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Decoding Radiodermatitis in Breast Cancer: From Pathogenesis to Patient Care

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Abstract

Radiodermatitis is a prevalent and debilitating complication endured by breast cancer patients receiving radiotherapy, substantially affecting their quality of life and potentially compromising therapeutic outcomes. This comprehensive review provides an in-depth analysis of radiodermatitis in breast cancer patients, covering its incidence, intricate pathophysiology, and profound implications, as well as exploring contemporary and emerging management and preventative measures. The review illuminates the high prevalence rates and diverse risk factors associated with radiodermatitis, elaborating on the immediate and delayed radiation effects on the skin. The multi-dimensional impacts of radiodermatitis on patients - physical, psychological, and social - are highlighted, as is its potential to disrupt the broader cancer treatment trajectory. We delve into existing and novel management and prevention approaches, emphasizing the variability in evidence supporting their effectiveness and underscoring potential limitations. The review further identifies pressing gaps in current understanding, including the need for more precise and universally accepted guidelines, enhanced comprehension of factors predisposing to radiodermatitis, and robust, high-quality trials evaluating novel preventative strategies. Addressing these identified shortcomings promises to advance patient care and therapeutic outcomes for breast cancer patients embarking on radiotherapy.

Keywords: Radiodermatitis, Breast Cancer, Radiotherapy, Management Strategies

Full-length article **Corresponding Author*, e-mail: *rhandykarafl@fk.unbrah.ac.id*

1. Introduction

Dental Breast cancer remains a predominant health concern, being one of the most frequently diagnosed malignancies in women globally. Characterized by its complex and heterogeneous nature, it manifests in various subtypes, each having unique molecular attributes, prognosis, and treatment responses, which necessitate individualized therapeutic strategies. A multi-modal approach, often combining surgery, chemotherapy, hormone therapy, targeted therapy, and radiotherapy, has been the cornerstone in managing breast cancer effectively [1]. Radiotherapy, particularly, plays a pivotal role as an adjuvant treatment post-surgery to minimize the risk of local recurrence by targeting residual malignant cells, consequently enhancing survival rates [2]. Despite its benefits, radiotherapy can induce a range of side effects, significantly affecting patients' quality of life. Radiodermatitis, also known as radiation dermatitis or radiation-induced skin injury, stands as a prominent adverse effect, marked by an inflammatory response in the skin due to radiation exposure [3].

Radiodermatitis encompasses a variety of skin alterations, ranging from mild conditions like erythema and dry desquamation to more severe manifestations, including moist desquamation, skin necrosis, or ulceration. Given the close proximity of the skin to the treatment site in breast cancer cases, patients are notably susceptible to radiodermatitis, with the irradiation invariably involving the overlying skin and resulting in a significant incidence of skin reactions [4]. The prevalence of radiodermatitis varies considerably, attributed to diverse factors such as differential assessment methods, treatment protocols, and individual patient characteristics. Mild to moderate forms of radiodermatitis appear to be almost universal among patients undergoing breast cancer radiotherapy, with severe manifestations occurring less frequently but still presenting a significant clinical concern. The incidence of these reactions are around 98% for breast cancer, particularly severe forms like moist desquamation, has been reported to reach up to 30-40% in some studies [5].

Understanding and addressing this prevalent and distressing side effect is paramount, as it can cause substantial discomfort, alter treatment schedules, and impact the general well-being of patients. However, the management and prevention strategies for radiodermatitis are yet to be standardized, and practices vary considerably across settings. This narrative review endeavors to provide a nuanced understanding of radiodermatitis in the context of breast cancer radiotherapy, examining its incidence, dissecting current management approaches, and scrutinizing preventive measures implemented to reduce its occurrence. Moreover, this review aims to spotlight gaps in existing literature and pave the way for future research directions, fostering enhanced management and understanding of radiodermatitis in breast cancer patients subjected to radiotherapy.

