 6, 185-206 (2016).
- [9] Kim, J. H., Kolozy, A. J. J., Jenrow, K. A., Brown, S. L.: Mechanisms of radiation-induced skin injury and implications for future clinical trials. *Int J Radiat Biol*. 89, 311-318 (2013).
- [10] DeHaven, C.: Chemotherapy and radiotherapy effects on the skin. *Plastic and Aesthetic Nursing*. 34, 192-195 (2014).
- [11] Yang, X., Ren, H., Guo, X., Hu, C., Fu, J.: Radiation-induced skin injury: pathogenesis, treatment, and management. *Aging (Albany NY)*. 12, 23379 (2020).
- [12] Xu, Y., Liu, Q., Li, W., Hu, Z., Shi, C.: Recent advances in the mechanisms, current treatment status, and application of multifunctional biomaterials for radiation-induced skin injury. *Theranostics*. 15, 2700 (2025).
- [13] Wang, Y., Tu, W., Tang, Y., Zhang, S.: Prevention and treatment for radiation-induced skin injury during radiotherapy. *Radiat Med Prot*. 1, 60-68 (2020).
- [14] Denham, J. W., Hauer-Jensen, M.: The radiotherapeutic injury-a complex 'wound.' *Radiotherapy and Oncology*. 63, 129-145 (2002).
- [15] Warnock, C., Lee, N.: Skin reactions from radiotherapy. *Cancer nursing practice*. 13, (2014).
- [16] Salvo, N., Barnes, E., van Draanen, J., Stacey, E., Mitera, G., Breen, D., Giotis, A., Czarnota, G., Pang, J., De Angelis, C.: Prophylaxis and management of acute radiation-induced skin reactions: a systematic review of the literature. *Current oncology*. 17, 94 (2010).
- [17] Montpetit, C., Singh-Carlson, S.: Engaging patients with radiation related skin discomfort in self-care. *Canadian Oncology Nursing Journal*. 28, 191 (2018).
- [18] Obrador, E., Salvador-Palmer, R., Villaescusa, J. I., Gallego, E., Pellicer, B., Estrela, J. M., Montoro, A.: Nuclear and radiological emergencies: biological effects, countermeasures and biodosimetry. *Antioxidants*. 11, 1098 (2022).
- [19] Marchi, S., Guilbaud, E., Tait, S. W. G., Yamazaki, T., Galluzzi, L.: Mitochondrial control of inflammation. *Nat Rev Immunol*. 23, 159-173 (2023).
- [20] Liu, C., Wei, J., Wang, X., Zhao, Q., Lv, J., Tan, Z., Xin, Y., Jiang, X.: Radiation-induced skin reactions: oxidative damage mechanism and antioxidant protection. *Front Cell Dev Biol*. 12, 1480571 (2024).
- [21] Kamen, L. E., Janusz, M., Berry, C. E., Downer Jr, M. A., Parker, J. B., Morgan, A. G., Valencia, C., Griffin, M., Li, D. J., Liang, N. E.: A review of radiation-induced vascular injury and clinical impact. *Ann Plast Surg*. 92, 181-185 (2024).
- [22] Peter, R. U.: Diagnosis and treatment of cutaneous radiation injuries. In: *Radiation treatment and radiation reactions in dermatology*. pp. 185-188. Springer (2014).
- [23] Bentzen, S. M.: Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. *Nat Rev Cancer*. 6, 702-713 (2006).
- [24] Griffin, M. F., Huber, J., Evan, F. J., Quarto, N., Longaker, M. T.: The role of Wnt signaling in skin fibrosis. *Med Res Rev*. 42, 615-628 (2022).
- [25] Flanders, K. C., Major, C. D., Arabshahi, A., Aburime, E. E., Okada, M. H., Fujii, M., Blalock, T. D., Schultz, G. S., Sowers, A., Anzano, M. A.: Interference with transforming growth factor- β /Smad3 signaling results in accelerated healing of wounds in previously irradiated skin. *Am J Pathol*. 163, 2247-2257 (2003).
- [26] Zhang, Y., Chen, Z., Feng, L., Jiang, P., Li, X., Wang, X.: Ionizing radiation-inducible microRNA-21 induces angiogenesis by directly targeting PTEN. *Asian Pac J Cancer Prev*. 20, 1587 (2019).
- [27] Farrugia, C.-J. E., Burke, E. S., Haley, M. E., Bedi, K. T., Gandhi, M. A.: The use of aloe vera in cancer radiation: An updated comprehensive review. *Complement Ther Clin Pract*. 35, 126-130 (2019).
- [28] Wei, J., Wang, B., Wang, H., Meng, L., Zhao, Q., Li, X., Xin, Y., Jiang, X.: Radiation - induced normal tissue damage: oxidative stress and epigenetic mechanisms. *Oxid Med Cell Longev*. 2019, 3010342 (2019).
