[18]KRONICLE OF DENTAL SCIENCE.
Volume 2 Issue 1 Jul - Dec 2017.Pages 17-24

A Review

Radiation Induced Fibrosis Syndrome: A Narrative Review

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Keywords: Radiation; radiation-induced fibrosis; radiotherapy; fibrosis and radiation

ABSTRACT

Background and Setting: Radiation fibrosis syndrome/ Radiation-induced fibrosis (RFS/RIF) occurs as a consequence of the progressive fibrotic sclerosis that occur following the radiation (various types) therapy for cancer; and the term has been used to describe its innumerable clinical manifestations. Fibrosis is the primary complication of radiation and is said to influence the quality of life of a cancer survivor. For treatment of the Radiation Induced Fibrosis, understanding the pathogenesis of RIF is essential.

RIF is a consequence of a defective response to the wound healing. The response is the after-effect of the inflammatory changes that set in, due to the direct DNA damage and the free radicals generated from the ionising radiation. Inflammation, resulting in an increased TGF-β along with a host of other cytokines and growth factors, leads to fibrosis, that is manifested by increased collagen deposition, poor vascularity and scarring. The drugs for RIF have been directed against these molecules and their associated signaling pathways.

Conclusion: The main purpose of this article is to provide reasoning and stronger know-how of issues related to RIF and to suggest methods to prevent the radiation morbidity.

INTRODUCTION

The radiation therapy is used in treatment of head and neck cancers especially the squamous cell carcinoma: either alone or in combination with surgery and chemotherapy. [1] The immediate effect (usually 4–12 months), of irradiation on normal tissues is influenced by the radio-sensitivity of the individual patients. For, e.g., the mutated ATM (ataxia telangiectasia mutated) in the patients, diminishes the ability of cells to repair the radiation-induced DNA damage; thereby indicating a high radio-sensitivity. On the other hand, there is a variation in severity of the late effects of radiation that depends on the radiation dose, volume of the site treated, and the size of the lesion. [2] Radio-sensitizers and radio-protectants are introduced to limit the radiation exposure to noncancerous cells, thereby reducing its adverse effects. [3] The recurrent lesions, when viewed on the radiograph, may appear very perplexing and may sometimes be mistaken for a recurrent or a residual tumour. These lesions may lead to a condition called as the Radiation fibrosis syndrome (RFS) that may be seen clinically, years after the treatment.[2] Radiation-induced fibrosis (RIF), may commonly occur in the skin and subcutaneous tissues, gastrointestinal tract, lungs, and genitourinary tracts, as well as other organs that are in the path of the treatment. Patient-related factors, like pre-existing connective tissue

diseases, like for, e.g., Marfan syndrome, systemic scleroderma and (SLE) systemic lupus erythematosus are more likely to develop severe RIF.

Epigenetic modifications to DNA and histones have been associated with RIF as noticed by the inhibition of cutaneous radiation syndrome by inhibitors of histone deacetylase. These types of DNA alterations are long term, and as such, they produce fibrosis in response to radiation injury that remains even after the initial insult is no longer present. [2]

The patient and the clinicians do not formulate the steps required to encounter the late effects of head and neck cancer (HNC) therapy, as the stint during the active treatment is tough, exhausting and time-consuming; for both the patient and provider. The patient, therefore, looks to relax and heal, on completion of the therapy. The immediate post-treatment period is when the rigorous rehabilitation needs to be implemented, to improve the post-therapy functioning of the patient. It is, therefore, the duty of the clinician to warn the patient of the impending dangers; thereby helping in improving the life and reducing the symptoms of the long-term survivors of HNC. There is a lack of appropriate therapies that are available; to counter the late effects of HNC therapy, which doubles up the attempts in optimising the long-term supportive care outcomes. [4]

