Research Article

Integrating Radioprotective Agents into Post-Mastectomy Radiotherapy: Optimization of Reconstructive Outcomes in Breast Cancer

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Abstract

Surgical intervention utilizing various approaches is a cornerstone in the management of breast cancer. The surgical approaches include lumpectomy, mastectomy, axillary lymph node dissection, and primary or delayed reconstruction. Post-mastectomy radiotherapy is frequently recommended in cases of advanced tumors and extensive lymph node involvement. However, there are several adverse effects of radiotherapy. In this article, we critically reviewed the various complications. Additionally, we discussed the biological basis of radiation-induced tissue damage, the impact of implant-based and autologous tissue reconstruction, and the functional and aesthetic results of the reconstruction. Indeed, several radioprotective agents can attenuate the adverse effects of post-mastectomy radiotherapy while sustaining oncologic efficacy. Radioprotective agents, including free radical scavengers and antioxidants, offer promising strategies to protect tissues from the oxidative stress and inflammation induced by radiotherapy. The role of several radioprotective agents, including amifostine, N-acetylcysteine, tempol, manganese superoxide dismutase (MnSOD) plasmid liposomes, vitamin E, and beta-carotene has been analyzed with a focus on their logistical applications in breast reconstruction. Despite several challenges, the integration of radioprotective agents into post-mastectomy radiotherapy protocols offers significant potential to improve reconstructive outcomes. Development of novel radioprotective agents with improved selectivity and fewer side effects and large-scale clinical trials in diverse group of patients are warranted to determine long-term safety and efficacy.

Introduction

Breast cancer remains a predominant cause of morbidity and mortality among women today [1]. With over 2.3 million new cases and 660,000 deaths globally in 2022 alone, this disease presents an ongoing burden to individual patients, families, and healthcare systems worldwide [2]. The distribution of this burden is not proportional, however, as less developed countries consistently face much higher mortality rates, largely due to insufficient screening protocols, limited access to diagnostic centers for early detection, and lower healthcare standards altogether [3,4]. Although substantial progress has been made over the years, particularly with the advancement of screening

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mammography, targeted therapies, and reconstructive surgical techniques, these persistent disparities underscore the urgent need for innovative strategies to address the challenges of breast cancer across diverse global contexts [5].

The treatment of breast cancer is inherently multidisciplinary, encompassing a wide array of modalities designed to address both localized and systemic disease [6–8]. Surgical intervention is a cornerstone of treatment, with various approaches including breast-conserving surgery (lumpectomy), mastectomy, axillary lymph node dissection, and primary or delayed reconstruction [9,10]. The choice of surgical strategy is often guided by tumor characteristics and patient preferences [10]. Concurrently, adjuvant therapies such as radiotherapy, chemotherapy, and hormone therapy are essential in reducing the risk of recurrence and improving oncologic outcomes [11,12].

Radiotherapy, in particular, plays a pivotal role in treatment for patients undergoing breast-conserving surgery, or those at high risk of recurrence following mastectomy [13]. In such cases, post-mastectomy radiotherapy (PMRT) is frequently recommended due to the presence of advanced tumors and extensive lymph node involvement [14,15]. The primary objective of PMRT is to eradicate any residual microscopic disease within the chest wall and adjacent tissues, thereby significantly decreasing the likelihood of locoregional recurrence [16–18]. Evidence supporting the efficacy of PMRT is robust, with numerous studies demonstrating its ability to improve overall survival rates in selected patient populations [17,19]. However, the therapeutic benefits of PMRT are offset by its tendency to adversely affect the surrounding normal tissues, notably those involved in breast reconstruction [20].

Radiotherapy works by damaging the DNA of rapidly dividing cells. Although this mechanism is effective against cancer cells, it can negatively affect healthy cells as well [21]. In the context of breast reconstruction, radiotherapy can induce a variety of complications, which will be discussed in this review. Moreover, as a result of these complications, the functional and aesthetic results of the reconstruction may be compromised, necessitating additional surgical interventions to address these complications [22]. For instance, radiation-induced fibrosis can lead to an irreversible stiffening and hardening of connective tissue, causing a decrease in size and greater distortion of the reconstructed breast [23,24]. Similarly, capsular contracture, characterized by the formation of a thickened capsule around a breast implant, can cause immense pain and deformity [25].

