Radiation-Induced Fibrosis in Patients with Head and Neck Cancer: A Review of Pathogenesis and Clinical Outcomes

Clinical Medicine Insights: Oncology
Volume 16: 1–7

DOI: 10.1177/11795549211036898

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ABSTRACT: Radiotherapy-related fibrosis remains one of the most challenging treatment related side effects encountered by patients with head and neck cancer. Several established and ongoing novel therapies have been studied with paucity of data in how to best treat these patients. This review aims to provide researchers and health care providers with a comprehensive review on the presentation, etiology, and therapeutic options for this serious condition.

KEYWORDS: Radiotherapy, head and neck radiation, fibrosis, prevention

RECEIVED: March 4, 2021. **ACCEPTED:** July 15, 2021.

TYPE: Review

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Head and neck cancers are a significant cause of morbidity and mortality worldwide, with more than 650,000 cases and 330,000 deaths per year.[1] Radiation therapy (RT) in the adjuvant or upfront setting, with or without chemotherapy, is a cornerstone of treatment. Nevertheless, RT presents with many acute and long-term complications, several manifesting months to years following treatment. Specifically, fibrosis and scarring of the surrounding skin and musculature is a common adverse effect occurring up to 1 year after completing treatment, and worsening over time.[2] This can be the attributed to a chronic inflammatory process due to repetitive injury induced by RT. The exact mechanisms of fibrosis are not fully clear but may be due to the excess production of fibroblasts and dysregulation of the wound healing processes.[3,4] This process can manifest as neck stiffness, trismus, and pain and may be associated with lymphedema often leading to decreased quality of life for long-term cancer survivors of head and neck cancer.[5–10]

There have been several attempts to decrease the incidence and severity of postradiation fibrosis. These involve improvement in radiation techniques, physical therapy, and topical and systemic treatments.[11–21] The aim of this review is to discuss the clinical presentation, underlying pathogenesis and current treatments for patients with postradiation fibrosis in the head and neck area. This review aims to uniquely highlight the up-to-date knowledge on molecular mechanisms and offer clinicians a summary of all historic therapies as well as novel treatment options that have emerged over the past few years.

Methods

A comprehensive literature review was performed using Medline and PubMed search engines using Mesh terms and keywords, such as "radiation therapy," "head and neck neoplasms," "adverse events," "fibrosis," and other related terms. Additional articles were recommended by colleagues and co-authors of this manuscript. More than 300 articles were retrieved, of which 86 were found relevant and revised for this review. The relevant data was further sorted in the following order (1) signs and symptoms of head and neck fibrosis, (2) the molecular mechanism of radiation-induced fibrosis formation, and (3) suitable treatment strategies

Clinical Presentation

The severity of radiation fibrosis in the head and neck area is affected by several factors and tends to be worse in older patients, larger tumors, higher radiation doses, treatment volume, and in patients who have undergone other treatment modalities such as surgery and chemotherapy.[22,23] The incidence of grade-2-or-higher neck fibrosis can sometimes exceed 50% after surgical dissection, and 34% with definitive chemoradiation.[16,24] Even in patients treated with modern techniques, such as intensity-modulated radiation therapy (IMRT), the occurrence still remains as high as 30%.[15] A prospective study comparing acute and late side effects of 3D versus IMRT in 60 head and neck cancer patients receiving definitive (chemo) radiation therapy showed a lesser degree of grade-2-or-higher late subcutaneous fibrosis in patients treated with IMRT.[25]

