Review Article

# Radiation Fibrosis Syndrome: the Evergreen Menace of Radiation Therapy

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## ABSTRACT

Fibrosis is a descriptive appellation referring to the obliteration of normal tissue components replaced by matrix and disorganized and varied collagen fibrils that result in the loss of organ function and frequent tissue contraction leading to death or significant deterioration in the quality of life. Radiation fibrosis syndrome (RFS) is a progressive fibrotic tissue sclerosis with various clinical symptoms in the irradiation field. It is usually a late complication of radiation therapy and may occur weeks or even years after treatment. It may affect the musculoskeletal, soft tissue, neural tissue, and cardiopulmonary systems. RFS is a serious and lifelong disorder that, nevertheless, may often be prevented when identified and rehabilitated early. Genetic factors likely play a significant role in the development of chronic fibrotic response to radiation injury that persists even after the initial insult is no longer present. Management of this syndrome is a complex process comprising medication, education, rehabilitation, and physical and occupational therapy. A bibliographical search was carried out in PubMed using the following keywords: "radiation fibrosis," "radiation fibrosis syndrome," and "radiation-induced fibrosis." We also reviewed the most relevant and recent series on the current management of RFS, and the reviewed data are discussed in this article. This review discusses the pathophysiology, evaluation, and treatment of neuromuscular, musculoskeletal, and functional disorders as late effects of radiation treatment.

**Key words:** Ionizing radiation, radiation fibrosis syndrome, radiotherapy

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## Introduction

Cancer patients are treated with external beam radiation therapy (EBRT) either alone or with concurrent chemotherapy and surgery. Radiation damages not only rapidly proliferating tumor cells but also normal tissues other nearby organs that are at risk of being present within the planned radiation field. The adverse effect of ionizing radiation on healthy tissues is largely influenced by the radiosensitivity of individual cells.[1] Majority of the late effects of radiation vary in severity depending on radiation dose, fraction size, and treated volume.[2] Apart from these factors, the mode or type of EBRT, such as two-dimensional radiotherapy (2DRT), three-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), and image-guided radiotherapy (IGRT), also plays a very crucial role.[3] Highly conformal RT techniques such as IMRT and IGRT have resulted in minimal acute and chronic side effects compared to 2D and 3D techniques. Both IMRT and IGRT generally result in the development of acute effects at around 5th–6th week, whereas 2D/3D RT causes similar effects at around 3rd–4th week of RT.[3] One of the most important late effects of RT affecting a patient's quality of life (QOL) and causing significant morbidity is radiation fibrosis syndrome (RFS), which may occur in the skin, subcutaneous tissue, pulmonary system, gastrointestinal and genitourinary tracts, and in any other organ within the radiation field.[4] Radiation injury triggers inflammation and ultimately stimulation of the production of myofibroblasts from differentiated fibroblasts that in turn produce excess collagen and different constituents of extracellular matrix, aided by the reduced secretion of remodeling enzymes.[2] Subsequent fibrosis reduces tissue compliance and causes cosmetic and functional impairment that significantly impacts the QOL in the majority of cancer patients, and particularly those with head-and-neck (H and N) cancer.[5]