The detrimental impact of radiotherapy on reconstructive outcomes highlights the need for strategies that can mitigate its adverse effects, whilst still preserving its oncologic efficacy. This necessity drives the exploration of radioprotective agents: substances that can protect normal tissues from the harmful,

oxidative effects of radiation [26,27]. These agents hold the potential to enhance both functional and surgical outcomes of breast reconstruction, as they can minimize the incidence of complications [28]. Subsequent investigation and integration of these agents into clinical practice holds promise not only for improving surgical outcomes, but also the overall quality of life for breast cancer survivors, a critical focus in modern oncologic care. Given these considerations, this novel review aims to evaluate the integration of radioprotective agents into post-mastectomy radiotherapy protocols, focusing on their mechanisms and potential to optimize reconstructive outcomes. The biological underpinnings of radiation-induced damage, the differential impact on implant-based versus autologous reconstructions, and the clinical implications for functional and aesthetic results will be explored. Through a comprehensive analysis, the review seeks to contribute to the advancement of breast cancer treatment, particularly in the context of post-mastectomy radiotherapy and reconstruction, an area yet to be thoroughly explored by existing literature.

Biological Basis of Radiation-Induced Tissue Damage

The effectiveness of radiotherapy in treating breast cancer stems from its ability to induce DNA damage in rapidly proliferating cancer cells, primarily through the infliction of double-stranded breaks (DSBs) in DNA [16, 29]. This lethal mechanism is central to the cytotoxic effects of radiotherapy, leading to cell death if not sufficiently repaired [29,30]. Moreover, the cytotoxicity of radiotherapy is driven by direct and indirect pathways, as illustrated in Figure 1. Both can inadvertently damage the DNA of normal cells in the surrounding tissue and cause significant side effects, such as chromosomal aberrations and an increased risk for cardiac and pulmonary toxicity, and secondary malignancies [31,32].

In the direct mechanism, ionizing radiation interacts with the DNA molecules directly, breaking the phosphate backbone and creating DSBs [31]. For cancer cells, this kind of damage is particularly difficult to repair, with defects present in DNA damage response (DDR) pathways [33]. This commonly leads to cell death either through apoptosis or mitotic catastrophe, a process whereby cells fail to undergo typical chromosomal segregation and division [34,35]. While normal cells in the irradiated area can also suffer from DSBs, they can more readily attempt to repair the damage through various mechanisms, such as single-strand alignment, non-homologous end joining, and conservative homologous recombination [36]. Nevertheless, they remain highly vulnerable, as this damage can result in cell death and, in some cases, new malignancies due to improper repair [37].

The indirect mechanism involves the ionization of water molecules within the cell, producing reactive oxygen species (ROS), including hydroxyl radical, superoxide, and hydrogen peroxide [35,38]. These ROS overwhelm the cell's natural

antioxidant defenses and induce oxidative stress by attacking cellular components like lipids, proteins, and nucleic acids [39,40]. In cancer cells, such oxidative damage contributes to the formation of single-strand breaks (SSBs) and DSBs, driving cell death. In normal cells, however, the oxidative stress can also lead to chronic inflammation and tissue alterations, perpetuating a cycle of damage that extends beyond the initial exposure to radiation and potentially compromising reconstructive success [41].
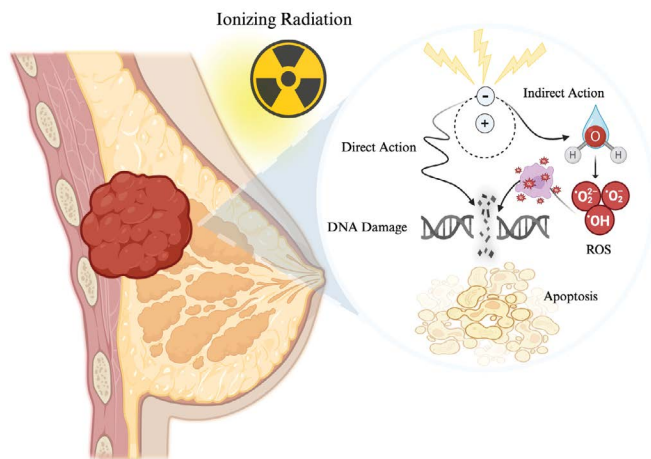

Figure 1: Radiotherapy-induced cytotoxicity. Ionizing radiation works through both direct and indirect mechanisms. Directly, radiation inflicts double-stranded DNA breaks, leading to cellular apoptosis. Indirectly, ionizing radiation generates reactive oxygen species (ROS) through water molecule ionization, which further damages cellular components, including DNA. Both pathways contribute to the cytotoxic effects of radiotherapy on cancer cells but also harm surrounding healthy tissues, increasing the risk of secondary malignancies, fibrosis, and other radiation-related complications. Created with BioRender.com.

