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Topical Fibronectin Improves Wound Healing in Postmastectomy Breast Cancer Radiation Therapy : A Review

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ABSTRACT

Breast cancer is the most common cancer among women worldwide. Breast cancer provides an excellent example of how multidisciplinary management has improved patient outcomes. This paper synthesizes the complex and evolving evidence regarding the role of radiation therapy after mastectomy. Although substantial evidence indicates that radiation therapy can reduce the risk of locoregional failure after mastectomy. This therapy is known as PMRT. Postmastectomy radiotherapy (PMRT) is an essential component of combined therapy for early - stage, high - risk breast cancer. Breast reconstruction (BR) is often considered for patients with breast cancer who have undergone mastectomy. There has been a considerable amount of discussion about the optimal approach to combining PMRT with BR in the treatment of breast cancer. PMRT may increase the risk of complications and prevent good aesthetic results after BR, while BR may increase the complexity of PMRT and the radiation dose to surrounding normal tissues. The goal of a PMRT plan is to achieve optimal coverage of the target volume while minimizing the irradiation dose to normal tissues.

The purpose of this review is to give a broad overview and summary of the current topical fibronectin improves wound healing in postmastectomy breast cancer radiation therapy.

In summary, Exogenous fibronectin diminishes wound progression, by increasing angiogenesis & cell proliferation. This suggests that enhances healing by stimulating the appearance of fibroblasts into the wound site and development of granulation tissue. This acceleration of the repair process may have an important application in the healing of skin chronic wounds.

Keywords: Fibronectin, Postmastectomy radiation therapy, Breast reconstruction, Skin ulcer, Breast cancer.

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I. INTRODUCTION

Breast cancer (BC) is the most frequently diagnosed cancer among females and the second leading cause of cancer deaths [1]. Metastasis accounts for the vast majority of patient mortality [2,3]. During disease progression, distinct changes occur in the extracellular matrix (ECM) architecture and biochemical composition, which facilitate primary tumor growth and successful metastasis [3].

Breast cancer screening and improvement of comprehensive treatment have significantly improved the prognosis for breast cancer patients; however, better prognosis would be necessarily relying on further development of comprehensive treatments [4, 5]. In the era of precision medicine, individualized treatment strategies are formulated according to the patient's tumor stage, recurrence risk, and treatment sensitivity [6]. Axillary lymph node status is not only an important reference for accurate staging of breast cancer but also an important index for evaluating prognosis and guiding treatment [4, 7, 8]. And the number of lymph node metastases is closely related to prognosis [7–9].

Radiation therapy is the process of delivering lethal doses of radiation to areas of malignancy to kill cancerous cells. Skin is particularly radiosensitive, and over 95% of patients receiving RT develop moderate to severe skin reactions [10,11].

Radiation therapy has evolved to allow for more specific targeting of cancerous cells and reduction of the "bystander response" in neighbouring healthy tissue [12].

Radiation exposure, the skin typically becomes erythematous and may desquamate or ulcerate. On the molecular level, cytokine cascades and fibro-inflammatory pathways are up-regulated due to radiation which can progress for many years leading to substantial fibrosis, i.e. the hallmark of chronic RT damage [13].

RT can utilized alone or can be combined with other treatment modalities–such as chemotherapy or surgery–to treat primary malignancies as well as metastatic disease [14].

Within hours of radiation, a number of cytokines signaling and inflammatory cascades are initiated. Radiation therapy form ions that pass-through tissues which can directly induce double-stranded breaks in genetic material [15]. Cell death ensues via apoptosis, mitotic cell death, necrosis, and/or senescence including the release of damage-associated molecule pattern (DAMP) molecules [16,17]. Release of DAMPs activates the innate and adaptive immune systems that allows for additional antitumor responses [18,19]. Energy from ionizing radiation also acts on other molecules within cells, such as water, to generate reactive oxygen species (ROS), such as superoxide, hydrogen peroxide, and hydroxyl radical, which indirectly cause further damage of the DNA and other cellular components (e.g. proteins, lipids) [20,21]. Generation of ROS are thought to account for more than 60% of the total radiation induced damage [22,23].