## Pathophysiology of Radiation Fibrosis Syndrome

The pathophysiology of RFS generally includes an event comprising the interplay of inflammatory macrophages, differentiation of fibroblasts, and modifications of vascular connective tissues with excessive production and deposition of collagenous and other extracellular matrix proteins. The most prominent player in this complex event is the product of radiation stimulated inflammatory, epithelial, and mesenchymal cells known as transforming growth factor-β (TGF-β) that converts fibroblasts into matrix-synthesizing myofibroblasts.[6] The myofibroblasts on their part secrete excess matrix-forming substances such as collagen, proteoglycans, and fibronectin that result in subsequent and progressive avascularity, thickening, stiffness, scarring, atrophy, and nonfunctionality of the affected tissue.[7] TGF-β reduces the activity of matrix metalloproteinase (MMP)-2 and MMP-9 and therefore results in excess matrix deposits. TGF-β also regulates the production of fibroblast growth factor, tumor necrosis factor, epidermal growth factor, and interleukin-1 that act in various cell lines such as the fibroblasts, smooth muscle cells, and endothelial cells, thus contributing to the process of fibrosis. Various pathophysiological mechanisms have been postulated for RFS including induction of free radical (FR)-mediated DNA damage and subsequent apoptosis as a predisposing event.[6] Pohlers *et al*.[8] described three histopathological phases of RFS such as (1) prefibrotic phase comprising endothelial cells, (2) fibrotic phase of active fibrosis containing myofibroblasts, and (3) fibroatrophic phase characterized by subsequent loss of parenchymal cells. Radiation-induced accumulation of excess fibrin in the extravascular, intravascular, and perivascular compartments has been described for RFS.[9] Ionizing radiation may directly result in RFS by causing vascular endothelial injury and indirectly by activating the inflammatory, epithelial regeneration, and tissue remodeling pathways and the coagulation cascade.[10] Another important event is the activation of Janus kinase (JAK) and signal transducer and activator of transcription (STAT) proteins along with nuclear factor kappa-light-chain-enhancer of activated B-cell (NF-KB) pathways by radiation resulting in the release of pro-inflammatory cytokines and growth factors. The two mechanisms involved in radiation injury to both tumor and normal cells are the direct and indirect DNA damage through the generation of reactive oxygen species and FRs that destroy protein, lipid, and nucleic acid molecules, thus causing ischemia and thrombosis through the secretion of cytokines and chemokines.[11,12] Khan *et al*.[13] in 2003 had described the potential role of reactive nitrogen species in causing radiation fibrosis in rats, but no such mechanism has been described in humans.

## Risk Factors Predisposing to Radiation Fibrosis Syndrome

As the terminology RFS suggests, ionizing radiation during EBRT is the primary treatment-related risk factor of inducing tissue fibrosis. Parameters such as high EBRT dose, higher dose per fraction as in hypofractionated RT during palliative settings, larger volume of irradiated tissues, larger radiation field, inhomogeneity of dose delivery, and prolonged therapy were observed in frequent treatment breaks.[14] The effects of radiation are additive, and patients with a history of reradiation for recurrences at the same

primary site are known to develop severe fibrosis.[10] Fibrosis in the skin and underneath the subcutaneous tissue is most prone to radiation effect. Therefore, to reduce the aforementioned effect, a reference radiation penetration depth range of 3.3–5.5 mm with an optimal depth of 4.1 mm and an alpha/beta ratio of 1.8 was described in 1988.[15] However, as this depth range was within the steep dose gradient build-up zone of EBRT delivery by 2DRT and 3DCRT techniques, it was not practically implemented. The advent of IMRT and IGRT has allowed maximum tumor dose and minimal exposure to normal tissues based on the process of dose painting, thereby reducing radiation-induced fibrosis (RIF). The impact of radiation in causing RFS can either be individually or in combination with chemotherapy or surgery whichever provides a cumulative effect. Neoadjuvant and adjuvant EBRT in a surgical candidate has shown a higher incidence of subcutaneous fibrosis than those without surgery.[16] Exhibition of concurrent chemoradiotherapy[17] has been described as a risk factor for RFS;[16] thus, apart from the dosimetric accuracy in radiation delivery, the effects of multimodality therapy should also be considered. Suarez *et al*.[18] in 2014 described Marfan syndrome, apart from other connective tissue disorders such as systemic lupus erythematosus (SLE) or scleroderma, as an important predisposing factor the development of RFS. Various studies have also described that RFS is associated with genetic predisposing factors such as its association with epigenetic modifications to DNA and histones,[19] X-ray repair cross-complementing proteins 1 and 3 (XRCC1 and XRCC3), double-strand-break repair protein rad21 homolog (RAD21), and TGF-β1.[20] Other genetic variations implicated to be a risk factor for RFS are signaling lymphocyte activation molecule family member-6, cyclin-dependent kinase inhibitor-1, cell adhesion molecule,[21] thioredoxin reductase-2 encoding a mitochondrial enzyme,[22] and mutated variant of ataxia-telangiectasia gene in carcinoma breast cases.[23]