The effects of post-mastectomy radiotherapy can manifest both acutely and in the long-term, with profound implications for reconstructive outcomes. Acute effects typically include fatigue, sore throat, and radiation dermatitis [16,42]. Radiation dermatitis is experienced by as many as 95% of patients within days to weeks of receiving radiotherapy, characterized by symptoms such as skin erythema, dryness, rash, hyperpigmentation, and moist desquamation arising from the immediate inflammatory response to cellular damage [43]. While these effects typically resolve within weeks, they set the stage for more severe, long-term complications that may not emerge until months, or even years after radiotherapy and reconstruction, including fibrosis, fat necrosis, tissue atrophy, and lymphedema [44–46].

Fibrosis, one of the most debilitating delayed effects, results from a complex cascade of cellular and molecular events that transform acute injury into chronic tissue scarring (Figure 2). The pathogenesis of radiation-induced fibrosis progresses through three stages. First, the inflammatory stage occurs when ionizing radiation triggers the release of pro-inflammatory cytokines like TNF-α, IL-1, and IL-6, which further promote ROS generation [47-49]. In the fibrotic stage, fibroblasts are activated and recruited by cytokines such as PDGF and TGF-β, leading to their differentiation into myofibroblasts and the excessive production of extracellular matrix (ECM) components like collagen. Finally, the fibro-atrophic stage is marked by tissue thickening, microvascular damage, and ischemia, contributing to tissue necrosis and atrophy. Another significant long-term effect of radiotherapy, fat necrosis, involves the death of adipose tissue [50,51]. As will be discussed, this is particularly relevant for autologous tissue reconstruction, where the tissue may have a compromised blood supply [52]. Moreover, fat necrosis not only affects the aesthetic outcome of breast reconstruction, but can also necessitate additional surgical interventions to remove necrotic tissue [50].

Given the severity of radiation-induced fibrosis and fat necrosis, therapeutic strategies that target the underlying pathologies of radiation-induced complications are critical for improving patient outcomes. Effective strategies could focus on inhibiting TGF-β signaling, neutralizing ROS, and restoring overall vascular integrity. In this context, radioprotective agents emerge as a promising option. However, before delving into an overview of prospective agents, it is important to first examine the impact of radiotherapy on different reconstructive techniques. This understanding will serve as a foundation for then discussing how radioprotective agents can be integrated into PMRT protocols to optimize surgical results.

Impact on Reconstructive Techniques

Although post-mastectomy radiotherapy (PMRT) is integral in reducing locoregional recurrence in breast cancer patients, it can significantly affect functional and aesthetic outcomes after reconstruction. This impact varies, however, based on the type of reconstruction (implant-based or autologous), as well as the timing of reconstruction (immediate or delayed).

Implant-based reconstruction is often favored for its shorter recovery period and the absence of donor-site morbidity that can result from an autologous tissue transfer. Nevertheless, the interaction between PMRT and implant-based reconstruction can introduce various complications. Capsular contracture, a condition where a fibrous capsule forms and tightens around the implant, is one of such complications commonly associated with PMRT. This tightening can lead to pain, distortion of breast shape, and additional corrective surgeries [53]. Furthermore, current literature indicates that patients who undergo both PMRT and implant-based reconstruction are at a markedly higher risk of developing capsular contracture, experiencing reconstructive failure, and being less satisfied with the cosmetic outcome, regardless
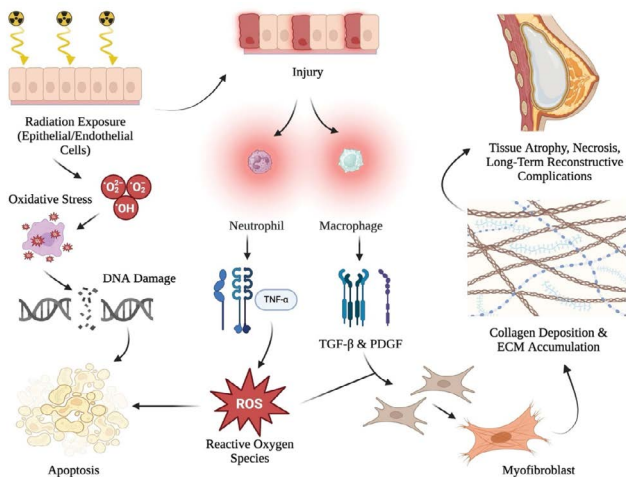
Figure 2: A comprehensive overview of the pathogenesis of radiation-induced tissue injury and fibrosis. Radiation exposure to epithelial and endothelial cells triggers oxidative stress, resulting in DNA damage and the initiation of apoptosis. This injury releases chemokines that recruit neutrophils and macrophages to the affected tissue, which subsequently release pro-inflammatory cytokines such as TNF-α, as well as growth factors like TGF-β and PDGF. These factors contribute to the excessive formation of reactive oxygen species (ROS), which further exacerbates tissue damage and cell death. Over time, fibroblasts differentiate into myofibroblasts, leading to collagen deposition and accumulation in the extracellular matrix (ECM). These changes, characterized by fibrosis, result in tissue stiffness, atrophy, necrosis, and long-term reconstructive complications such as capsular contracture, breast asymmetry, and compromised aesthetic outcomes. Created with BioRender.com.