- [29] Horton, J. A., Li, F., Chung, E. J., Hudak, K., White, A., Krausz, K., Gonzalez, F., Citrin, D.: Quercetin inhibits radiation-induced skin fibrosis. *Radiat Res*. 180, 205-215 (2013).
- [30] Bogdanowicz, P., Roulet, N., Bensadoun, P., Bessou - Touya, S., Lemaitre, J., Duplan, H.: Reduction of senescence - associated secretory phenotype and exosome - shuttled miRNAs by Haritaki fruit extract in senescent dermal fibroblasts. *Int J Cosmet Sci*. 45, 488-499 (2023).
- [31] Elbakrawy, E., Kaur Bains, S., Bright, S., Al-Abedi, R., Mayah, A., Goodwin, E., Kadhim, M.: Radiation-induced senescence bystander effect: the role of exosomes. *Biology (Basel)*. 9, 191 (2020).
- [32] Munk, R., Panda, A. C., Grammatikakis, I., Gorospe, M., Abdelmohsen, K.: Senescence-associated microRNAs. *Int Rev Cell Mol Biol*. 334, 177-205 (2017).
- [33] Chen, W., Wang, Y., Zheng, J., Chen, Y., Zhang, C., Yang, W., Wu, L., Yang, Z., Wang, Y., Shi, C.: Characterization of cellular senescence in radiation ulcers and therapeutic effects of mesenchymal stem cell-derived conditioned medium. *Burns Trauma*. 11, tkad001 (2023).

- [34] Kowzun, M. J., Rifkin, W. J., Borab, Z. M., Ellison, T., Soares, M. A., Wilson, S. C., Lotfi, P., Bandekar, A., Sofou, S., Saadeh, P. B.: Topical inhibition of PUMA signaling mitigates radiation injury. *Wound repair and regeneration*. 26, 413-425 (2018).
- [35] Chen, L., Liao, F., Wu, J., Wang, Z., Jiang, Z., Zhang, C., Luo, P., Ma, L., Gong, Q., Wang, Y.: Acceleration of ageing via disturbing mtor - regulated proteostasis by a new ageing - associated gene PC4. *Aging Cell*. 20, e13370 (2021).
- [36] Rube, C. E., Freyter, B. M., Tewary, G., Roemer, K., Hecht, M., Rube, C.: Radiation dermatitis: radiation-induced effects on the structural and immunological barrier function of the epidermis. *Int J Mol Sci*. 25, 3320 (2024).
- [37] Ryan, J. L.: Ionizing radiation: the good, the bad, and the ugly. *Journal of Investigative Dermatology*. 132, 985-993 (2012).
- [38] Jaschke, W., Schmutz, M., Trianni, A., Bartal, G.: Radiation-induced skin injuries to patients: what the interventional radiologist needs to know. *Cardiovasc Intervent Radiol*. 40, 1131-1140 (2017).
- [39] Yu, Z., Xu, C., Song, B., Zhang, S., Chen, C., Li, C., Zhang, S.: Tissue fibrosis induced by radiotherapy: current understanding of the molecular mechanisms, diagnosis and therapeutic advances. *J Transl Med*. 21, 708 (2023).
- [40] Li, D. J., Berry, C. E., Wan, D. C., Longaker, M. T.: Clinical, mechanistic, and therapeutic landscape of cutaneous fibrosis. *Sci Transl Med*. 16, eadn7871 (2024).
- [41] Abe, J. I., Allen, B.G., Beyer, A.M., Lewandowski, D., Mapuskar, K.A., Subramanian, V., Tamplin, M.R. and Grumbach, I.M.: Radiation-Induced macrovessel/microvessel disease. Arteriosclerosis, thrombosis, and vascular biology. 44(12), 2407-2415 (2024).
- [42] Boraldi, F., Lofaro, F. D., Bonacorsi, S., Mazzilli, A., Garcia-Fernandez, M., Quaglino, D.: The role of fibroblasts in skin homeostasis and repair. *Biomedicines*. 12, 1586 (2024).
- [43] Hwang, J.-H., Heo, W., Park, J. Il, Kim, K. M., Oh, H. T., Yoo, G. D., Park, J., Shin, S., Do, Y., Jeong, M. G.: Endothelial TAZ inhibits capillarization of liver sinusoidal endothelium and damage-induced liver fibrosis via nitric oxide production. *Theranostics*. 13, 4182 (2023).
- [44] Bedini, N., Cicchetti, A., Palorini, F., Magnani, T., Zuco, V., Pennati, M., Campi, E., Allavena, P., Pesce, S., Villa, S.: Evaluation of mediators associated with the inflammatory response in prostate cancer patients undergoing radiotherapy. *Dis Markers*. 2018, 9128128 (2018).