## Clinical Manifestations of Radiation Fibrosis Syndrome

RFS is generally a late complication of radiation that may either not manifest clinically for years after treatment known as delayed RFS,[4] within a year as chronic RFS,[2] or even during treatment in few cases as acute RFS.[10] RFS causes both functional and cosmetic impairment and may cause severe morbidity and mortality, resulting in a significant deterioration of QOL. This syndrome can affect almost any part of the body exposed to ionizing radiation, and its clinical manifestations depend on the type of tissue exposed. Acute RFS usually may start during or right after treatment and last for several weeks after it ends, and then, they get better. In general, acute RFS may manifest as skin darkening, scarring [Figure 1], dermatitis [Figure 2], mucositis and ulceration [Figure 3], decreased salivation, hair loss, and ultimately pain. More regionally specific chronic manifestations of RFS include trismus, xerostomia, reduced voice quality, skin induration [Figure 4], osteoradionecrosis [Figure 5], dysphagia, and aspiration in patients with H and N malignancy,[24] muscle atrophy, soft-tissue edema [Figure 6], lymphedema [Figure 7], restricted joint mobility, mucosal thickening, ulceration, fistula, and stenosis of hollow organs. Lung and breast carcinomas may present with interstitial fibrosis, dyspnea, brachial plexopathy, and depleted oxygen concentrations,[25] while urinary frequency, urgency, hematuria, diarrhea, loss of reproductive function, and dyspareunia may occur with genitourinary malignancies.[26] Long-term complications occurring due to RFS may include progressive thickening and skin fibrosis [Figure 8]; subcutaneous tissue; muscle fibers, ligaments, tendons, bones, nerves, and lymphatic system; progressive ischemia; and adherence to underlying subcutaneous and fibro-fatty tissues [Figure 9]. RIF causes easy fatigability, weakness, myopathy, and painful spasms in the skeletal muscles as evidenced by severe contracture and wasting of sternocleidomastoid and scalene muscles in H and N cases, which may cause neck weakness, head drop, and torticollis [Figure 10].

RFS causes shortening and contracture with loss of elasticity of the tendons and ligaments, thus resulting in restricted joint mobility, joint swelling, and loss of functionality. Osteoporosis and osteopenia are the delayed complications of RFS leading to pathological fracture of weight-bearing long bones, such as the femur and pelvic bones, in patients treated for pelvic malignancies,[27] which make shielding the femoral head very important during EBRT planning. The effects of RFS on the nervous tissue