of the timing of the procedure relative to radiotherapy [54–57]. Additionally, PMRT can lead to numerous other complications that impact the outcomes of implant-based reconstruction. Radiotherapy induces acute toxicity, which increases the risk of wound complications such as infection, dehiscence, seroma, and delayed healing [24,58]. These skin changes are particularly problematic in prepectoral implant-based breast reconstruction, where the implant is placed directly beneath the skin without vascularized muscle coverage. Moreover, as described previously and illustrated in Figure 2, PMRT causes a chronic inflammatory response in irradiated tissue, leading to the deposition of excess collagen and subsequent fibrosis. This process can stiffen the skin and subcutaneous tissues surrounding the implant, reducing their elasticity and pliability. The result is a firmer, less natural breast contour, increased asymmetry, and a higher likelihood of implant malposition [59,60]. These fibrotic changes detract from the overall aesthetic outcome and patient satisfaction. The functional implications could also involve restricted movement and chronic discomfort, which can significantly impact daily activities and well-being. Interestingly, the addition of fat grafting to traditional implant-based reconstruction has shown potential in mitigating some of these complications, offering a way to improve outcomes

[60]. Another common strategy to reduce complications is a two-stage approach involving tissue expanders followed by permanent implants. Tissue expanders are initially placed beneath the skin to gradually stretch the tissue, and once PMRT is complete, they are replaced with permanent implants [61]. This strategy allows the tissue to recover from radiation before final reconstruction, potentially lowering the risk of capsular contracture and improving overall aesthetic outcomes. However, these outcomes are influenced by the specific timing of expander-implant exchange [62].

Autologous tissue reconstruction, on the other hand, involves using the patient's own tissue, often retrieved from the back, abdomen, buttock, or thigh, to reconstruct the breast. This technique decreases the rate of complications, such as capsular contracture and mastectomy skin flap necrosis, relative to implant-based [55]. Consequently, autologous reconstruction remains the preferred choice for patients with previously irradiated chests, or those planning to undergo radiotherapy [63–65]. Nonetheless, this approach still carries its own set of flaws. Fat necrosis, for instance, is a common complication in the context of autologous reconstruction [66,67]. This occurs when irradiated adipose tissue undergoes ischemia and subsequent cell death, forming firm, painful masses that can compromise the aesthetic and functional outcomes of the reconstruction. Radiation can also impair the microvascular networks within the transferred tissue, increasing the risk of flap loss, or vascular thrombosis [68,69]. This is particularly concerning when autologous reconstruction is performed immediately after mastectomy, as the newly transferred tissue is highly susceptible to the damaging effects of radiation. Studies have consistently shown that autologous reconstructions performed after PMRT, specifically within an interval of about 12 months after radiotherapy, tend to have better outcomes, as the tissue is not exposed to radiation while healing from the reconstructive procedure [70]. However, even in delayed reconstructions, the irradiated chest wall tissue can present challenges, including intraoperative vascular complications and impaired wound healing [69].

The timing of reconstruction, whether immediate or delayed, plays a critical role in determining the success of reconstruction. Numerous studies note the immense psychosocial benefit that immediate reconstruction can offer to patients [71–74]. Indeed, the immediate reconstruction, performed concurrently with mastectomy, exposes the newly reconstructed tissue to the effects of radiation, which can exacerbate complications such as capsular contracture in implants and fat necrosis. Delayed reconstruction, performed after the completion of radiotherapy, allows the tissues to recover from radiation-induced damage before undergoing the stress of reconstruction. This approach may significantly reduce the risk of complications [75]. Nevertheless, irradiated tissue can still present challenges such as altered vascularity,

increased fibrosis, and reduced elasticity, making the surgical procedure more complex.