Radiation-induced damage can include “myelo-radiculo-plexo-neuro-myopathy” causing muscle weakness and dysfunction and also contributing to the neuromuscular injury. [2] The general manifestations of RIF include skin induration, limited joint mobility, muscle shortening and atrophy, mucosal fibrosis, lymphedema, ulceration, fistula and pain. Other local manifestations include xerostomia, trismus, osteoradionecrosis, decreased vocal quality, aspiration and dysphagia in patients with head and neck malignancies; brachial and cervical plexopathy, hypoxia, interstitial fibrosis, dyspnea with breast or lung malignancy; and the manifestations of increased urinary frequency, urinary urgency, dyspareunia, diarrhoea, loss of reproductive function in patients with abdominopelvic malignancy. [5]

Pathogenesis of RIF

Animal model studies on cancer therapy-related tissue toxicities have shown that the pathways during the normal healing process and in the case of the RIF are the same; wherein the TGF β superfamily and a multitude of pro-inflammatory cytokines are involved. The only difference between the two is that, in fibrosis, these signalling pathways escapes the standard cellular regulation. This result in a permanent injury state and the processes involved in normal healing are upstaged. [6] Anaemia, thrombocytopenia, and neutropenia are among the most common complications linked to radiation and chemotherapy; and the cancer patients may also be at a high risk for a varied sequence of non-hematological toxicities.

The molecular mechanisms following the cancer therapy have mostly been obtained from animal models. It has been stated that the immediate insult following chemotherapy and radiation, is a cellular response involving a specific cell type that occurs in stages:

- The inflammatory phase, in which the inflammatory cells are engaged; release cytokines that draw the immune cells and the fibroblasts to the site of injury.

- The proliferative phase, where the proliferating fibroblasts, migrate to the site of injury to form a scaffold on a temporary fibronectin matrix to deposit collagen type III to form a new barrier. [4]

- Where the proliferated fibroblasts, remodel themselves, with the help of both matrix building proteins and the secreted proteases, from local fibroblasts, to build up a new ECM (extracellular matrix), by the converting the flexible collagen type III into the more permanent collagen type I. These fibroblasts (myofibroblasts) are said to be heterogenous with the recruited fibroblast having various forms each assigned a specialized function; and vary in rates of proliferation, in response to inflammatory signals and ECM production. Fibro-nectin, collagen, and proteoglycans, resulting in the increased thickening and stiffness of the tissue. [5]

- The TGF-β also, promotes a reduced matrix metalloproteinase (MMP) activity (especially MMP-9 and MMP-2) and an additional activity of tissue inhibitors of metalloproteinases (TIMPs), adding to

the already disproportionate ECM deposition.

• Although the myofibroblasts stimulate angiogenesis and endothelial cell proliferation by secretion of basic fibroblast growth factor (βFGF), the excess collagen reduces the vascularity over time. Therefore the fibrotic areas would be more susceptible to gradual ischemia and physical trauma, leading to the loss of function, reduced fibroblasts and necrosis and also the tissue atrophy. But surprisingly, no relation has been found between the severity of early fibrotic lesions and the development of late effects of RIF. [5]

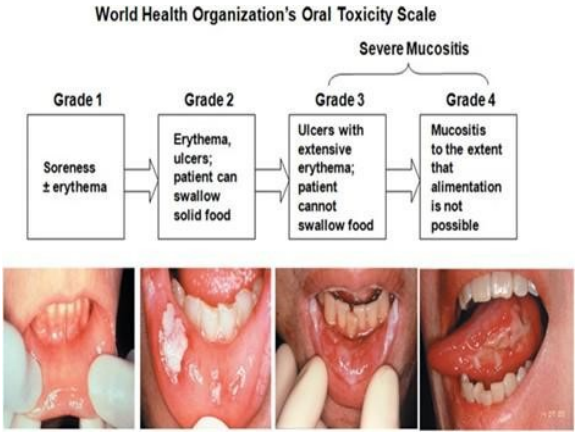

FIGURE 1: Oral mucositis. Picture Courtesy: Osama Muhammad Maria, et al. Front Oncol. 2017; 7: 89. Republished with the permission of Dr Patrick Stiff, Loyola University Medical Center, Maywood, IL, USA.