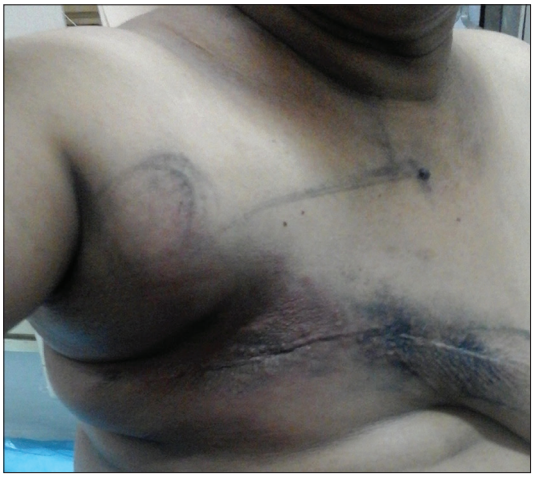

**Figure 1:** Skin darkening and scarring in a case of carcinoma breast post radiation therapy

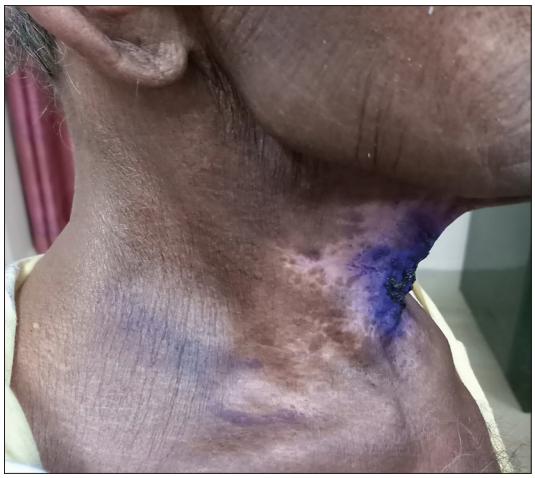

**Figure 2:** Radiation dermatitis in a case of H and N carcinoma during radiation therapy

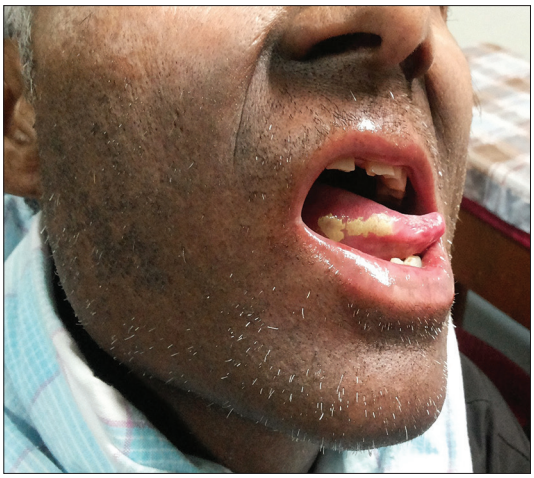

**Figure 3:** Mucositis and ulceration in a case of H and N carcinoma post radiation therapy

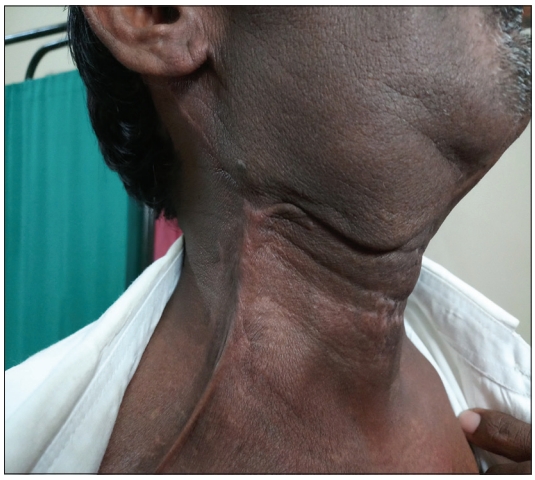

**Figure 4:** Skin induration post radiation therapy

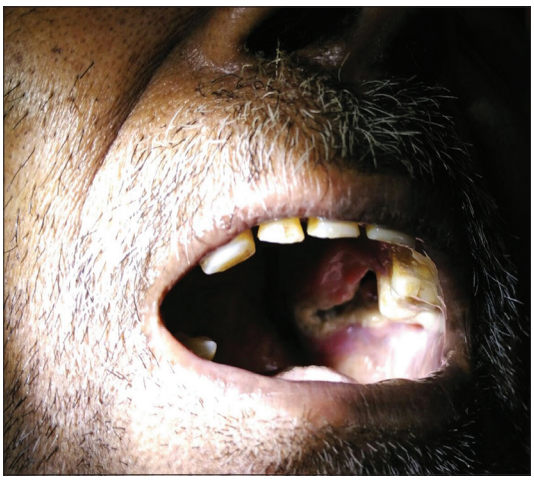

**Figure 5:** Osteoradionecrosis of left upper alveolus post radiation therapy

**Figure 6:** Soft tissue oedema post radiation therapy in a case of carcinoma urethra

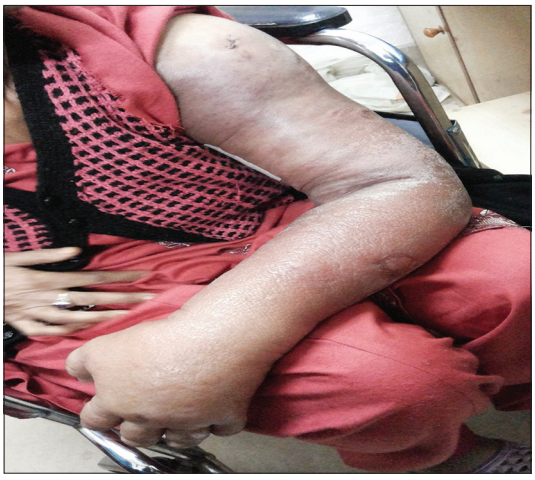

**Figure 7:** Lymphedema as a sequelae to radiation therapy in an operated case of carcinoma breast

result in neuropathic pain, sensory loss, paresthesia, numbness, and weakness. Neuropathic pain is often accompanied by loss of sensation, whereas a sensory loss can exist without pain but inclusive of diminished sensations of touch, pain, temperature, vibration, and