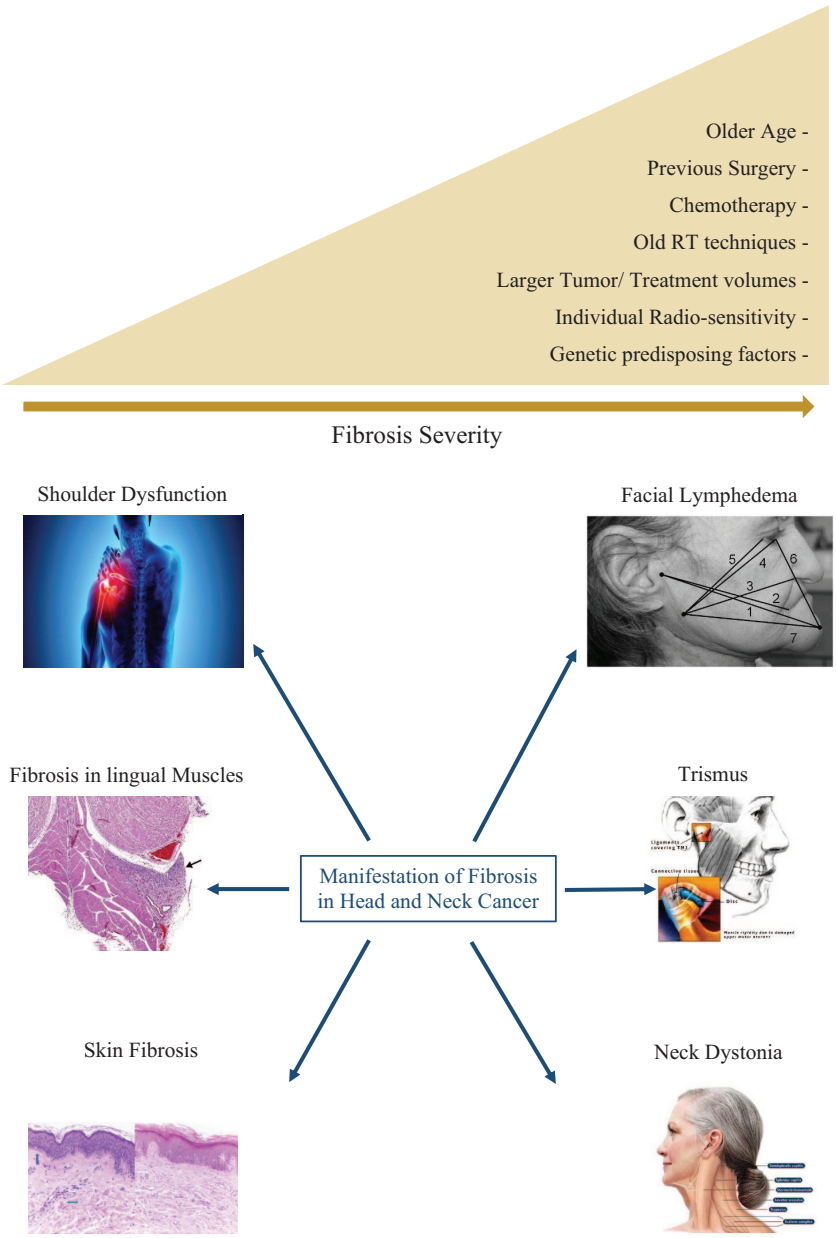

Figure 1. Head and neck radiation-induced fibrosis manifestations and risk factors.

The severity of fibrosis in the head and neck area, similar to other disease subsites, is also greatly affected by individual radiosensitivity and the presence of genetic syndromes such as ataxia telangiectasia and others[26–29] (Figure 1).

One common side effect of fibrosis in the head and neck area is shoulder dysfunction. This can be attributed to capsulitis as well as tendinitis and hardened tissues limiting the range of motion of the shoulder joint. This is usually managed with physical therapy and steroid injections into the joint to relieve pain and improve range of motion.[30] Radiation may also cause dystonia and spasms of the neck musculature. This can lead to contracture and fixed neck positions, or weakness and difficulty supporting head posture.[30–32] Furthermore, fibrosis in lingual muscles and constrictor muscles may limit tongue mobility and swallowing. Trismus, which is a dysfunction in motion of the tempo-mandibular joint (lock jaw) is also a side effect attributed to the assimilation of fibrotic tissue in the joint and surrounding musculature, particularly the lateral pterygoids, often causing poor oral hygiene and nutrition as well as decreased quality of life.[33–36] A suggested parameter to define trismus is a mouth opening of less than 35 mm.[37] It is a functional cut-off point for trismus in head and neck cancer patients. Incidence can approach 25% on long-term follow-up and dose to the ipsilateral masseter muscle was noted to be a significant risk factor.[14,20,33,38,39] Early physical therapy focusing on range of motion has been shown to decrease the incidence of trismus, and specialized splinting, physical exercises, and botulinum toxins have been used for symptomatic relief.[14,20,21,33] Lymphedema is also a common side effect due to radiation fibrosis and may be subdivided into internal and external components. It has been associated with worse quality of life and is more frequent in patients receiving multiple