Diagnosis of RIF

Diagnosis of RIF is likewise is dependent on the site affected. In the skin or subcutaneous tissue, for instance, it may be done by palpation; in the muscle, by Young's modulus measurements (tensile or stiffness), using ultrasound to provide more quantitative measurements. As it stands, there remains no uniform consensus, with respect to objectively quantifying the degree of fibrosis, and there is an inconsistency in the grading scales like the version 4.0 of the Common Terminology Criteria for Adverse Events and the Radiation Therapy Oncology Group (RTOG), and the latter does not specifically address the RIF and the overall radiation toxicity. [4]

How can this action be suppressed?

Animal models have shown that the epithelium that is engineered to suppress Smad3 has a reduced fibrotic response and that the Smad3 null animals demonstrate an accelerated wound repair characterised by enhanced re-epithelialization with a reduced inflammatory response. A meta-analysis of other studies has failed to show a relationship between the three SNPs commonly associated with TGFβ1 and the hazard of late radiation-induced normal tissue damage.

TNF- α has been found to be a negative regulator of TGF-β and therefore has anti-fibrotic activity. Also, the auto grafted TNF-α applied directly to injured skin minimises the deposition of collagen.

Oral mucosal lesions comprise of deep, diffuse, and extremely painful ulcers that involve mobile mucosa. (Figure 1) This occurs when the radiation is subjected daily for five days/ week, in small, fractionated doses of 2Gy, amounting to a cumulative dose of 60–70Gy. On the other hand, the chemotherapy is given either every three weeks or weekly during the radiation period (days 0, 21, and 42), but in smaller doses. The mucositis occurring as a consequence is routine. At the end of the first week of treatment (where a cumulative radiation dose of 10Gy is subjected) the mucosa becomes erythematous are may sometimes be accompanied by a degree of pain equivalent to a bad food burn. By subjection to a cumulative dose of 30Gy, ulceration develops. As compared to the aphthous ulcers, these are more extensive and profound and painful which may require analgesics which may prove ineffective. Subepithelially, these ulcers undergo fibrosis which may result in trismus, characterised by a restriction of mouth opening often referred to as "lock jaw."

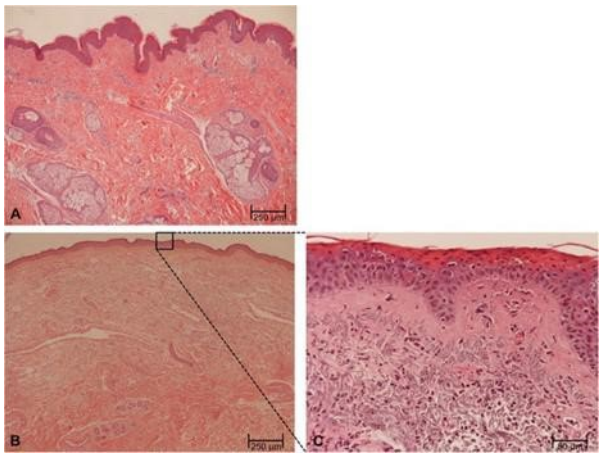

FIGURE 2: HE-Stain. In previously not irradiated tissue (a; scale) sebaceous glands, eccrine sweat glands, hair follicles as well as collagen and elastic fibres can be found in the epidermis. In irradiated tissue (b; scale bar = 250 µm) an epidermal atrophy with the ratification of sweat and sebaceous glands could be found. No intact hair

follicles could be identified. A detailed enlargement (c; scale bar = 50 μm) shows hypereosinophilic superficial epidermal layers as well as inflammatory cells in the dermis. Not shown in this enlargement are hyperpigmentations in the epidermis and numerous melanophages. Pic Courtesy: Steffen Koerdt, et al. Radiat Oncol. 2015; 10: 202.