Ultimately, the choice of reconstruction technique and timing must be carefully accounted for, considering the patient's oncologic status, the likelihood of requiring PMRT, and the potential impact on functional and aesthetic outcomes. A multidisciplinary approach involving oncologists, reconstructive surgeons, and radiation therapists is essential to optimize patient care and outcomes. As will be discussed in the next portion of this review, if the deleterious effects of radiotherapy can be minimized or even eliminated altogether, the potential for enhancing reconstructive outcomes and quality of life for breast cancer survivors becomes exponentially greater.

Radioprotective Agents: An Overview

The adverse effects of ionizing radiation can be mitigated by several pharmacological agents. These agents are in general classified according to the timing of administration and differential biological responses. Three major classes of the modifiers of ionizing radiation include radiosensitizers, radiomitigators, and radioprotectors. Radiosensitizing agents are usually administered during radiotherapy to maximize its killing effect on tumor cells by accelerating DNA damage. Radiomitigators are administered in parallel to radiation exposure or post-radiation to attenuate the adverse effects. Radioprotective agents are garnering attention for their potential to mitigate the adverse effects of post-mastectomy radiotherapy (PMRT), whilst sustaining and enhancing oncologic efficacy.

In the following section, we will focus on radioprotective agents since these agents are crucial in the context of breast reconstruction, as radiation-induced complications can impair both functional and aesthetic outcomes. Radioprotective agents induce protective and beneficial effects via several mechanisms, including free radical scavengers, antioxidants, immunomodulation, anti-inflammatory, anti-fibrotic, anti-proliferative, anti-angiogenesis, prevention of DNA damage and enhancing DNA repair, decrease lipid peroxidation (Figure 3). Thus, radioprotective agents offer promising strategies to protect tissues from the adverse effects of ionizing radiation during radiotherapy (Figure 3).

Indeed, many radioprotectors have been reported in the literature. These include natural products such as flavonoid and non-flavonoid polyphenols, polysaccharides, synthetic molecules, DNA-binding agents, hormones, cytokines, nitroxides such as tempol, immune modulators, autophagy inhibitors, vitamins, metformin, inhibitors of poly-(adenosine diphosphate-ribose)-polymerase (PARP), and others. The goal is to use an effective radioprotector with minimal adverse effects of its own or the ionizing radiation to normal tissue and enhance efficacy of the radiotherapy in the management
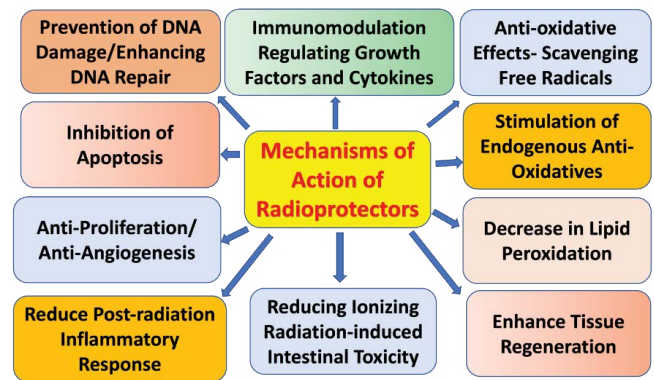

Figure 3: Schematic diagram showing the potential mechanisms of action of radioprotectors to mitigate adverse effects of ionizing radiation and enhance efficacy of radiotherapy.

of breast cancer. Accordingly, in the following section we discussed the role of selected radioprotective agents, such as amifostine, N-acetylcysteine (NAC), tempol, manganese superoxide dismutase (MnSOD) plasmid liposomes, vitamin E, and beta-carotene, with a focus on their logistical applications in breast reconstruction.

Amifostine

Amifostine is among the most extensively researched radioprotective agents, primarily functioning as a prophylactic free radical scavenger which neutralizes the reactive oxygen species (ROS) generated during radiotherapy. Its selective accumulation in normal tissues is facilitated by its uptake through membrane-bound alkaline phosphatase, predominantly in healthy cells (Figure 4) [76,77]. Due to a deficiency in such enzymes, the uptake of amifostine by tumor cells is extremely limited. This selectivity is critical, allowing amifostine to significantly reduce radiation-induced complications, particularly those affecting the skin and soft tissues, without compromising oncologic outcomes [78]. In breast reconstruction, where post-mastectomy radiotherapy (PMRT) often results in complications such as fibrosis, capsular contracture, and impaired wound healing, amifostine presents a promising adjunct to mitigate these effects. Although its oncologic safety in breast cancer has been established in vitro, further clinical trials and investigation in vivo are warranted to solidify its role in optimizing outcomes in breast reconstruction after radiotherapy [28].