To improve targeting of malignant cells with radiation therapy. Inhibiting additional DNA repair mechanisms, cell cycle checkpoints, and signal transduction pathways [24]. Breast cancer cells with BRCA1 or BRCA2 mutations already have an impaired ability to repair double-stranded breaks in DNA via homologous recombination and rely on other mechanisms of DNA repair, such as base excision repair and single-strand break repair, to survive [24].

Inhibition of alternative survival and signaling pathways would thus render cancer cells more vulnerable to radiation-induced DNA damage while sparing normal cells that retain other mechanisms of repair.

RT to deliver sufficient levels of radiation to induce death of cancer cells, damaging effects on surrounding healthy cells should be minimized. Substantial progress has been made towards this goal, but damage to

healthy soft tissue within the radiation field remains a significant problem. The proliferative nature, high oxygen requirement, and superficial nature of the skin make it the most frequently damaged tissue following RT [26,27]. Collectively, damage to the skin following RT is known as radiodermatitis and is typically categorized into acute and chronic stages (Figure 1).

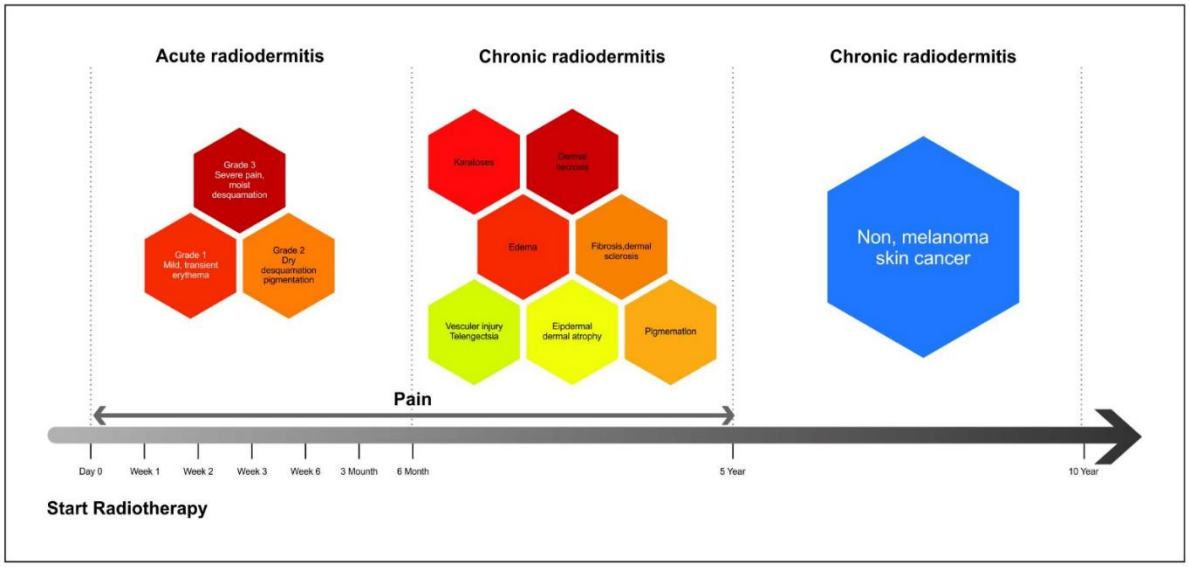


Figure 1. Progression of clinical manifestations and symptoms of RID. Iacovelli NA, Torrente Y, Ciuffreda A, et al. Drugs in Context 2020; 9: 2020-4-7. DOI: 10.7573/dic.2020-4-7