The initial phase shows oxidative stress and stimulation of the innate immune response, mainly in the endothelium and stroma after the radiation exposure. This leads to a canonical pathway causing a cytokine cascade resulting in a fibronectin breakdown, and proliferation of pro-inflammatory cytokine signaling cascades like the TGFβ and TNF-α pathway. Finally, ulceration occurs (Figure 4). Secondary bacterial infection and an exposed surface epithelium cause the stimulation of the macrophages to produce additional cytokines. The mucosa makes all attempts to prevent this invasion by causing an altered fibrosis. This results in trismus causing difficulty to the patient. The salivary function is disturbed due to parenchymal replacement with fibrous tissue and development of oesophagal strictures. Of these, the mucositis is acute, whereas the fibrosis-related changes are more chronic and may cause complications in the otherwise healed cancer patient. [7]The lining of the small blood vessels comprising of endothelial cells is destroyed, resulting in subsequent fibrosis, following the ischemia, edema, inflammation and finally a delayed fibrosis. (Figure 2) All tissues that surround the blood vessels of the head and neck may be affected, due to the interstitial edema, or the edema that develops in the surrounding soft tissues during the radiation therapy; or the ensuing months after radiation therapy. This is seen as a thickening of skin (Figure 3) and platysma muscle, edema in deep neck spaces such as the carotid sheath and reticulation of subcutaneous and deep fat tissues, on MRI images.

The salivary glands and thyroid tissues also become edematous and appear heterogeneous, with the images on MRI showing altered signal intensity (low on T1, high on T2). The degree of enhancement differs, but is typically diverse, in the early post-treatment stages. Xerostomia occurs as a follow-up to parotid atrophy, and thyroid atrophy may produce hypothyroidism.

Complications of Radiation Therapy

Any growing mass, bone or chondroid destruction or lymphadenopathy, must be viewed with suspicion for recurrence. A neoplasm is considered radiation- induced if it has an altered histopathology; different from that of an original neoplasm; developing within an irradiated field; more than 5 years after treatment.

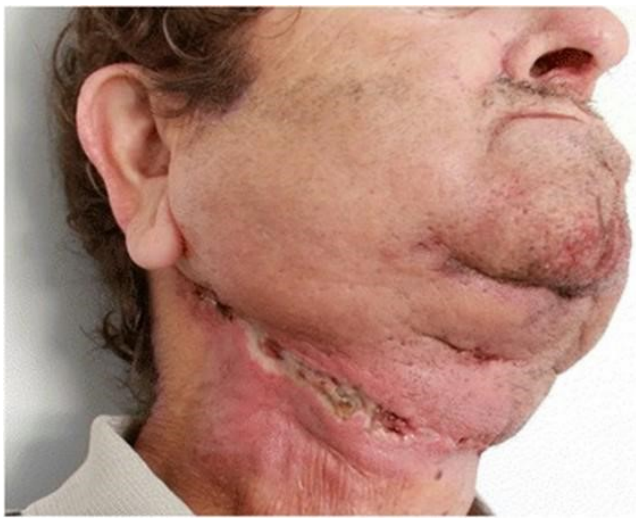

FIGURE 3: *Radiation-induced damage in the cervical region (radiation dose of 64 Gy). Picture Courtesy: Steffen Koerdt, et al. Radiat Oncol. 2015; 10: 202.*