2. Factors Influencing the Risk of Radiodermatitis in Breast Cancer Patients

Radiodermatitis is not an indiscriminate side effect; rather, its development and severity are influenced by a multitude of patient-specific and treatment-related factors. Patient-specific factors are inherent characteristics of the individual that can predispose them to more severe radiation-induced skin reactions. Larger breast size, for instance, has been repeatedly identified as a risk factor for severe radiodermatitis, with a higher incidence of moist desquamation observed in these patients. This is hypothesized to be due to increased skin-on-skin contact and moisture accumulation in larger breasts, which can exacerbate radiation-induced skin damage [6]. Other patient-related factors associated with an increased risk of radiodermatitis include smoking and a higher body mass index (BMI). Smoking impairs tissue oxygenation and wound healing, thereby potentially exacerbating radiation-induced skin damage. Similarly, a higher BMI is thought to increase the risk of radiodermatitis through mechanisms such as increased skin folding and friction, reduced tissue oxygenation, and a pro-inflammatory state [7]. Treatment-related factors also play a significant role in the development of radiodermatitis. The total radiation dose, dose per fraction, and the use of bolus material are key variables that can influence the incidence and severity of radiodermatitis. High-dose per fraction regimens, also known as hypo fractionated regimens, have been associated with a higher risk of skin reactions compared to conventional fractionation, though the clinical significance of this difference is still a subject of ongoing research. The use of bolus, a material placed over the skin to bring the radiation dose closer to the skin surface, can also increase the severity of skin reactions [8]. Further, certain concurrent treatments may exacerbate radiodermatitis. For example, chemotherapy, particularly anthracycline-based regimens, when given concurrently with radiotherapy, has been associated with an increased risk of radiodermatitis [9]. Understanding these risk factors is crucial for predicting which patients are at a higher risk of developing severe radiodermatitis and may benefit from proactive management and preventive measures. However, further research is needed to elucidate the complex interplay of these factors and to develop predictive models for individualized risk assessment.

3. Pathophysiology of Radiodermatitis

Radiodermatitis is a complex pathology, springing from both the direct deleterious effects of radiation and a subsequent inflammatory reaction. This chain reaction notably impacts the cellular components within the epidermis, dermis, and vascular system. The radiation therapy process commences with the administration of an initial dose of ionizing radiation, which quickly triggers tissue destruction by generating secondary electrons and reactive oxygen species (ROS). These harmful elements attack cell structures, including cell membranes and DNA, leading to acute radiation impacts. Each subsequent radiation fraction intensifies the recruitment of inflammatory cells, further escalating the damage. Upon radiation exposure, a cascade of effects sets in. Skin pigmentation alterations occur due to melanosome migration. Hair growth is interrupted, and the damage penetrates to the deeper layers of the dermis, even though the uppermost layer of the epidermis remains relatively unharmed. The dermis's impairment disrupts the usual skin cell regeneration process, resulting in initial symptoms such as erythema - a reaction caused by the dilation of dermal vessels and the release of histamine-like substances [10]. As the skin grapples with the escalating damage from intensifying radiotherapy, it attempts to compensate by accelerating the mitotic rate in the basal keratinocyte cell layer, responsible for the constant replenishment of dying cells in the skin's outermost layer, the stratum corneum. The high turnover rate of the epidermis becomes insufficient when radiation-induced cell death surpasses the basal cell's replenishing capacity, compromising the skin's integrity and exacerbating radiodermatitis grades. This rapid generation of new cells overtakes the elimination of old ones, culminating in a thickening of the skin and a scaly appearance, otherwise known as dry desquamation. This condition results from the accumulation of dead cells in the stratum corneum due to inadequate replacement from the basal layer. When radiation doses increase further, the basal layer's recovery capability falters, leading to the secretion of an exudate and resulting in moist desquamation. This severe condition involves the weeping of serous fluid from raw, eroded skin areas, occurring when the cell loss pervades the full thickness of the epidermis [11][12]. These damaging stages undermine the skin's physical barrier and immune functionalities, heightening the risk of infection - particularly in areas of moist desquamation, where the wound healing process can be further complicated by ongoing radiation exposure, the inflammatory environment, and potential vascular supply impairments due to radiation-induced damage to dermis blood vessels [13]. Radiation-induced damage to the vascular endothelium leads to hypoxia and instigates an upregulation of Transforming Growth Factor (TGF)-b, a cytokine instrumental in mediating radiation-induced fibrosis. Fibrosis and tissue hypoxia, in turn, result from vascular injury and lead to the production of additional ROS. Such ROS inflict considerable damage on cellular structures and stimulate the production of inflammatory cytokines in the skin. During radiation treatment, the generation of ROS dramatically amplifies, overwhelming the body's defensive antioxidant system. While radiation-induced inflammation's precise mechanism remains not fully understood, it is known that keratinocytes, fibroblasts, and endothelial cells activate