In the early phase following radiation exposure, the skin appears discolored, erythematous, and inflamed. Severely damaged skin may desquamate, atrophy and/or ulcerate [28-30]. The chronic phase of radiation damage is marked by radiation-induced fibrosis–the final common pathology across multiple tissue types.
Chronic radiation-induced fibrosis typically develops within 4 to 12 months after therapy but may continue for many years in a progressive fashion [31]. Cancer cells are also responsible for causing radiodermatitis.
Immediately following exposure there is an inflammatory response, and neutrophils are attracted to the site of irradiation by cytokines that are released by damaged skin and endothelial cells. Upon entry to the irradiated area, neutrophils are stimulated further and release pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6, which perpetuate inflammation and increase formation of ROS. Monocytes and lymphocytes subsequently migrate to irradiated skin. Upon entry into irradiated tissue, monocytes differentiate into macrophages or dendritic cells, and release platelet-derived growth factor (PDGF) which stimulates angiogenesis and the migration of fibroblasts [32]. Finally, macrophages, along with the native endothelial cells, fibroblasts, and epidermal cells, secrete transforming growth factor-beta (TGF-β) [33], a potent pro-fibrotic factor which is elevated in the early phases of radiation damage and heavily implicated in the pathogenesis of RIF. TGF-β binds the TGβRI receptor and thus induces phosphorylation, and activation of the intracellular receptor-associated Smads (R-Smads). Activated R-Smads form heteromeric complexes with a co-Smad (Smad4), translocate to the nucleus, and induce pro-fibrotic gene transcription, either by directly binding DNA or by associating with other transcription factors [34-36].
TGF-β activates a number of pro-fibrotic pathways that drive the pathogenesis of radiodermatitis. Following radiation, TGF-β stimulates the differentiation of fibroblasts into myofibroblasts [37], which in turn secrete excessive amounts of ECM proteins including collagen, fibronectin, and proteoglycans [38]. Increased ECM production is further compounded by impaired matrix degradation. TGF-β decreases the activity of matrix

metalloproteinase (MMP) activity, specifically MMP-2, MMP-9, and MMP-1, within fibroblasts [28,29,39]. Consequently, there is net gain of ECM that amounts to increased tissue stiffness and thickness, characteristic of chronic RIF. TGF-β in radiation also activates the process of epithelial to mesenchymal transition (EMT) and the interferon (IFN)-γ response [40] which can also contribute to soft tissue fibrosis. Chronic activation of many of these fibrotic pathways is thought to persist for years after initial exposure. Indeed, elevated levels of collagen type I, collagen type III, and TGFβ1 are detectable in breast biopsies even 20 years post-radiotherapy[5].

The fibrotic changes in skin are also accompanied by damage to the vasculature. Histologically there is evidence of decreased microvascular network density and alterations to the morphology of blood vessels [41]. Acutely following radiation exposure, in mice model, the vessels become plugged with fibrin and leukocytes, with evidence of endothelial swelling and hyperplasia and perivascular fibrosis [37,42]. These changes decrease blood supply to the tissue and lower oxygen tension, which further stimulates fibrosis by increasing expression of collagen type 1 alpha 1 (COL1A1) [43].

The consequences of RIF are profound, and up to 30% of patients that receive RT to the breast or chest wall experience severe RIF [44-49]. RIF reduces tissue perfusion and further worsens the quality and function of the irradiated skin [41]. Tissue fibrosis can disrupt lymphatic and vascular drainage, which produces hypoxia and predisposes to ulceration and impaired wound healing [50,51]. This often results in severe soft tissue defects that may require coverage with vascularized tissue. As increasing numbers of individuals are surviving cancer, more patients are living with the long-term effects of radiation treatment [53]. Radiation-induced fibrosis is therefore especially undesirable for patients with malignancies where treatment can be curative [54].

Radiotherapy improved the cancer-specific survival in patients with three nodes positive have a higher tumor burden and possibly higher risk of recurrence and metastasis than those of patients with one or two lymph nodes positive[6,23]. It is proven by a series of clinical studies that combined radiotherapy after mastectomy can improve the survival of patients with four or more positive lymph nodes [85-88].

Post-mastectomy radiotherapy (PMRT) could improve prognosis for breast cancer patients with one to three lymph node metastases remains controversial [85, 88-90].

Postmastectomy radiation therapy (PMRT) is recommended for patients with more advanced breast cancer and/or certain high-risk pathologic features.

In select patients, post-mastectomy radiation therapy has been shown to improve local control and overall survival. Locally advanced breast cancer encompasses a heterogeneous group of patients including those with advanced primary tumor size, extensive or widespread nodal disease, and inflammatory breast cancer.

The role of post-mastectomy radiotherapy (PMRT) reduce the risk of locoregional failure (LRF).