Mucosa and Submucosa

During the early days of treatment, there is commonly a mucosal irritation [8] and edema, which may result in pain and dysphagia and that, may limit the oral intake, and in extreme cases, it may also cause an airway obstruction. Necrosis of the pharynx and larynx is maximum during the first 12 months after treatment, or sometimes more than 10 years after radiation therapy. Mucosal ulceration, if deep, should alert the patient and clinician. The end stage of all these steps is the fibrosis and atrophy of the affected tissue and a reduction in the capacity of all tissues of the neck. Muscles may undergo fibrosis; mainly the pterygoid and temporomandibular joint. MRI images reveal a loss of muscle volume with hyperintense T2 signal and enhancement with a linear boundary that would indicate a defined radiation field. This finding indicates a differentiation in the radiation effect arising from the denervation. Muscle T2 signal hyperintensity is said to be maximum at approximately 12–18 months after radiation, whereas on the other hand, the accompanying muscle atrophy tends to slow at approximately 18 months.

Bone and Cartilage

Osteoradionecrosis (ORN) of the mandible, hyoid, skull base, or upper cervical spine occurs when the cell injury and the radiation fibrosis reduces the ability of tissues to adjust to normal turnover, therefore resulting in tissue breakdown. [1]The exposed irradiated bone tissue that does not heal over a period of 3 months; without a residual or recurrent tumor; (Marx gives a similar definition but with a healing period of 6 months) results in ORN. [3] Osteoradionecrosis (ORN) occurs predominantly in the first 6–12 months after radiation therapy; but may persist years after therapy. [1]Clinical manifestations of ORN: are exposed necrotic bone, ulceration, sequestra, purulent discharge, pain, paraesthesia, swelling, trismus, cutaneous fistula and pathologic fractures. ORN is more frequently observed in the mandible than the maxilla; due to its reduced vascularity and cortical nature of the bone and that it receives more irradiation than the latter. ORN mainly occurs 4 months to 2 years after completion of radiation therapy. [3]

To prevent ORN, the extraction should be done at least 21 days before the imitation of the radiation therapy to enable the initial healing process and also to enable the recently formed tissues to better withstand irradiation. Otherwise, if required post radiation, the extraction should be done within 4 months of therapy completion; beyond which the ORN risk increases. Once the safe period is over, alternatives, such as restoration or root canal treatment, are preferred. Marx's theory states that the HBO therapy should be used in case the teeth need to be extracted outside these periods. [3]The ORN on CT is seen as cortical disruptions and the loss of trabeculations. The development of new heterogeneous signal within the marrow of an irradiated area (intermediate or low T1 signal, intermediate or high T2 signal) on an MRI should be attended to. It is extremely difficult to differentiate an osteoradionecrosis either with or without osteomyelitis from a recurrent tumor, but frank bone destruction without a soft-tissue mass is most likely an ORN.

- An imbalance between the normal homoeostasis of cell repair and cell death, collagen synthesis and collagen breakdown could be responsible for this phenomenon.
- A second theory suggests that the suppression of osteoclasts by radiation directly affects bone turnover. This alteration is thought to occur earlier than vascular damage.
- Also, a fibro-atrophic theory proposes that it is the reduced ability of fibroblasts to produce collagen that renders tissues weak and fragile

Intense enhancement of the adjacent edematous muscles may be seen, which may be mistaken for a recurrent tumour if osseous changes are not visible in CT. The presence of a bulky soft-tissue mass together with bone destruction would indicate tumour recurrence, in which case a biopsy is mandatory.

Nervous System

When cancer of the skull base or nasopharyngeal carcinomas has been treated by radiation therapy, the temporal lobe necrosis is a complication; occurring months or < 5 years after treatment. The other complications may be a vagal neuropathy and hypoglossal palsy that can occur 2–10 years after radiation which may be caused by the entrapment of the nerve by fibrosis. Early months after treatment (1-2 years) may show an acute spinal cord injury which is usually reversible, whereas an enlargement indicates a delayed radiation myelopathy, which is uncommon. It manifests as a T2 hyper intensity, and enhancement. Radiation-induced brachial plexopathy, as a recurrence of squamous cell carcinoma, is uncommon, and peaks at about 2–4 years after treatment especially of the breast carcinoma—the reason being that the nodal groups associated with head and neck tumors are separated and protected from the supraclavicular plexus by the anterior scalene muscle. Brachial plexus tumor manifests as pain, rather than numbness and weakness.