N-Acetylcysteine

N-Acetylcysteine (NAC) is a free radical scavenger known for its ability to replenish intracellular levels of glutathione, one of the most powerful endogenous antioxidants, and enhance the neutralization of oxidative stress in the cell [79]. NAC effectively decreases ROS production and inhibits ROS-mediated signaling, which contribute to cancerous cell survival and metastasis in breast cancer [26,27]. Additionally, several studies involving
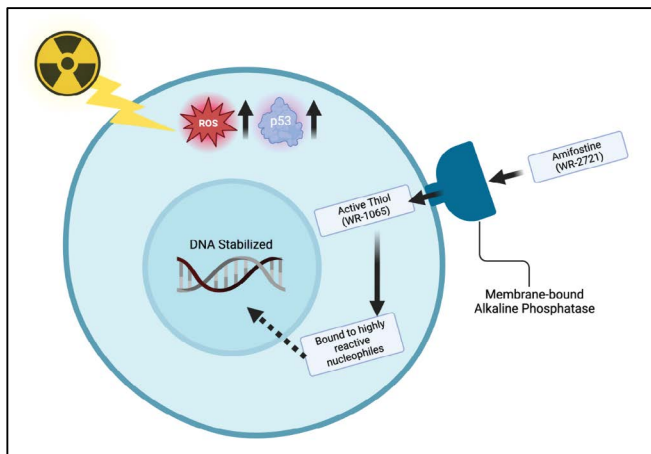
Figure 4: The mechanism of action of amifostine, a radioprotective agent. After administration, amifostine is converted into its active thiol metabolite through dephosphorylation by membrane-bound alkaline phosphatase, which is predominantly found in healthy tissues. This active form binds to highly reactive nucleophiles, stabilizing DNA and mitigating radiation-induced damage. By scavenging reactive oxygen species (ROS) and increasing p53 levels, amifostine protects normal tissues from apoptosis and other radiation-induced effects, while its uptake in tumor cells is limited. Created with BioRender.com.

in-vitro assays and animal models have shown that NAC bears the potential to protect against a number of radiation-induced injuries, including radiation dermatitis, reduced skin elasticity, and impaired wound healing [80-83]. In the context of breast reconstruction, NAC could be particularly valuable in autologous tissue reconstructions where radiation often impairs tissue perfusion, increasing the risk of fat necrosis. By improving tissue oxygenation and reducing fibrosis, NAC can help maintain the pliability and appearance of the reconstructed breast, enhancing both functional and aesthetic outcomes. Furthermore, NAC may aid in preventing capsular contracture in implant-based reconstructions by reducing inflammatory cytokine production and collagen deposition [84].

Tempol

Tempol is a free radical nitroxide that acts as a potent ROS scavenger and antioxidant, neutralizing superoxide radicals and protecting tissues from oxidative stress [85]. Tempol has been studied extensively, demonstrating efficacy in reducing radiation-induced skin toxicity and fibrosis [86,87]. Such complications are common in patients undergoing PMRT and can significantly compromise breast reconstruction outcomes. In implant-based approaches, where the implant is placed pre-pectorally without muscle coverage, the skin and subcutaneous tissues are more vulnerable to radiation damage. The ability of tempol to reduce oxidative damage may help preserve skin elasticity and vascular integrity, reducing complications like skin necrosis, wound dehiscence,

and implant exposure. Given these benefits, tempol could improve both the functional and aesthetic results of breast reconstruction by minimizing radiation-induced tissue damage.

Manganese Superoxide Dismutase Plasmid Liposomes

Manganese superoxide dismutase (MnSOD) plasmid liposomes represent a gene therapy-based approach to radioprotection. MnSOD is a mitochondrial enzyme that converts superoxide radicals into less harmful molecules like hydrogen peroxide and oxygen, thus protecting tissues from oxidative stress [88]. By enhancing the natural endogenous antioxidant defense, MnSOD has been shown to reduce radiation-induced fibrosis and skin damage, protecting microvascular integrity in normal tissues [89-91]. In breast reconstruction, MnSOD plasmid liposomes may be especially beneficial in autologous tissue reconstructions, where flap viability is closely tied to the integrity of the microvascular networks. As mentioned earlier, radiation-induced microvascular damage can result in ischemia, fat necrosis, and flap failure. The use of MnSOD could help prevent these complications, improving flap survival and reducing the need for revision surgeries. By protecting the vascular system, MnSOD also holds promise in enhancing the cosmetic outcomes of autologous reconstructions.