In general, postmastectomy radiation therapy is very well tolerated, and patients can continue their normal routine. Postmastectomy radiation therapy does not lead to decreased immunity nor feelings of illness, and patients are not radioactive; therefore, they are safe to be around other people. Complications associated with postmastectomy radiation therapy will be discussed in terms of Intermediate and late.

Post-mastectomy radiation therapy	Time	Complications
Intermediate	Weeks to months	Skin erythema Moist desquamation Hyperpigmentation
Late	Months to years	Chronic wound Radiation induced malignancy

This review paper demonstrates that optimal long-term treatment benefit of high-risk breast cancer can only be achieved if both loco-regional and systemic tumor control are aimed for. Therefore, radiotherapy has an important role in the multidisciplinary treatment of breast cancer. The PMRT treatment is an important technique to reduce the recurrence risk. PMRT is also responsible for deal healing and wound convert into Chronic and is difficult in healing after postmastectomy radiation therapy.
The systemic therapy of breast cancer has also evolved since many of the studies were conducted, raising the issue of how best to incorporate topical application of fibronectin into current clinical practice for skin injury healing.

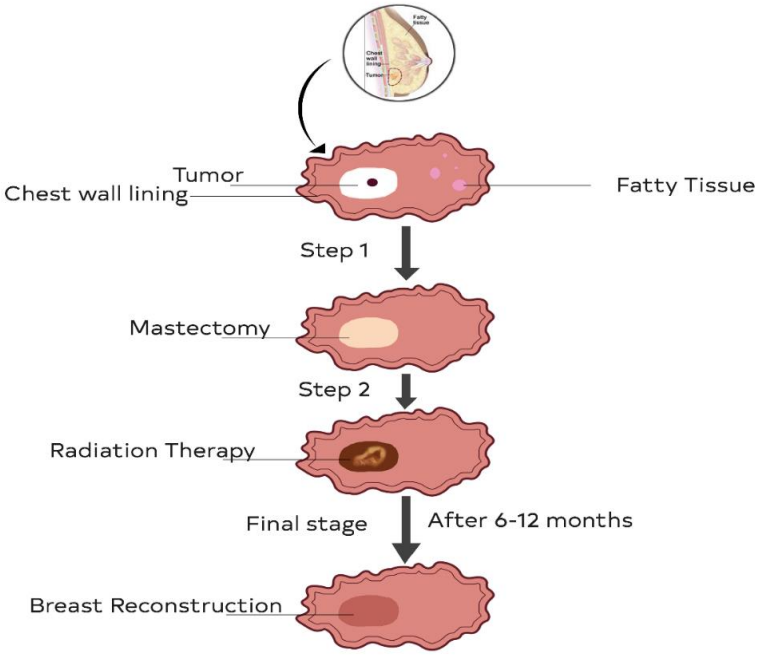
CHANGES DURING POST MASTECTOMY RADIOTHERAPY IN BREAST CANCER PATIENTS

Postmastectomy radiotherapy (PMRT) has been shown to decrease local recurrence and improve survival in women with node-positive breast cancer[1] . It reduces the risk of local recurrence and improves overall survival by 24% in woman[2]. Besides preventing recurrence of breast cancer, PMRT usually causes side effects in the skin. Up to 90% of patients experience acute dose-dependent skin reactions in treated areas, ranging from mild erythema to severe ulcerations[1] . Late possible chronic injury includes skin atrophy, dryness, telangiectasia, dyspigmentation, dyschromia, tissue scaring and fbrosis[3–5]. The chronic changes that lead to radiation induced fibrosis (RIF) can take months to years before full manifestation[6]. It has been speculated that the radiosensitivity of the skin is due to its high proliferative capacity and oxygenation requirements of its basal epidermal cells[7] , potentially secondary to hypovascularity and development of chronic tissue hypoperfusion. An impaired microcirculatory function is further thought to be a potential cause for wound infections and implant extrusion in patients that is breast reconstructed and previously received PMRT. The exact mechanism of radiation-induced injury is however not completely understood. On a molecular level, ionizing radiation (IR) induces several types of cell damage[8] . The resulting cellular death activates the immune system with an additional antitumor response[9,10]. Ionizing radiation generates reactive oxygen species (ROS) in the nucleus which also contributes to cellular damage and death by apoptosis[11,12]. Many patients who have undergone mastectomy with subsequent radiotherapy later desire restoration of the breast. Successful breast reconstruction strongly relies on a functional vascular bed in the reconstructed tissue, both when implants are used and with autologous breast reconstruction. The skin microcirculation has been regarded as a representative vascular bed for the assessment of tissue microvascular function[13]. Measurable effects on skin microcirculation that are associated with PMRT could be a marker for impaired healing properties, and may indicate an increased risk for ensuing tissue morbidity when reconstruction of the breast is done. Assessing the effects of radiation on the skin microcirculation after resection may thus help decide which patients are at risk for complications after specific reconstruction procedures.