Sarcomas occur approximately 10 years after radiation. The squamous cell carcinomas of the external auditory canal and the less common cerebral neoplasms are observed 10–15 years after the skull base radiation therapy. [1]

Loss of function due to lymphedema and fibrosis

Lymphedema is a consequence of an accumulation of fluid and proteins in the soft tissues, proximal to and surrounding the damaged lymphatic vessels. The damage could be a surgical error or following

radiation-induced sclerosis. Lymphedema may cause the damage of soft tissues and may worsen a post-radiation swelling. In the later stages, the lymphedematous tissue becomes fibrotic, with a subsequent loss of tissue flexibility and function. Thus, lymphedema may be followed by fibrosis, and patients may suffer from both concurrently. The lymphedema may be internal (involving structures such as the pharynx and larynx) or maybe external (involving structures such as the neck, face and the sub-mental region. Lymphedema and fibrosis are common complications of patients treated for HNC notwithstanding the treatment modality and maybe associated with significant symptoms and function deficits.

Dysphagia

In patients treated with surgery, removal of vital structures would result in dysphagia and the patient would require a feeding tube later. The causes for dysphagia were proposed to be: a consequence of radiation-induced fibrosis or a chronic lymphedema leading to fibrosis. Persistent use of feeding tube was suggested as another reason for the dysphagia, following which there was a disuse atrophy of the musculature that aggravated the underlying physiologic change leading to the disturbance in function. There have been attempts to reduce the occurrence of long-term dysphagia, by minimising the radiation to structures, vital for swallowing; and the use of aggressive swallowing therapy during and after treatment.

Earlier, the swallowing therapies were initiated only after swallowing difficulties arose; but this logic has found no takers. Anyways, it is important for preventive measures to be implemented for optimal long-term swallowing functions.

The swallowing dysfunction has been reported to be bi-modal, with most patients experiencing an acute reduction in their swallowing function right after surgery and/or radiation therapy. So if swallowing therapy is implemented immediately, it would result in a substantial improvement in the swallowing, for most patients. Chronic inflammation and late tissue damage are unfortunate consequences of the cancer treatment–induced fibrosis and lymphedema. As late soft tissue damage manifests, patients may experience a slow decline in their swallowing functions.

Strictures may follow either surgery or radiation, but not much information is available from the modulated radiation dose, volume, and target by IMRT (Intensity modulated therapy). Mucositis precedes stricture formation, and the simultaneous use of chemotherapy increases the incidence of stricture formation. Strictures have been successfully treated with dilation therapy regardless of the cause. The patient's diet intake may suffer and more so if he has a history of smoking. The occurrence of the strictures as a late feature of radiation has made the clinician more cautious in treating the HNC. The patients are referred to a speech and language pathologists to be educated about consuming food orally and to reduce the dependence on the feeding tubes as soon as possible. The health care providers also monitor the swallowing function as part of routine follow-up.

Trismus

Both methods of treatment: surgery and radiation; damage vital structures that cause jaw movement, namely the tempero-mandibular joint and muscles of mastication. Wherever there is tissue damage, it results in an uninhibited proliferation of fibroblasts leading to stricture formation and fibrosis. Trismus, as a consequence of the fibrosis, reduces the inter-incisal distance to >35 millimetres in dentulous patients and >40 millimetres in edentulous patients. The occurrence of this probability has been reported to be approximately 45%, and the prevalence was found much more reduced with IMRT than the conventional radiotherapy. Chemoradiotherapy either together with or postoperatively, with the above-mentioned treatment methods, further worsens the prevalence of trismus. Chewing, swallowing and speaking are affected as a consequence of trismus. Maintaining the oral health of these patients is also affected. Oral intubation is affected in those cases where it is being used.