immune cells in the skin's epidermal and dermal layers, as well as in the bloodstream [14]. This cellular activation sequence incites a cascade of cytokines and chemokines, such as interleukin (IL)-1a, IL-1b, tumor necrosis factor (TNF)-a, IL-6, IL-8, C-C motif chemokine ligand (CCL)-4, C-X-C motif chemokine ligand (CXCL)-10, and CCL2. These factors, in turn, accelerate skin fibrosis, generate matrix metalloproteases that degrade the dermal constituents and the basal cell layer, and influence vascular endothelial cells to upregulate adhesion molecules [15][16]. The long-term effects of radiodermatitis and the development of persistent dermatitis and skin fibrosis are primarily attributable to dermal fibroblasts' activities. TGF-b cytokine is considered a vital factor in this process. Radiation's impact on the coagulation cascade, particularly an associated surge in thrombin-induced TGF-b activation, significantly contributes to chronic damage. After radiation exposure, bone marrow-derived cells (BMDCs), including mesenchymal cells, endothelial progenitor cells, and myelomonocytic cells, play crucial roles in recovery. These cells are attracted to sites of radiation damage due to the chemotactic effects of stromal cell-derived factor (SDF)-1 and CXCR4 overproduction. By releasing angiogenic factors, growth factors, and anti-inflammatory cytokines, these cells promote wound healing and tissue repair. They may also differentiate into various cell types to directly replace damaged cells [17]. However, the process is complex and has the potential for long-term damage. Ionizing radiation can trigger an increase in Thrombin production, initiating a protease-activated receptor (PAR-1)-mediated response, which induces the activation and release of TGF-β1. This, in turn, stimulates Smad3 proteins, promoting fibrotic processes and leading to chronic fibrosis and skin hardening, or dermal atrophy, after radiation therapy. In chronic radiodermatitis, TGF-β1 also amplifies the synthesis and deposition of extracellular matrix (ECM) proteins and reduces ECM degradation, leading to collagen accumulation and fibrosis development. This fibrosis can affect both the epidermal and dermal layers of the skin, causing skin hardening, pigmentation changes, and potentially resulting in the loss of sweat and sebaceous glands [18]. In extreme cases, extensive cell death and tissue damage can lead to skin necrosis or ulceration. This typically happens in areas where the skin is under tension or pressure, and it's more common with higher radiation doses and certain patient-specific factors like poor nutrition and smoking. Overall, radiodermatitis pathogenesis involves a multifaceted interplay of numerous factors and cell types, both immediately after radiation exposure and in the long-term as shown in figure 1. Our understanding of these processes has significantly improved over the years, yet many aspects remain to be fully elucidated. Continued research into this area could lead to more effective prevention and treatment strategies for this common and often debilitating radiation therapy side effect.

4. Impact on Patients

Radiodermatitis, particularly in its severe forms, can have profound implications for breast cancer patients' physical well-being, psychological state, and social interactions.

4.1. Physical Impact

The physical discomfort associated with radiodermatitis is often significant. Early symptoms such as erythema and dry desquamation can cause itching and tenderness, while late effects like moist desquamation, ulceration, and fibrosis can lead to severe pain. These physical symptoms can interfere with patients' daily activities and reduce their overall quality of life. Furthermore, the physical symptoms can disrupt the continuity of the radiotherapy regimen, leading to treatment delays or even premature termination of therapy [19][20].

4.2. Psychological and social Impact

The psychological impact of radiodermatitis should not be underestimated. The visible changes in the skin, combined with the physical discomfort, can lead to distress, anxiety, and depression. Patients may experience fear or apprehension about the progression of their skin reactions and the potential for long-term disfigurement. This can result in a decline in self-esteem and body image, which could further exacerbate feelings of anxiety and depression [21][22]. Radiodermatitis can also impact the social interactions of breast cancer patients. Visible skin changes and physical discomfort may cause patients to withdraw from social activities, leading to feelings of isolation. The need for frequent medical appointments for wound care and treatment adjustments can also place a burden on patients' time and resources, potentially affecting their work or family life. Additionally, the cost of managing and treating radiodermatitis can lead to financial stress, especially for patients without adequate health insurance coverage. This can contribute to the overall social and psychological burden of radiodermatitis [23][24]. In conclusion, radiodermatitis significantly impacts the physical, psychological, and social well-being of breast cancer patients. Comprehensive care strategies that address these different facets of patient well-being are essential for effective management of radiodermatitis.

5. Management Strategies for Radiodermatitis

The management of radiodermatitis employs an integrative approach, encompassing pharmacological and non-pharmacological treatments. The main objectives are to mitigate symptoms, foster healing, and inhibit progression to more severe skin reactions.