Post mastectomy radiotherapy (PMRT) can increase the rate of local control and the survival of patients with locally advanced breast cancer [55]. Therefore, PMRT is often employed for the prevention of local relapse in those who have closed or positive mastectomy margins, or in the case of recurrent breast cancer [56,57].
Prompt breast reconstruction after mastectomy has been demonstrated as an effective approach to achieving satisfactory clinical, aesthetic, and psychological outcomes in patients with breast cancer [58,59].
Breast myotomy is a procedure for filling in the space of a breast flap with a pectoralis major muscle. This method does not require lifting or removing the pectoralis, adjoining muscles, and facial features. This allows

the pectoralis major to remain in an anatomic location, allowing for a more natural look of the chest and less pain after surgery [61-63]. Furthermore, anterior thoracic reconstruction reduces the risk of movement abnormalities, implantation bias and muscular cramps [64]. PMRT has been shown to be of great importance in the management of regional relapse and the improvement of disease-free survival in patients with locally advanced breast cancer [65,66]. In spite of those benefits, PMRT has had a disastrous effect on breast reconstruction. PMRT decreases the volume and quality of microvasculature in the breast. This PMRT reduces the integrity of the skin, causing the growth of fibrosis and the development of scar [67,68]. PMRT is hard to repair, resulting in a permanently unacceptable aesthetic outcome [69,70]. Even with such destructive complications, PMRT is still a necessary therapy in the case of breast reconstruction [71].

In fact, the existence of a reconstruction may make it more difficult to schedule radiation therapy. A number of studies have shown that PMRT can impair the beauty of the patient and raise the incidence of complications in the immediate reconstruction of the breast [72-74]. This review paper reported that PMRT can cause changes in breast tissue perfusion and possibly cause certain complications associated with injury. The aim of this paper is to explore the efficacy of PMRT in treating wound infection, injury dehiscence, blood loss, and necrosis. Knowing those results would allow physicians to inform patients about PMRT's potential risks and benefits for those who would like to have a surgery done immediately. At Final stage, Breast reconstruction takes 6-12 months after postmastectomy radiation therapy [75].



Schematic diagram showing the timing of healing after postmastectomy radiation therapy[75]

TOPICAL FIBRONECTIN IMPROVE WOUND HEALING IN PMRT PATIENTS

Topically applied fibronectin was found to significantly improve wound healing in irradiated skin and was associated with decreased inflammatory infiltrate and increased angiogenesis. Fibronectin treatment may be a useful adjunctive modality in the treatment of non-healing radiation wounds. Wound healing is significantly delayed in irradiated skin. Of the 210 proteins studied, fibronectin was the most significantly and consistently