Glutamine

Glutamine is an abundant amino acid that plays a critical role in preventing free radical damage and maintaining tissue integrity. In radiotherapy, glutamine supplementation has been studied for its potential to reduce radiation-induced mucositis and enhance recovery in irradiated tissues [92]. With breast reconstruction, glutamine's ability to support tissue repair and reduce inflammation could help mitigate complications such as necrosis and poor wound healing, particularly in irradiated tissue flaps [93,94]. Furthermore, this antioxidant could contribute to faster healing and reduced fibrosis in implant-based reconstruction, helping to maintain the aesthetic contour of the breast. In autologous reconstructions, it may improve flap survival by promoting microvascular recovery and reducing ischemic injury.

Pentoxifylline

Pentoxifylline (PTX) is a vasodilator with anti-inflammatory properties that has been used to reverse established radiation-induced fibrosis when combined with vitamin E [95-97]. By enhancing blood flow and reducing collagen deposition and inflammation, PTX could potentially improve tissue elasticity and the incidence of capsular contracture in implant-based reconstructions [98,99]. In autologous reconstructions, PTX may help prevent fat necrosis and improve flap viability by promoting microvascular integrity and reducing ischemic injury.

Vitamin E

Vitamin E is a powerful antioxidant that protects cell membranes from radiation-induced oxidative damage [100]. Its radioprotective effects have been studied in the context of skin toxicity, and it has been shown to reduce the severity of radiation dermatitis and fibrosis [13,101]. In breast reconstruction, vitamin E may help preserve the softness and elasticity of irradiated tissues, reducing the risk of capsular contracture and improving overall aesthetic outcomes. Moreover, when combined with PTX, vitamin E has been shown to reverse established fibrosis, making it a valuable agent in managing radiation-induced complications in breast reconstruction [95].

Integration of Radioprotective Agents into Clinical Practice

The integration of radioprotective agents into post-mastectomy radiotherapy (PMRT) protocols presents an opportunity to critically advance and optimize reconstructive outcomes, with the potential to simultaneously reduce complications and preserve oncologic efficacy. Although there are many others that have been investigated, radioprotective agents such as amifostine, N-acetylcysteine, tempol, MnSOD plasmid liposomes, vitamin E, and glutamine offer promising strategies to mitigate the damage caused by PMRT, due to their respective mechanisms of action. However, successfully integrating these agents into clinical practice involves addressing key factors such as optimal timing, dosage, patient selection, and potential combination therapies.

Optimal Timing and Dosage

The efficacy of radioprotective agents is highly dependent on their timing and dosage. Agents like amifostine exhibit peak effectiveness when administered prophylactically before radiation exposure, allowing for selective accumulation in normal tissues and the neutralization of reactive oxygen species (ROS) before significant damage occurs [28]. In implant-based reconstructions specifically, the strategic use of radioprotective agents, either before or after shortly after radiation, can help reduce associated complications [102]. Evaluating the dose reduction factor, which quantifies the effectiveness of a given radioprotector, ranges from 40 to 200 rads/min [103]. Nevertheless, the optimal dosage for each agent remains to be fully defined, necessitating careful consideration of patient-specific factors such as radiation dose, tissue characteristics, and underlying comorbidities, to inform clinical decisions regarding the most appropriate dosage and timing [104].

Patient Selection Criteria

Patient selection is critical to the effective use of radioprotective agents, as those at the highest risk for radiation-induced complications like capsular contracture, fat necrosis, or impaired wound healing, are prime candidates to receive such therapies. Individuals with poor skin elasticity, pre-existing fibrosis, or those undergoing pre-pectoral implant-based reconstruction, which entails increased tissue vulnerability due to the lack of vascularized muscle coverage, may particularly benefit from agents like N-acetylcysteine and tempol, as they work to mitigate oxidative damage and support tissue integrity. Similarly, in autologous reconstructions, where ischemic injury poses a significant risk for flap failure, agents such as MnSOD plasmid liposomes and glutamine hold promise for enhancing microvascular function and promoting flap survival. By tailoring radioprotective therapies to the specific risks and reconstructive techniques of each patient, clinicians may enhance both functional and aesthetic outcomes, underscoring the importance of individualized treatment planning in post-mastectomy radiotherapy protocols.

Combination Therapies

Combining radioprotective agents with one another, or even various other therapeutic modalities, holds considerable promise in enhancing reconstructive outcomes. For instance, the combination of antioxidants, such as vitamin E and pentoxifylline (PTX), has demonstrated synergistic benefits like the reversal of radiation-induced fibrosis, offering potential solutions for managing capsular contracture and improving tissue elasticity [95]. While these combination therapies appear beneficial, further clinical trials are required to fully understand their safety, efficacy, and appropriate clinical applications in the context of breast reconstruction.

