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REVIEW ARTICLE

RADIOTHERAPY AND ORAL HEALTH

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ABSTRACT

Approximately one million people develop invasive cancer each year. Of these, 40% will receive curative benefit from surgery, radiation, chemotherapy, or a combination modality. In dealing with patients with cancer of the head and neck a team approach is required for effective management. When radiation therapy is indicated, it is imperative that health of the oral cavity be assessed initially as well as throughout therapy and post therapy. All members of the cancer treatment team should be informed of the oncologic treatment plan. Oral care should be initiated at the onset of treatment, with the goal of reducing morbidity and improving compliance. Total body irradiation and irradiation to the head and neck cause both direct and indirect effects on oral and related structures, and may be acute or chronic in nature. These complications may include mucositis, xerostomia, dental caries, loss of taste, trismus, infection, osteoradionecrosis, and abnormalities of growth and development. The objective of this literature review is to summarize information about the radiation effects, diagnosis and administer treatment to protect a patient's oropharyngeal health and quality of life.

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INTRODUCTION

Radiations have high linear energy which is transferred to tissues with an intent to kill cancer or neoplastic cells. During this procedure even normal cells are damaged but because cancer cells have more replicative potential than normal cells, there are more chances that the cancer cells are irradiated at a considerably more vulnerable time in their respective cell cycle as compared to normal cells. (Marx, first edition) When the oral cavity and salivary glands are exposed to high doses of radiation, there can be dramatic effects on the patient's oral health. Depending on the location of a malignant disease (primary tumors, lymph-node metastases), inevitably, the salivary glands, oral mucosa, and jaws have to be included in the radiotherapy portals. In addition to the undisputed anticancer effects of ionizing irradiation, it will cause damage in healthy tissues located in the field of radiation. This effect becomes especially evident in the head and neck region, where several dissimilar structures (skin, mucosa, subcutaneous connective tissue, salivary gland tissue, teeth, and bone) are located. These tissues usually show different reactions to radiotherapy, which vary from acute or transient changes (mucosa, taste, salivary glands) to intermediate (taste, salivary glands) and late (salivary glands, bone) effects. Since the overall 5-year rate for oral cancer survival is fairly good for the early stages of oral cancer and about 35% for advanced stages, the late or longterm alterations (salivary glands, dentition, periodontium, bone, muscles, joints) are increasingly moving into the focus of interest.This paper provides an overview of the possible consequences which a patient may undergo following radiotherapy and help in combating the same in association with the medical team.

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Assesment of oral cavity before starting radiotherapy

In approximately 90–100% of patients whose irradiation fields include any part of the oral cavity, there will be at least some degree of oral complication which may be acute as well as of chronic nature. (Herrstedt, 2000) So the assessment prior to initiation of radiotherapy holds a lot of importance. Oral problems which may result out of radiation therapy can be minimized to a significant level through prior thorough examination. The acute effects resulting out of radiation therapy include mucositis and altered functions of salivary

gland which further increases the risk of mucosal infection. The long-term or the chronic effects are due to large scale changes in the blood supply or vascularity and cellular morphology of soft tissue as well as hard tissue most important of which includes damage to the salivary glands. There is also an increase in collagen synthesis which subsequently results in fibrosis. These changes lead to triple H called hypo-vascularity, hypo-cellularity and hypoxia of the tissues. So the assessment prior to initiation of radiotherapy holds a lot of importance. (Carl, 1993; Simon and Roberts, 1991) Many oral conditions, most prevalent of which is poor oral hygiene, broken teeth, defective restorations and periodontal disease, are more than likely to precipitate above mentioned complications both during and after irradiation. Along with clinical examination, radiographic examination should also be carried out thoroughly to know the prognosis of all dental hard as well as soft tissues. After clinical judgement extractions should be carried out for these teeth Caries (nonrestorable), Active periapical disease (symptomatic teeth), Moderate to severe periodontal disease, Lack of opposing teeth, compromised hygiene, Partial impaction or incomplete eruption, Extensive periapical lesions (if not chronic or well localized). (https://www.cda-adc.ca/jcda/vol-69/issue-9/585.html) The periodontium is sensitive to the effects of radiation at high doses (Guglielmotti *et al*., 1986; Wright, 1987; Marx, 1983; Arcuri and Schneider, 1992; Fattore *et al*., 1987; Fujita, 1986; Medak and Burnett, 1954; Chambers *et al*., 1958). Blood vessels in the periodontium, periosteum and the periodontal ligament (Guglielmotti *et al*., 1986; Marx, 1983) may be affected leading to widening of the periodontal ligament space (Fujita *et al*., 1986; Medak and Burnett, 1954; Chambers *et al*., 1958). These changes may result in a increased risk of periodontal disease, and impaired capacity of bone remodeling and repair (Guglielmotti *et al*., 1986; Silverman and Chierici, 1965; Joyston-Bechal, 1992) and rampant periodontal destruction may occur in the absence of good oral hygiene. (Silverman and Chierici, 1965) Endodontic and periodontal intervention should be done wherever possible after clinical judgement. (Epstein and Stevenson-Moore, 2001)

During radiotherapy

Clinically, irradiated tissue develops an initial erythema and dermatitis as an acute response to the radiation damage. Caused by vascular hyperemia indicative of vascular damage and tissue inflammation, these conditions will subside and the tissue will normalize clinically over the next 4 months. Sub clinically, however, the damaged endothelium induces thrombosis, and fibroblasts die without being replaced by daughter cells, leaving behind extracellular collagen. The tissue becomes fibrotic and inelastic, radiation hyper and hypopigmentation of skin often develop, and radiation telangiectasias become apparent. It is this type of tissue, involving skin, mucosa, and bone that is at risk of nonhealing if wounded by an injury or from surgery. Such tissue is more likely to become an avascular, nonhealing wound such as osteoradionecrosis of bone or soft tissue radiation necrosis several years after radiation. (Marx, First edition)