5.1. Pharmacological Treatments

Topical corticosteroids often serve as the first-line therapy for radiodermatitis, stemming from their potent anti-inflammatory properties. They are effective in reducing erythema and alleviating discomforting symptoms such as itching and burning sensations. However, while corticosteroids can adeptly manage mild to moderate radiodermatitis, their efficacy for severe cases may be limited. Prolonged usage can also induce skin thinning and other adverse effects [25]. In cases where moist desquamation or skin ulceration has occurred, topical antibiotics are commonly utilized. These antibiotics aid in preventing or treating secondary bacterial infections, thereby supporting wound healing [26]. Recent studies have begun to explore the benefits of non-traditional pharmacological agents.

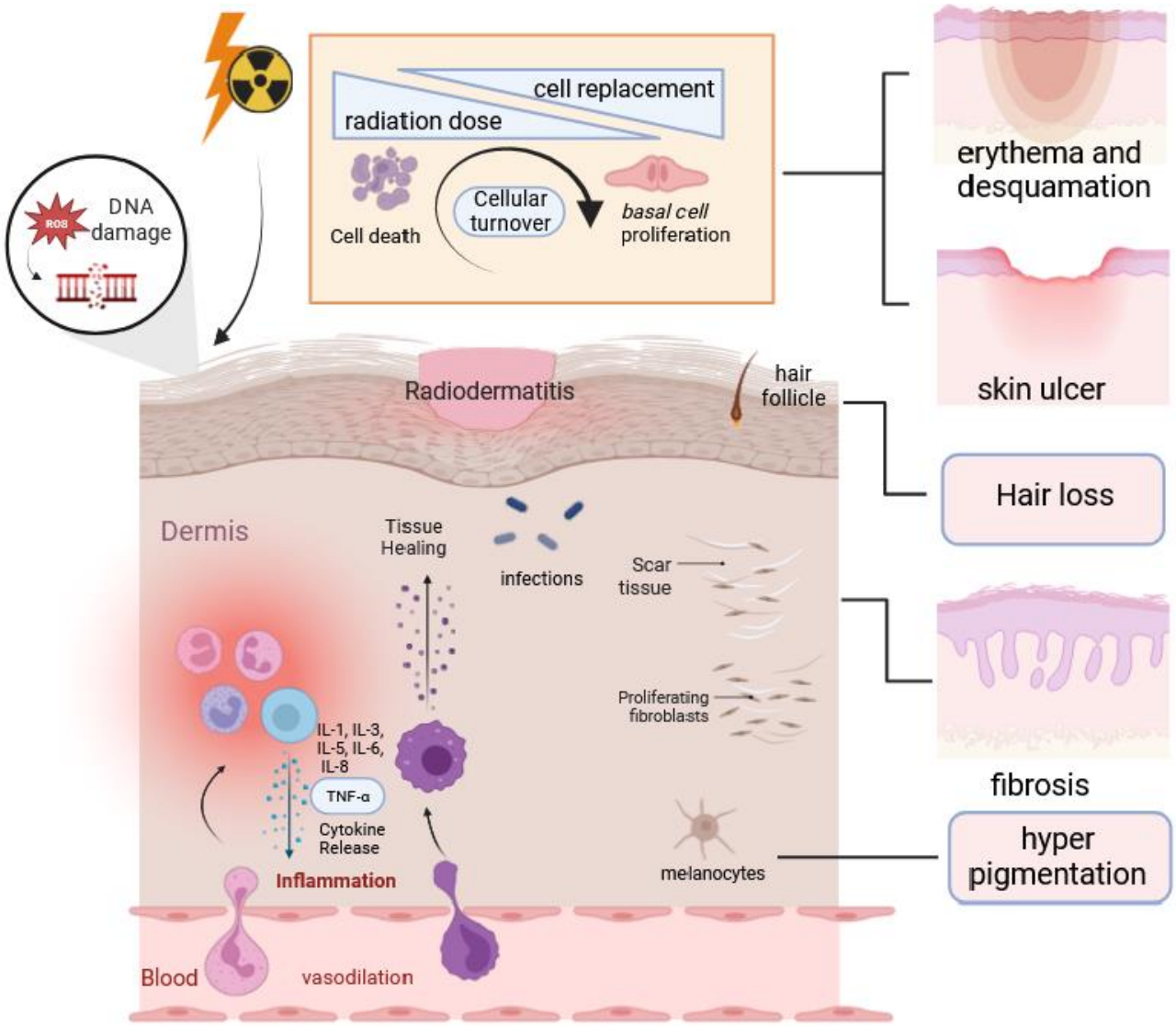

Figure 1. Increasing radiation doses to the skin disrupt cellular turnover, culminating in a series of adverse reactions including erythema, desquamation, and at higher doses, ulceration. This radiation-induced damage triggers a cascade of cytokines and chemokines, initiating a complex process of inflammation and tissue healing, which in turn promotes fibrosis. Furthermore, the recruitment of melanocytes can induce hyperpigmentation. Concurrently, damage to the hair follicles may result in hair loss.