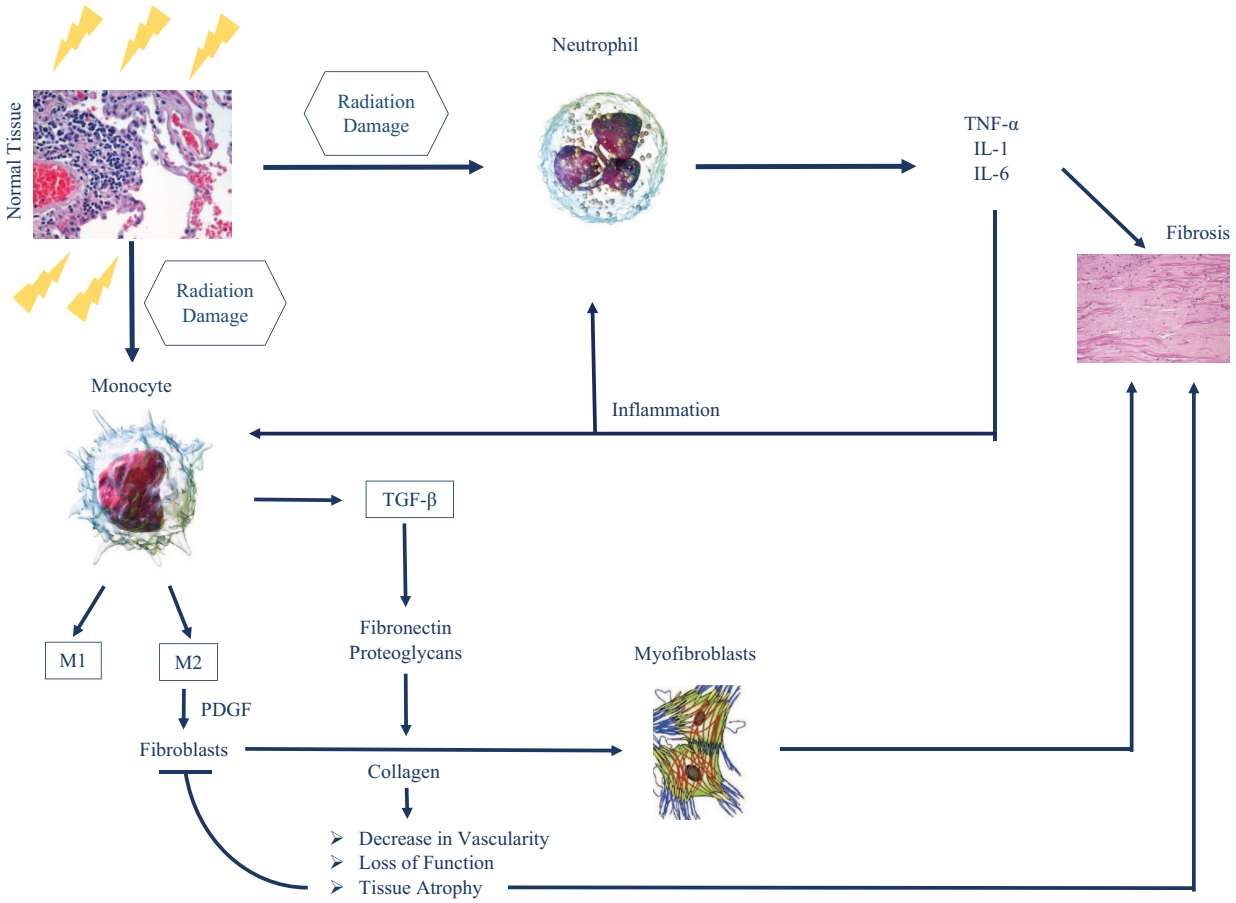

Figure 2. Molecular pathogenisis of radiation induced fibrosis.

treatment modalities including surgical dissection and re-exploration surgical interventions[9,32,40] (Figure 1).