- [45] Najafi, M., Motevaseli, E., Shirazi, A., Geraily, G., Rezaeyan, A., Norouzi, F., Rezapoor, S., Abdollahi, H.: Mechanisms of inflammatory responses to radiation and normal tissues toxicity: clinical implications. *Int J Radiat Biol*. 94, 335-356 (2018).
- [46] Abbas, H., Bensadoun, R.-J.: Trolamine emulsion for the prevention of radiation dermatitis in patients with squamous cell carcinoma of the head and neck. *Supportive Care in Cancer*. 20, 185-190 (2012).
- [47] Kammona, O., Tsanaksidou, E., Kiparissides, C.: Recent developments in 3D-(bio) printed hydrogels as wound dressings. *Gels*. 10, 147 (2024).
- [48] Su, Y., Cui, H., Yang, C., Li, L., Xu, F., Gao, J., Zhang, W.: Hydrogels for the treatment of radiation-induced skin and mucosa damages: An up-to-date overview. *Front Mater*. 9, 1018815 (2022).
- [49] Shen, Y., Jiang, X., Meng, L., Xia, C., Zhang, L., Xin, Y.: Transplantation of bone marrow mesenchymal stem cells prevents radiation - induced artery injury by suppressing oxidative stress and inflammation. *Oxid Med Cell Longev*. 2018, 5942916 (2018).
- [50] Radwan, R. R., Mohamed, H. A.: Mechanistic approach of the therapeutic potential of mesenchymal stem cells on brain damage in irradiated mice: Emphasis on anti-inflammatory and anti-apoptotic effects. *Int J Radiat Biol*. 99, 1463-1472 (2023).
- [51] Hajikarimloo, B., Kavousi, S., Jahromi, G. G., Mehmandoost, M., Oraee-Yazdani, S., Fahim, F.: Hyperbaric oxygen therapy as an alternative therapeutic option for radiation-induced necrosis following radiotherapy for intracranial pathologies. *World Neurosurg*. 186, 51-61 (2024).
- [52] Fernández, E., Morillo, V., Salvador, M., Santafé A., Beato, I., Rodríguez, M., Ferrer, C.: Hyperbaric oxygen and radiation therapy: a review. *Clinical and Translational Oncology*. 23, 1047-1053 (2021).
- [53] Mapuskar, K. A., Anderson, C. M., Spitz, D. R., Batinic-Haberle, I., Allen, B. G., Oberley-Deegan, R. E.: Utilizing superoxide dismutase mimetics to enhance radiation therapy response while protecting normal tissues. In: *Seminars in radiation oncology*. pp. 72-80. Elsevier (2019).
- [54] Holley, A. K., Miao, L., St. Clair, D. K., St. Clair, W. H.: Redox-modulated phenomena and radiation therapy: the central role of superoxide dismutases. *Antioxid Redox Signal*. 20, 1567-1589 (2014).
- [55] Diehl, C.: Use of Topical Superoxide Dismutase in the Management of Radiation-induced Fibrosis: A Neglected Opportunity? *matrix*. 37, 38 (2012).
- [56] Masha, R. T.: Effect of Laser Irradiation on Enzyme Activity and Expression of Mitochondrial Respiratory Chain Complexes. University of Johannesburg (South Africa) (2011).
- [57] Huang, Y.-Y., Chen, A. C.-H., Hamblin, M. R.: Advances in low-intensity laser and phototherapy. In: *Handbook of Photonics for Biomedical Science*. pp. 723-752. CRC Press (2010).
- [58] Hourelid, N. N.: Laser irradiation in the visible wavelength stimulates wound healing in vitro. *WALT*. 41 (2013).
- [59] Wang, K.-X., Cui, W.-W., Yang, X., Tao, A.-B., Lan, T., Li, T.-S., Luo, L.: Mesenchymal stem cells for mitigating radiotherapy side effects. *Cells*. 10, 294 (2021).
- [60] Wu, M., Shi, J., He, S., Wang, D., Zhang, N., Wang, Z., Yang, F., He, J., Hu, D., Yang, X.: cGAS promotes sepsis in radiotherapy of cancer by up-regulating caspase-11 signaling. *Biochem Biophys Res Commun*. 551, 86-92 (2021).

- [61] Zhang, W., Chen, S., Guan, H., Zhou, P.-K.: Radiation-induced non-targeted effect of immunity provoked by mitochondrial DNA damage triggered cGAS/AIM2 pathways. *Radiat Med Prot.* 3, 47-55 (2022).
- [62] Liu, J., Zhou, J., Luan, Y., Li, X., Meng, X., Liao, W., Tang, J., Wang, Z.: cGAS-STING, inflammasomes and pyroptosis: an overview of crosstalk mechanism of activation and regulation. *Cell Communication and Signaling.* 22, 22 (2024).