Cost-effectiveness and Ethical Considerations

While radioprotective agents present clear clinical benefits, cost and accessibility must be accounted for before integration into standard practice. Agents, particularly synthetic chemical compounds, are associated with high production and processing costs [105]. This raises concerns about equitable access in resource-limited settings. Moreover, ethical considerations regarding the allocation of these therapies and ensuring that patients with limited financial means still receive high-quality care, are crucial. Policymakers and healthcare providers must thoroughly weigh the long-term benefits of radioprotective agents, such as reduced rates of revision surgery and improved quality of life, against their upfront costs.

Challenges and Future Directions

Despite the potential of radioprotective agents to transform reconstructive outcomes following PMRT, their clinical integration faces several challenges. Foremost among these is the lack of robust, large-scale randomized controlled trials to establish standardized protocols for the timing, dosage,

and combination of these agents. The current literature, while promising, largely consists of preclinical studies and small clinical trials, many of which focus on singular agents. To ensure these therapies become a mainstay in breast reconstruction, future research must focus on large-scale trials that include diverse patient populations to determine long-term safety and efficacy. Another key challenge is the identification of novel radioprotective agents. While some agents have demonstrated effectiveness in reducing radiation-induced damage, there remains a need for newer agents with improved selectivity and fewer side effects. The ongoing development of agents targeting specific molecular pathways, such as inhibitors of TGF-β signaling, could offer more targeted radioprotection, minimizing damage to normal tissues and preserving oncologic efficacy. Investigating the application of radioprotective agents with emerging technologies like proton therapy or advanced imaging-guided radiotherapy presents another area for future research. Furthermore, the successful integration of radioprotective agents into PMRT protocols necessitates a collaborative, multidisciplinary approach involving oncologists, reconstructive surgeons, and rehabilitation specialists. Close coordination among these professionals is crucial to developing individualized treatment plans that incorporate radioprotective agents effectively, while also ensuring that oncologic outcomes are maintained. Multidisciplinary teams can optimize the timing of radiotherapy and surgery, select appropriate radioprotective agents, and adjust dosages based on patient-specific factors. This approach fosters holistic patient care, which is essential for improving both the functional and aesthetic outcomes of breast reconstruction [7]. Finally, the development of personalized treatment approaches is crucial for maximizing the benefits of prospective agents. Given the variability in patient responses to both radiotherapy and radioprotective modalities, personalized medicine offers an opportunity to tailor these therapies to individual needs, considering genetic, environmental, and clinical factors. Future research could even focus on the identification of biomarkers that predict patient response to radioprotective agents, further enabling the development of customized treatment plans that optimize both reconstructive and oncologic outcomes.

To summarize, while the integration of radioprotective agents into PMRT protocols offers significant potential to improve reconstructive outcomes, considerable challenges remain. Addressing these challenges through robust clinical research, novel agent development, multidisciplinary collaboration, and personalized treatment strategies will be crucial to fully realizing the promise of radioprotective agents in breast reconstruction. As the field continues to evolve, the combined efforts of clinicians and scientists will be integral to ensuring that these advances translate into improved outcomes and quality of life for breast cancer survivors.

Key points

- Indeed, post-mastectomy radiotherapy reduces the risk of reoccurrence of breast cancer but may induce adverse effects.

- Radioprotective agents can mitigate the adverse effects of ionizing radiation and improve the outcomes in breast cancer patients, reduce relapse rates, and decrease morbidity and mortality.

- Integration of radioprotective agents into post-mastectomy radiotherapy protocols offers significant potential to improve reconstructive outcomes.

- The characteristics of an ideal radioprotective agent include protective effect before or after radiotherapy with high activity, high selectivity, and low toxic side effects, prevention and/or repair of tissue damage following radiotherapy, and rapid onset with long-half life.

- Radioprotective agents induce protective and beneficial effects via several mechanisms, including free radical scavengers, antioxidants, immunomodulation, anti-inflammatory, anti-fibrotic, anti-proliferative, anti-angiogenesis, prevention of DNA damage and enhancing DNA repair, decrease lipid peroxidation.

- There is a need to identify biomarkers that can predict response to radioprotective agents to optimize both reconstructive and oncologic outcomes and thus enhance the development of customized treatment plans.

- There is a need to develop effective radioprotective agent that can be given orally.

- Well-designed and placebo-controlled clinical trials are warranted to fully understand the safety, efficacy, and clinical application of radioprotective agents in breast reconstruction.

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Consent for publication

All authors have read the manuscript and consented for publication.

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