Forestalling this complication, the patients should be subjected to jaw-stretching exercises to maintain health. Stretching devices should be used in cases where such complications develop. Postural abnormalities

Postural abnormalities may also develop as an HNC. They may include the central collapse of the anterior chest, loss of normal lordosis in the lower back, kyphosis, and internal rotation of the humerus and protrusion of the head in a forward direction. The extent of this complication has not been reported. There are some processes that may contribute to postural abnormalities:

- Primarily, the radiation and dissection in the neck may result in the soft tissue damage followed by fibrosis and contracture.
- Secondly, the atrophy and the neurologic damage following radiation and/or surgery cause denervation and associated weakness; which may be apparent after prolonged activity.
- Finally, alignment of the spine is affected due to severe deconditioning and muscle weakness.

This may result in aspirational complications; musculoskeletal pain reduced pulmonary function as a result of the compression of the chest wall.

Vascular Complications

In 1983, Marx presented the 3-H concept: hypovascular, hypocellular and hypoxic environment (hence the name 3-H). [3] HNC therapies may cause vascular complications such as the stroke and the carotid artery rupture. Whenever the recurrence is seen close to the vascular structures, there is the likelihood for a carotid rupture but a possibility of it occurring, following chemotherapy would be as a pharyngo-cutaneous fistula or non-malignant ulceration of the lateral wall of the hypopharynx. Whatever be the cause, since the mortality rate is high, prompt treatment needs to be advocated either by a surgical or endovascular approach. Radiation therapy may also cause pathologies in the medium and large arteries, such as increased intimal thickening that may further lead to ischemic attacks and strokes. This has been confirmed by a meta-analytic study, and its incidence will only increase as the prognosis following cancer therapy, improves. Currently, the screening for asymptomatic carotid artery stenosis is not advisable. Not much care is being taken for the anticipation of vascular complications, and therefore it would be advisable to monitor such patients who have a risk for cerebrovascular disease. [2]

It can, therefore, be concluded that once a patient develops cancer, whatever be the treatment modality followed, he must be under observation throughout his entire life. Interventional therapies that are more evidence-based should be applied. Or at least, the patients should be educated regarding these complications, so as to decrease the stress and the anxiety of the patient. Also, researches need to be conducted so as to understand the late effects of radiation, better. [5]

The prevalence of the RIFP has reduced from 66% RIBP with 60 Gy in 5 Gy fractions to > 1% with 50 Gy in 2 Gy fractions from the 1960s to the present. [5]

Treatment for RIFP

Numerous therapies [9] have been proposed for RIFS, but none of them have shown positive results. The treatment includes analgesics, drugs targeting the antioxidant pathways, [10], etc.; and the measures to improve the everyday life of the patients are underway. [11]

CONCLUSION

The extent of the radiation field, the effect of the underlying tissues to the radiation effects and the resistance of the patient to radiation, determine the morbidity of the patient due to RFS. The patient's age, medical conditions, and other damaging disorders; the degenerative spine disease; cancer status; exposure to cardiotoxic, neurotoxic and other chemotherapies, influence the overall health of the patient; the type and duration of radiation therapy is also significant. The patients would not enjoy the benefits of an elaborate radiation