Their research showed Silymarin, an extract from the milk thistle plant, could be beneficial in preventing radiation-induced dermatitis [24]. Novel treatment strategies are also being explored, including the use of skin protectant and flexible wound dressings like Strata XRT for the prevention and treatment of radiation dermatitis [23]. While numerous studies have evaluated these management strategies' effectiveness, the results are mixed. Effectiveness can vary based on the severity and stage of radiodermatitis and individual patient characteristics. It's noteworthy to mention that the prevention and management practices are quite diverse across different regions. These management strategies, though beneficial, are not devoid of potential disadvantages. For instance, extended use of topical corticosteroids may lead to skin thinning, irritation, and increased susceptibility to infections. The misuse of antibiotics, on the other hand, could result in antibiotic resistance [24].

6. Prevention Strategies for Radiodermatitis

Preventing radiodermatitis from occurring in the first place is crucial, as this not only spares patients from unnecessary discomfort but also prevents potential disruptions in the treatment schedule. Prevention strategies can be broadly divided into two categories: skin care practices and prophylactic applications.

6.1. Skin Care Practices

Consistent, gentle skin care is the first line of defense against radiodermatitis. Patients are often advised to wash the irradiated area with lukewarm water and mild, fragrance-free soap, pat the area dry gently rather than rubbing, and avoid any potential irritants, such as perfumes or deodorants. Moreover, patients are advised to protect the irradiated skin from sun exposure, extreme temperatures, and friction from clothing. Maintaining optimal skin hydration is also crucial; however, patients should avoid applying any creams or lotions within two hours before radiation treatment, as this could potentially affect radiation dosage [26].

6.2. Prophylactic Applications

Prophylactic applications of various products have been investigated for their potential to prevent radiodermatitis. For example, topical corticosteroids have been shown to decrease the incidence and severity of radiodermatitis when applied from the onset of radiation therapy [27]. Additionally, some evidence suggests that the use of certain topical agents, such as creams containing hyaluronic acid, can help maintain skin integrity and reduce the risk of radiodermatitis. However, results have been mixed, and further research is needed to confirm these findings [28][29]. While these prevention strategies can potentially reduce the risk of radiodermatitis, they are not always fully effective. Some patients may still develop radiodermatitis despite following all preventive measures. Additionally, the prophylactic use of certain products, like topical corticosteroids, may be associated with side effects, such as skin thinning and irritation. In conclusion, while preventive strategies can potentially reduce the risk and severity of radiodermatitis, more research is needed to establish their effectiveness and to develop more effective prevention strategies.

7. Conclusions

Radiodermatitis continues to pose a significant clinical challenge in managing breast cancer patients undergoing radiotherapy. Despite considerable progress in delineating its incidence, risk factors, and pathophysiology, and efforts in evolving management and prevention strategies, substantial gaps and controversies persist in the field. A glaring issue is the absence of standardized guidelines based on robust evidence to govern the management and prevention of radiodermatitis, with practices diverging considerably at present. Further research is paramount to foster universally accepted protocols that can amplify patient outcomes. Moreover, the underlying reasons dictating the variance in patients' susceptibility to severe radiodermatitis remain partially elusive. Future studies should focus on pinpointing additional risk factors and unraveling the mechanisms governing susceptibility to facilitate more personalized interventions. Though numerous preventative measures have been proposed, their efficacy is yet to be substantiated by consistent evidence. The emphasis should be on conducting high-caliber randomized controlled trials to ascertain the effectiveness and safety of these interventions. Furthermore, the long-term implications of radiodermatitis on patients' quality of life and treatment outcomes are not fully comprehended. Launching longitudinal studies could grant critical insights into these aspects, shaping patient management strategies for the better. Integrating patient-reported outcomes into research endeavors can potentially render a holistic view of radiodermatitis' real-world impact and the efficiency of different management strategies. In summation, although the domain has witnessed considerable advancements, radiodermatitis still harbors numerous unresolved queries. Filling these research voids stands as a promising pathway to augment the management and prevention of radiodermatitis, thereby enhancing the quality of care for breast cancer patients embarking on radiotherapy. Anticipation is high for future research to further refine and revolutionize our approach to this pervasive and consequential complication.

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