Radiation fibrosis is most evident in the skin tissue and can be a long-term sequelae of radiation dermatitis. Notably, the severity of acute skin reactions at the end of radiation therapy have also been shown to be a prognostic factor for developing radiation fibrosis.[15] Chronic radiation skin fibrosis, in addition to its cosmetic burden, is a predisposing factor for complications due to poor wound healing and compromised vasculature. Fibrosis in the skin can cause xerosis, dyspigmentation, epidermal atrophy, as well as slow healing of painful ulcerations. Also, the skin itself may be a contributing factor to neck stiffness due to contractures and pain.[5,27]

The RTOG/EORTC late morbidity scoring schema takes into account radiation fibrosis in the grading of subcutaneous tissues but not of the skin.[41] Common terminology criteria for adverse events (CTCAE) do provide a graded clinical scale to measure fibrosis in superficial and deep soft tissues; however, there have been attempts to use more objective image-based severity scales using ultrasound and CT scans[11,42] (Figure 1).

Molecular Mechanisms of Radiation Fibrosis

Fibrosis is one of the many RT side effects linked to molecular and cellular events defining radiosensitivity.[43] It is characterized by the induction of DNA damage and tissue inflammation. In fact, irradiation instigates many different types of DNA damage, but studies have shown that DNA double-strand breaks (DSBs) are the most lethal, and most difficult to repair.[44–47] DNA DSB can be repaired via different pathways, such as the non-homologous end joining (NHEJ) repair and homologous recombination (HR).[46–48] The repair kinetics of DNA DSB is a major factor in determining radiosensitivity, and many studies have highlighted correlation between unrepaired DSB and radio-induced toxicities.[43,49–52] In parallel with DNA DSB induction, radiation causes the apparition of reactive oxygen species (ROS) that interacts with water molecules inside the nucleus, leading to the formation of hydroxyl radicals.[53] These radio-induced radicals are responsible for more than 2/3 of DNA DSB in the case of X-rays irradiation but can also damage other cellular components such as proteins, membranes, and RNA[54] (Figure 2).

Once damaged, cells release different types of molecules that stimulate the migration of inflammatory cells, such as neutrophils, monocytes, and lymphocytes. Neutrophils are known to be the first inflammatory cells recruited to the site of injured cells.[55] Their presence will lead to the release of several types of cytokines: tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), and 6 (IL-6). These cytokines have the capacity to exaggerate inflammation and are considered to be a direct cause of the onset of fibrosis. On the other hand, monocytes, once at the

damaged site, will be differentiated into M1 and M2 macrophages. Platelet-derived growth factors (PDGFs) are then released by the M2 macrophages and will stimulate the migration of fibroblasts to the damaged region.[56,57] More importantly, M2 will also secrete the transforming growth factor beta (TGF-β), a major player in radiation fibrosis.[27] There are 3 different isoforms of TGF-β, called TGF-β1 to β3, with TGF-β1being the most implicated in fibroproliferative diseases.[58]

In fact, TGF-β is a protein that can regulate fibrogenesis by inducing the proliferation of postmitotic fibrocytes from progenitor fibroblasts. These fibrocytes have the capacity to produce collagen. TGF-β can also induce a more excessive extracellular matrix deposition by (1) upregulating tissue inhibitors of metalloproteinases (TIMPs) and (2) dysregulating matrix metalloproteinase (MMP) activity (MMP-2 and MMP-9). Finally, TGF-β induces the secretion of more collagen, fibronectin, and proteoglycans by leading to the differentiation of fibroblasts into myofibroblasts. These secretions are known to cause the increased tissue rigidity and thickness.[59,60] Myofibroblasts are the major actor in fibrogenesis and are directly associated with the repair of tissues and fibrosis.[61] Moreover, excess collagen leads to a reduced vascularity over time.[62] This change in vascularity makes fibrotic regions more susceptible to loss of function, necrosis, tissue atrophy, and decrease in the number of fibroblasts.[3]