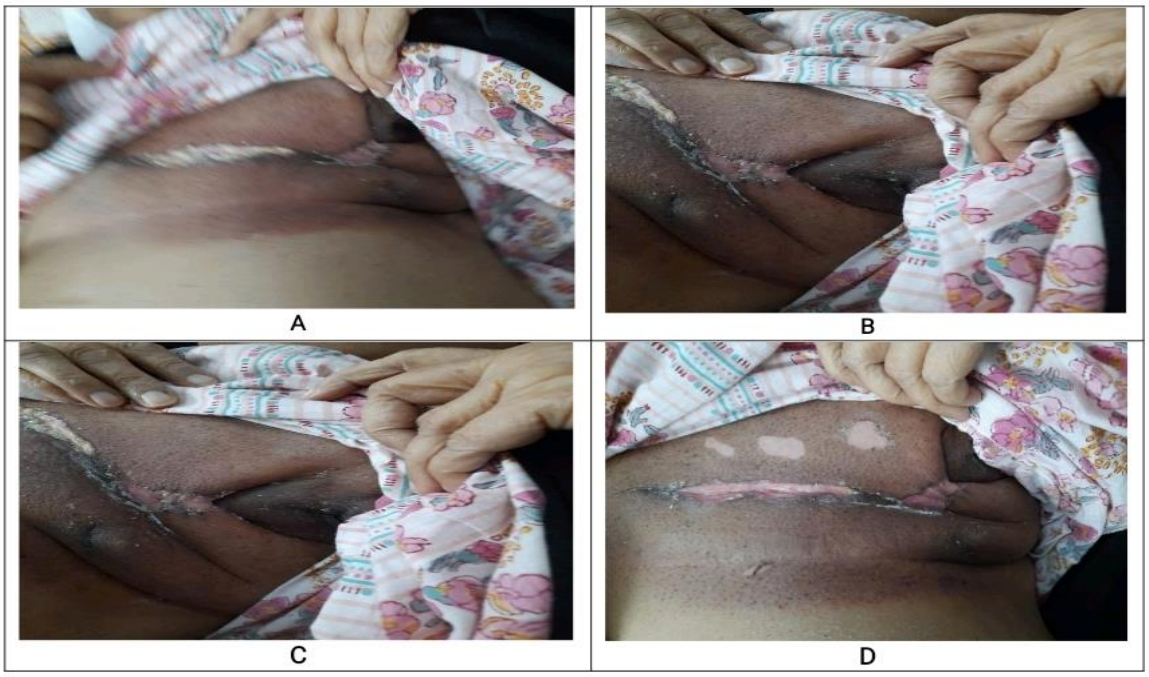
downregulated in radiation-damaged skin. Chronic radiation skin injury is characterized by dermal atrophy, fibrosis, vascular damage, chronic ulceration, and poor wound healing [76]. The mechanism of radiation-induced skin fibrosis is a complex, and involves terminal differentiation of fibroblasts, abnormal collagen deposition with loss of adnexal structures, disordered vasculature, and dysfunctional chronic inflammation. To better understand global changes in breast tissue expression after PMRT.

Although postmastectomy breast cancer radiation therapy is an important part of the treatment of solid tumors, it has dose-limiting ill effects on normal tissues.

In the present study, we performed a PMRT on BREAST CANCER patients undergoing post-oncologic reconstruction. We found that fibronectin was among the most significantly downregulated proteins in irradiated skin. Fibronectin is an ECM glycoprotein that is involved in a number of cellular mechanisms important to wound healing, including cell growth and migration, and serves as a binding site for a number of growth factors [77-79]. It promotes wound healing and is protective against irradiation [80-84].

Furthermore, topical fibronectin application led to significantly improved healing in irradiated wounds. This was associated with a significant reduction in acute inflammation and an increase in angiogenesis. These findings suggest that fibronectin may be involved in the pathogenesis of poor wound healing after radiation skin injury, and that exogenous supplementation may assist in the repair of radiation-damaged tissue. Generally, breast reconstruction takes 6-12 months after postmastectomy radiation therapy. But after immediately applying Exogenous fibronectin on the treated area results have been shown that breast reconstruction within 3-4 months.

Current Case Study of Topical Application in the Treatment of Left breast tumor through PMRT



Illustrations of Left Breast tumor. **A**, Breast fat necrosis. **B,** Skin retraction with breast fibrosis and Ischemic ulcer of the Breast with necrosis. **C**, Infected ulcer of the Breast with necrosis. **D**, Granulation tissue appears after using topical application.

Type of Wound:
Breast Tumor
Patient:
45year-old Female

Condition:
Challenging condition of patient with multiple comorbid conditions (T2DM, HTN, Hypothyroidism, Acute CKD on dialysis).
Introduction:
A 45-yearold Female with multiple comorbid conditions (T2DM, HTN, Hypothyroidism, Acute CKD on dialysis) presents and necrosis & ulceration. Left Breast (A) treated with FN application. The skin discoloration associated with radiation injury. Irradiated skin heals significantly slower than normal skin at Radiation Ulcer. Topical application of fibronectin at the time of wounding is associated with significantly accelerated wound healing.
Result:
Patient assessment and history indicated a whole necrosis tissue present around the treated area after PMRT.