**Figure 8:** Progressive fibrosis and thickening of the skin post radiation therapy as delayed sequelae

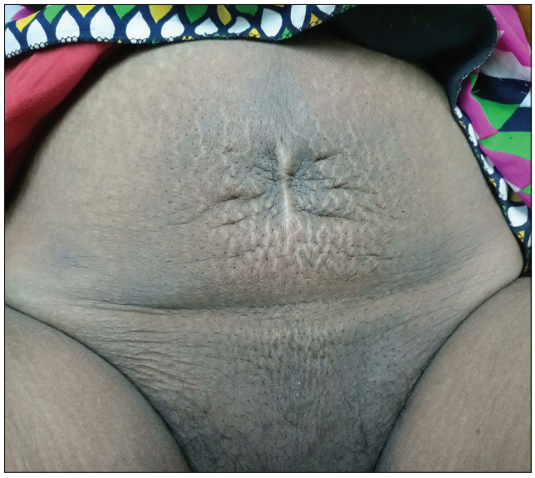

**Figure 9:** Progressive fibrosis, ischemia and adherence to underlying subcutaneous and fibro-fatty tissues seen in a case of carcinoma cervix post external beam radiation therapy

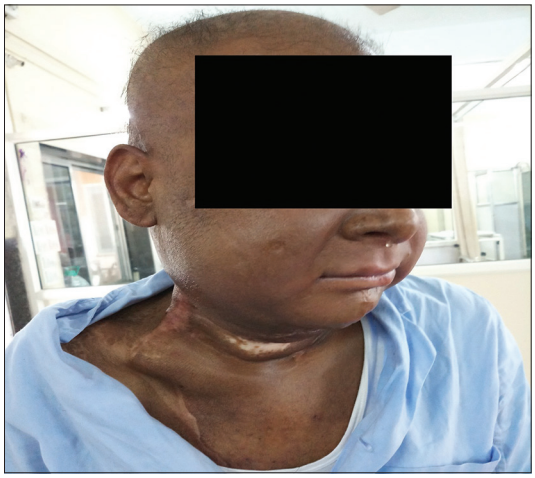

**Figure 10:** Torticolis as a delayed sequence of radiation therapy in a H and N carcinoma

position. RIF of the brachial, cervical, and lumbosacral nerve plexus can cause plexopathies and functional loss. Sciatic nerve mononeuropathy,[28] dorsal scapular nerve, and suprascapular nerve neuropathy caused by radiation may result in low backache and shoulder dysfunction, respectively. RIF affecting the autonomic nervous system may result in bladder, bowel, and sexual dysfunction.[29] The symptoms and signs of RFS may be nonspecific although it may be inadvertently associated with a history of prior EBRT or any form of radiation therapy. Evaluation should include the past radiation treatment history; medical and surgical comorbidities such as tendonitis, neuropathies, and radiculopathies; and connective tissue disorders such as SLE. Signs of RFS may be nonspecific, and the physician or oncologist must draw inferences from the patient's description of their disabilities, including thickening, cramping, pricking, pulling or burning pain, any neuropathic or muscular sensations, which make physical examination important. Radiological imaging used to evaluate the significance of RFS is magnetic resonance imaging, whereas computed tomography scan may be useful for the chest, abdomen, and pelvis imaging.[10] Histopathological analysis may reveal hyalinized fibrotic tissue with spotty hyalinizing necrosis infiltrating the striated muscular, adipose, vascular, and nervous tissues.[5,8] Immunohistochemistry may be used to differentiate between RIF and other pathologies of the primary tissue.[5]

## Prevention and Management of Radiation Fibrosis Syndrome

Prevention before treatment is the first step in the management of RFS. The advent of highly conformal EBRT techniques such as IMRT and IGRT has resulted in the lower incidences of RFS[30] due to higher radiation doses to the tumor and minimum doses to normal tissues, along with the highly precise dosimetric calculations. Therapeutic management of RFS has involved targeting TGF-β, the most important component of tissue fibrosis pathway resulting in the inhibition of matrix synthesis and inflammation. The small molecule inhibitor LY2109761, halofuginone, quercetin, and siRNA have been used to target the TGF-β pathway.[2] JAK-STAT and NF-KB pathway inhibitor, combination of pentoxifylline (PTX) and tocotrienol (testosterone replacement therapy [TRT]), has been used with excellent long-term effect in both oral[31] and topical formulations[32] against RFS in patients with breast carcinoma. Similarly, combined oral gamma and delta TRT 400 mg twice a day for 6 months has been used in patients with H and N cancer suffering from RIF-induced trismus with significant improvement of mouth opening.[33] Kumar *et al.*[34] in June 2018 demonstrated the efficacy of oral gamma and delta TRT