Many studies have shown that the levels of TGF-β proteins, mainly TGF-β1, increases after irradiation in human and animal models, while they remain unchanged in unirradiated tissues.[63] TGF-β levels also increase with the additional doses of RT.[64] Moreover, patients showing a higher TGF-β1 plasma level are more at risk of developing radiation-induced fibrosis. The high levels of TGF-β might even remain detectable for months and years after the end of the treatment.[58] Interestingly, when TGF-β was administered to nonirradiated healthy animals, tissue fibrosis was observed. On the other hand, when patients were treated with liposomal Cu/Zn superoxide dismutase, an agent that downregulates TGF-β, the radiation-induced fibrosis was reversed.[65]

Current Treatment Strategies

There is a paucity of data in the treatment of radiation fibrosis in the head and neck area with most clinicians extrapolating treatment from treatments applied to other subsites such as breast. The treatment approach consists of either systemic treatments, topical treatments, or mechanical treatments in addition to palliative measures. Palliative treatments can include botulinum toxin to relieve spasms as well as corticosteroids and nonsteroidal inflammatory drugs as well as other analgesics.[12,21] Mechanical maneuvers are often used preventatively; however, studies on their efficacy as treatment of trismus are not consistent.[14,19,20,66–69]

Pentoxifylline, a xanthine derivative, has been used off-label in combination with Vitamin E (tocopherol), a free radical scavenger, to treat of radiation-induced fibrosis. Pentoxifylline has favorable vascular properties, such as improving microvasculature, increasing oxygen release to tissues, and having multiple immunomodulatory features that drive anti-fibrotic properties. Pentoxifylline is involved in downregulating protein kinases and other inflammatory cytokines. It also inhibits intracellular signaling to TFG-β, a pathway significantly involved in radiation fibrosis.[70–72] Pentoxifylline, with and without tocopherol, displayed promising results in the treatment of fibrosis, osteonecrosis, and radiculopathy of different affected sites.[12,17,73–77] A randomized study in breast cancer patients showed superiority of combination treatment of pentoxifylline with tocopherol over monotherapy.[75] In the head and neck region, its use was focused on treating trismus in nasopharyngeal cancer patients, with modest results of 4 mm mean gap improvement in a pilot study (n = 20).[17] In a randomized trial recruiting head and neck (n = 7) and other tumors (n = 36), pentoxifylline (800 mg), and Vit E (1000 mg) were recorded to significantly reduce fibrosis severity in all treated patients. Notably, treatment effect was realized in the first 6 months without any additional benefit at 12 months.[73] Another small randomized trial of 78 patients used pentoxifylline as monotherapy prophylaxis and showed lower incidence of late fibrosis as compared with the control arm.[78]

Superoxide dismutase is a metalloenzyme found in many tissues that plays a role in the conversion of toxic superoxide radicals.[79] Topical use had shown promising results in patients with radiation fibrosis in the breast.[80] However, a recent randomized clinical trial studying 68 head and neck patients with radiation fibrosis treated with twice daily application of superoxide dismutase cream did not show any significant benefit as compared with the group receiving placebo. Of note, both the treatment and placebo arms had around 40% benefit at the end of the 3-month period, which may have been attributable to the massage/physical therapy that all patients received.[13]

Statins have been shown in in-vitro and vivo studies to downregulate the fibrotic cascade.[81] The PRAVACUR trial was a prospective phase II trial that included 60 head and neck squamous cell carcinoma patients with cutaneous and subcutaneous fibrosis. Patients received pravastatin 40 mg daily for 1 year and were assessed based on skin thickness changes measured using high-frequency ultrasonography. The intervention was well tolerated and uncommon toxicities included myalgias and arthralgias. Results were promising with one-third of the patients having more than 30% reduction in skin thickness, and overall 50% of patients had clinical decrease in severity of fibrosis.[16] These studies have been summarized in the table form (Table 1).