1. Death of tissue.
2. Highly brittle and malodorous.

After radiotherapy check the irradiation site for cleanliness and dryness, if required perform gentle cleaning and pat dry.
The wound continued to progress and was completely epithelialized at 7 days (Image #4) & showed no recurrence with normal skin lines returning (Images #2).
No secondary dressing is required, however if needed, use a paraffin based dressing as directed by the doctor.
Conclusion:
The clinical observation results show that the FN topical spray has a significant effect on the treatment of refractory ulcers, which can accelerate healing, shorten the course of treatment, and find no side effects. FN solution can effectively inhibit bacterial infection.
Other products take longer time to heal the wound compared to the topical application which was found to be easy and quick to use to the entire wound care team helping to simplify the delivery of wound preparation.

DISCUSSION

In this review paper, For women with stage three lymph node metastases, radiotherapy after mastectomy could improve the Breast reconstruction within 6-12months. For patients with one or two lymph node metastases, radiotherapy did not bring specific survival benefits. Lymph node status is an important indicator of prognosis and treatment. The number of node metastases reflected the tumor burden; the more node metastases, the higher the recurrence risk (5, 6). PMRT was an important technique to reduce the recurrence risk, and a series of studies had demonstrated that radiotherapy could improve the survival in patients with four or more lymph node metastases (11, 21, 22). However, the recommendations of local radiotherapy for stage T1-2 patients with one to three lymph nodes positive were obviously different (4, 19, 20). Previous study demonstrated that PMRT could reduce the local recurrence and improve survival (8, 11). In other clinical study found that the number of lymph node metastases was closely related to the benefit of radiotherapy. With the appropriate systemic treatment, the benefits of radiotherapy after mastectomy (PMRT)

were limited for patients with low recurrence risk. Therefore, PMRT should not be considered routinely for patients with one or two lymph node metastases after mastectomy and axillary dissection.

In addition, the radiotherapy group showed even worse survival benefits among T1-2 breast cancer patients with one lymph node positive. Patients with only one lymph node metastasis usually bear low tumor metastasis load and recurrence rate, and thus could expect relatively good prognosis with systematic treatment (chemotherapy, targeted therapy, and/or endocrine therapy) (26). For patients with a low risk of recurrence, adding radiotherapy after mastectomy may cause an interaction between radiation, tumor cells, and the immune system, which influenced the patients' survival (28, 29). The complications of radiotherapy, such as pneumonitis, lymphedema, and cardiac toxicities, et al. may lead to even worse results (20).

Radiotherapy can bring not only survival benefits but also side effects—lung injury, cardiac, and skin side effects, et al., which decreased the quality of life of patients (30, 31).

In conclusion, the benefit of topical fibronectin improves wound healing in PMRT of Breast cancer patients. PMRT should be recommended to patients with three nodes positive, should be suggested cautiously in those with two nodes positive, and could be omitted in those with one node positive. Exogenous fibronectin shows best results through clinical case reports of PMRT patients.

CONCLUSION AND DIRECTION FOR FUTURE RESEARCH

As reviewed previously, considerable evidence has been collected regarding the role of radiotherapy after mastectomy, and the subject has been one that has generated extensive controversy over the past few decades. Although substantial evidence indicates that radiation therapy can reduce the risk of locoregional failure after mastectomy (with a relative reduction of risk of approximately two-thirds), debate persists regarding the specific subgroups who have sufficient risks of residual microscopic locoregional disease after mastectomy to warrant treatment with radiation. The optimal targets of treatment and techniques to minimize toxicity, particularly in patients who also wish to pursue

reconstruction, continue to be the subjects of ongoing debate.

Future Perspectives for topical FN-application in Therapeutic Strategies of Postmastectomy radiation therapy.

FN and other ECM components necessary for the filling of the wound with the granulation tissue are degraded by radiation therapy.

The purpose of this topical application of pFn improves skin wound healing after Postmastectomy radiation therapy

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