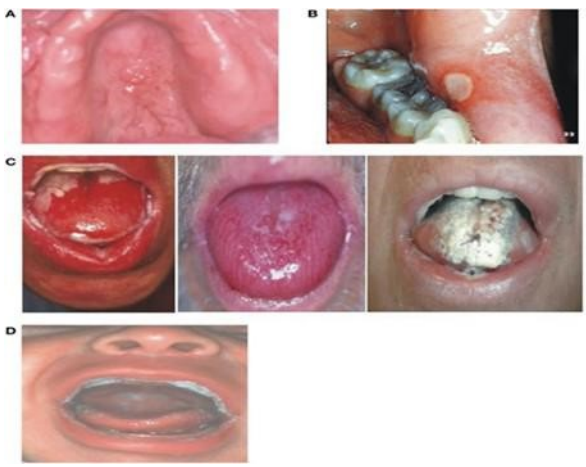

FIGURE 4: Differential Diagnosis of Oral Mucositis. Picture Courtesy- Osama Muhammad Maria, et.al. Front Oncol. 2017; 7: 89. Republished with the permission of Dr. Patrick Stiff, Loyola University Medical Center, Maywood, IL, USA. (A) Local, denture-related lesion, (B) aphthous ulcer, (C) oral mucositis, and (D) oral mucositis (E) Oral Thrush

therapy, due to a decreased tolerance to the therapies employed.

Therefore interventional therapies are mandatory to prevent or treat fibrosis that occurs as sequelae to regimen-related toxicities. Just a clinical examination or cross-sectional imaging would be insufficient to detect the residual or recurrent tumor, post radiation. If the evolution of changes in the neck irradiation is understood, it will facilitate the evaluation in response to treatment; and the detection of the persistent or recurrent tumor would enable early detection of radiation complications.

Competing Interests: The authors have no conflict of interest regarding this article.

REFERENCES

1. Christine M. Glastonbury, Ellen E. Parker, Jenny K. Hoang, Glastonbury CM, Parker EE. The Postradiation Neck: Evaluating Response to Treatment and Recognizing Complications. AJR. August 2010; 195: W164-W171

2. Jeffrey M. Straub, Jacob New, Chase D. Hamilton, Chris Lominska, Yelizaveta Shnayder, and Sufi M. Thomas. Radiation-induced fibrosis: mechanisms and implications for therapy. J Cancer Res Clin Oncol. 2015 November; 141(11): 1985–1994.

3. Katarzyna Hojana, and Piotr Mileck. Opportunities for rehabilitation of patients with radiation fibrosis syndrome. Rep Pract Oncol Radiother. 2014 Jan; 19(1): 1–6

4. Maria L. Mancini and Stephen T. Sonis. Mechanisms of cellular fibrosis associated with cancer regimen-related toxicities. Front. Pharmacol. 27 March 2014; 5: 51

5. Sylvie Delanian, Jean-Louis Lefaix, Pierre-François Pradat, Barbara A. Murphy, Jie Deng. Advances in Supportive Care for Late Effects of Head and Neck Cancer. Journal of Clinical Oncology. October 2015; 33(29): 3314-3321

6. Steffen Koerdt, H. Rohleder, Niklas Rommel, et al. An expression analysis of markers of radiation-induced skin fibrosis and angiogenesis in wound healing disorders of the head and neck. Radiat Oncol. 2015; 10: 202.

7. Bhandare N, Mendenhall WM. A Literature Review of Late Complications of Radiation Therapy for Head and Neck Cancers: Incidence and Dose Response. J Nucl Med Radiat Ther. 2012 S2:009

8. Fleta N. Bray, Brian J. Simmons, Aaron H. Wolfson, and Keyvan Nouri. Acute and Chronic Cutaneous Reactions to Ionizing Radiation Therapy. Dermatol Ther (Heidelb). 2016 Jun; 6(2): 185–206.

9. Ronny Kalash,a Michael W. Epperly,a Julie Goff, et al. Amelioration of Radiation-Induced Pulmonary Fibrosis by a Water-Soluble Bifunctional Sulfoxide Radiation Mitigator (MMS350).Radiat Res. 2013 Nov; 180(5): 474–490.

10. Osama Muhammad Maria, Nicoletta Eliopoulos, and Thierry Muanza. Radiation-Induced Oral Mucositis Front Oncol. 2017; 7:89.

11. Franklin J. Berkey. Managing the Adverse Effects of Radiation Therapy. Am Fam Physician. 2010 Aug 15; 82(4): 381-388.