Future Directions

At the time of writing this review, a search on clinicaltrials.gov was conducted for "radiation toxicity." Of the 234 trials shown, most trials listed were studying interventions, such as radio protectors, to decrease acute side effects. One active trial studying the effect of hyperbaric oxygen in the treatment of chronic

Table 1. Select studies in the treatment of radiation fibrosis in the head and neck.

STUDY	INTERVENTION	STUDY DESIGN AND POPULATION	RESULTS
Delanian et al.[73]	A combination of PTX (800 mg/d) and Vit E (1000 IU/d) was administered orally for at least 6 months	Phase 2 trial Forty-three patients presenting with 50 distinct zones of chronic radiotherapy damage	53% mean regression of fibrosis surface areas Mean linear dimensions diminished from 6.5–4.5 cm Mean subjective objective medical management and analytic (SOMA) scores improved significantly, from 13.2 to 6.9
Chua et al.[17]	8-week course of pentoxifylline at a dose of 400 mg two to three times daily	Pilot study Sixteen patients diagnosed with severe trismus (dental gap ⩽25 mm) after finishing radiotherapy for nasopharyngeal carcinoma	The mean dental gap before treatment was 12.5 mm compared with 16.5 mm at the end of treatment ($P = .023$)
Hartl et al.[21]	Botox (Allergan) or 250 units of Dysport (Ipsen)* injected transcutaneously into the masseters	Prospective, nonrandomized Nineteen patients in complete remission with radiation-induced pain and trismus with or without masticator spasms	No improvement in trismus at 1 month Improvement in the function ($P = .004$), pain ($P = .002$), and cramps ($P = .004$) No side effects occurred.
Landeen et al.[13]	Sodermix cream (280 IU/g superoxide dismutase) once daily on fibrotic area or placebo	Prospective, blinded study *d* Randomized, prospective, blinded. ⩾18 years, H&N radiation therapy-induced fibrosis	46.4% Improvement in study arm vs 43.3% in placebo (Not statistically significant)
Zatarain et al.[67]	Stretching exercises with or without Dynasplint device during treatment and 3 months post-treatment	Phase 3, randomized 40 patients undergoing radiotherapy treatment for head and neck cancer	No benefit from using Dynasplint device regarding jaw opening (only 25% compliance in intervention arm)
Bourgier et al.[16]	Pravastatin 40 mg/d for 12 months	Phase 2 trial Sixty NSCC cases in remission Grade ⩾2 cutaneous and subcutaneous neck radiation-induced fibrosis	35.7% had ⩾30% decrease in thickness 50% had decrease in severity

*Dysport ipsen: abobotulinumtoxinA injection Dynasplint® Dynasplint systems company, Maryland, USA.

radiation effects in breast (NCT04193722) was found. Notably hyperbaric oxygen has been studied for the treatment of other head and neck RT complications, such as osteonecrosis and xerostomia, with promising results despite its high costs and low availability.[82–84] In our search, there were no identified trials for interventions in the treatment radiation fibrosis in head and neck patients.

Conclusion

Radiation fibrosis is a common adverse event in patients treated with radiation therapy for head and neck malignancies. The pathogenesis is complex and involves dysregulation of the wound healing processes and upregulation of TGF-β and inflammatory cytokines. Clinical presentation is variable but can include trismus, neck stiffness, and fibrosis of cutaneous and subcutaneous tissues. There is a paucity of data for treating this condition; however, promising results have been displayed in small studies using pentoxifylline and Vitamin E as well as pravastatin. This condition continues to be understudied and trials based on molecular understanding should be conducted to better improve patients' therapeutic options.

Acknowledgements

Authors would like to acknowledge and thank Ms. Faryal Iqbal for helping with the figures.

Author Contributions

All the authors contirbuted equally in writing, reviewing and analyzing the manuscript.

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