400 mg twice per day along with oral PTX for 6 months in 22 patients with H and N cancer resulting in improved QOL and trismus. Mouse models have been used to assess the use of cell-based therapies, such as allogeneic and syngeneic bone-marrow stem-cell systemic infusion, to treat RFS.[35] Other therapeutic agents used in alleviating RIF are the HMG-CoA inhibitor (simvastatin) in murine lung RFS,[36] angiotensin-converting enzyme inhibitor (enalapril) in lung RFS,[37] tyrosine kinase inhibitor (imatinib) in skin fibrosis,[38] and corticosteroids (dexamethasone). Antiproliferative agent such as pirfenidone[2] and the vascular endothelial growth factor inhibitor such as bevacizumab have been postulated to be effective in preventing worsening of symptoms in patients with RFS.[2] Apart from the specific RFS therapy, associated symptoms of muscular pain, contractures, and spasms are managed with nonsteroidal anti-inflammatory drugs and are generally recommended along with muscle relaxants such as benzodiazepines and baclofen.[39] In case of neuropathic pain, treatment with newer nerve-stabilizing agents, such as pregabalin, is generally prescribed,[40] whereas opioids are usually reserved as an adjunct to nerve-stabilizing agents. Intramuscular injection of local anesthetics to the area of muscle spasm may cause good symptomatic relief.[41] Injection of botulinum toxin on the muscle and fascia has a proven benefit in radiation-induced painful facial muscle spasms, trismus, cervical dystonia, and neuropathic pain.[42] During and after the systemic therapy for RFS, patients usually benefit from mild exercises to improve their physical efficiency, sustainability, muscle strength, range of motion, and overall QOL.[43] Patients should abide by a maintenance exercise program with an insidious progression of fibrosis. Interventional techniques such as myofascial[44] and visceral relaxation have been beneficial in channeling blood optimally to the fibrosed tissues in postlaryngectomy patients.[45] Cervical and upper and lower limb splints/braces have also been used for the rehabilitation of many RFS cases affecting the respective parts.[46] Hyperbaric oxygen therapy (HBOT) induces angiogenesis, mobilization of stem cells from the bone marrow, wound healing, and recovery of normal-tissue radiation injury. The role of HBOT in the treatment of late radiation injuries such as cystitis and proctitis is well known, while its role in the management of RFS remains unclear and controversial,[2] lacking higher levels of evidence.[47,48] Teguh *et al.*[49] in 2016 demonstrated the efficacy of HBOT in the treatment of RFS in 57 patients with breast cancer with significant improvement in QOL. Working on rat model, Oscarsson *et al.*[50] in 2017 hypothesized that radiation-induced oxidative stress reactions and inflammatory and pro-fibrotic response in irradiated tissues could be reversed by HBOT.

Educating the affected patient on various aspects of RFS through proper communication tremendously helps them apart from physical and occupational rehabilitative measures that have been the cornerstone of supportive care and functional improvement.

## Conclusion

Similar to every other life-saving medication or drug that has an adverse effect, RT is also accompanied by unwanted adverse effects such as RFS, which has been the evergreen menace of this therapy. This has been primarily caused by excessive radiation dosage and volume of the exposed tissues. In this review, a precise and comprehensive coverage on the pathophysiology, risk features, predisposing factors, clinical manifestation, prevention, and management of RFS has been conducted. The plethora of molecular pathways associated with this complex disease process has been explored before and should be investigated further to establish novel treatment strategies. Certainly, no definitive cure has been developed for these chronic sequelae of RT with the management being primarily symptomatic and rehabilitative. Trivedi[3] in his retrospective analysis of 1010 patients postulated that IMRT and IGRT are the superior RT techniques compared to 2D and 3DCRT, not only because of the lesser number of people affected from the side effects but also because of the later onset of RFS. Both Kumar *et al.*[33] and Kumar *et al.*[34] found the significant benefit of tocotrienol in patients with radiation fibrosis that occurred after 6 months. In a systemic review by Feldmeier and Hampson,[47] all trials except seven studies showed significant benefit of $HBO_2$ on radiation-induced late injuries observed by other authors who have worked with $HBO_2$ as far as RIF is concerned. RFS is a debilitating and lifelong disorder. Educating patients regarding its signs and symptoms, encouraging them to report early, and visiting the institution for a regular follow-up may help initiate prompt therapeutic interventions and thus prevent further complications.

### *Declaration of patient consent*

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients has/have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### *Conflicts of interest*

There are no conflicts of interest.

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