Mucositis

Acute mucositis results from the loss of squamousepithelial cells because of radiation-induced mitotic death of basal keratinocytes. This process leads to a gradual linear decrease in the number of epithelial cells. As radiotherapy continues, a steady state between death and regeneration of mucosal cells could occur because surviving cells are produced at an increased rate. However, cell regeneration often cannot keep up with the rate of cell death, resulting in some or complete denudation of the mucosa. (Sciubba and Goldenberg, 2006) The development of mucositis depends on the dose of radiation, angulations to the beam location of tumor and the degree of oral hygiene, mucositis can occur anywhere there is oral mucosa including the oral cavity, esophagus, larynx, and pharynx, clinically, the oral mucositis appear to be due to epithelial thinning and vasodilatation. This can lead to ulceration or mouth sores, sloughing of the epithelium, and crusting of lips. Oral mucositis causes serve pain and increases the risk for the development of systemic infection from bacterial, fungal, or viral infection in the mouth. The discomfort of mucositis can be reduced with coating agents, topical anesthetics and analgesics, although systemic analgesics are frequently needed. (Carl, 1993) Aluminum hydroxide/ magnesium hydroxide (milk of magnesia-Maalox) and sucralfate have been suggested as coating agents for the oral mucosa. Sucralfate suspension may also be helpful in the treatment of oral pain, although the effect on mucositis has not been clearly documented (Makkonen *et al*., 1994; Allison *et al*., 1995; Franzén *et al*., 1995; Meredith *et al*., 1997; Carter *et al*., 1999) Topical anesthetics used in rinse form may result in intense but short-term anesthesia. However, the localized anesthesia can increase the risk of aspiration, and their systemic absorption can cause cardiac effects. When oral mucosal pain is present, benzydamine hydrochloride (Tantum), doxepin suspension 0.5% or an antihistamine such as diphenhydramine can be prescribed (Epstein *et al*., 2001; Epstein *et al*., 2001) Benzydamine is the only medication available that has been shown in multicentre, double-blind controlled studies to reduce mucositis and pain in patients with head and neck cancer. (Epstein *et al*., 2001; Epstein *et al*., 2001) Topical anesthetics, such as benzocaine, viscous lidocaine and topical benzocaine can be applied locally to sites of pain with a swab or a soft vinyl mouth guard (Carl, 1993). Of all available mouth rinses that can be used as treatments for mucositis, the least costly and easiest for patientsto prepare is a simple mouthwash comprising a teaspoon (10 mL) of salt and a teaspoon (10 mL) of baking soda (sodium bicarbonate) in 8 ounces (250 mL) of water. A comparison among salt and soda mouthwashes, mouthwashes prepared from lidocaine and diphenhydramine with Maalox, and mouthwashes of 0.12% chlorhexidine gluconate found that the 3 options were equally effectivein the treatment of chemotherapy-induced mucositis (Dodd *et al*., 2000). Although chlorhexidine may also decrease oral *Candida* counts and bacterial levels, studies on radiotherapy patients have shown no effect on mucositis. According to the current literature, good oral hygiene, topical fluorides for caries prevention and benzydamine offer the greatest benefits.

Caries

Fattore *et al*. said one of the earliest problems after RT is the development of abnormal caries. (Fattore *et al*., 1986) Irradiated patients are at increased risk for the development of a rapid, rampant carious process known as radiation caries. (Aguiar *et al*., 2009) Caries frequently becomes severe in the cervical and incisal edges of teeth and, if left untreated, can progress rapidly to involve the pulp. (Fattore *et al*., 1986) Dentists play an important role in the prevention of the condition via comprehensive oral health care before, during, and after the active cancer therapy. A good oral hygiene should be maintained throughout the treatment. It includes brushing 2–4 times daily with a soft-bristled toothbrush, daily flossing. To

control for plaque accumulation, chlorhexidine mouthwashes should be continued in conjunction with and after normal daily tooth brushing. Fluoride prophylaxis with custom-made carriers and high concentrated fluorides (5000 ppm) should be maintained. (Kielbassa *et al*., 2006) For the prevention of rampant dental demineralization and caries, patients should apply a 1.1% neutral sodium fluoride gel daily (for at least 5 minutes), using a custom fitted vinyl tray if possible. (Carl, 1993; Whitmyer *et al*., 1997) This practice may be started on the first day of radiation therapy and continued daily as long as salivary flow rates are low and the mouth remains dry. Other than radiation induced caries, xerostomia is another reason for caries. Salivary substitutes to relieve symptoms and sialogogic agents to stimulate saliva can be used. (Dost and Farah, 2013) A study indicated that the efficacy of oral pilocarpine was dependent on the dose distributed to the gland. (Brizel *et al*., 2000) Contraindications include asthma, iritis, and glaucoma. Caution is advised in patients with chronic obstructive pulmonary disease and cardiovascular disease. A newer muscarinic agonist, cevimeline, when administered 30–45 mg 3 times daily for 52 weeks produced very few adverse effects, increased unstimulated but not stimulated saliva. (Chambers *et al*., 2004) Lemon candy can be sucked to increase the amount of whole saliva secretion and hence improve oral dryness. Sugar-free gums containing xylitol may stimulate salivary flow, buffering, sugar clearance, and can prevent dental decay. (Edgar *et al*., 1994)

Infections

In patients undergoing head and neck radiotherapy, *Candida* colonization tends to increase throughout the course of treatment and remains increased if xerostomiaoccurs (Edgar *et al*., 1994; Epstein *et al*., 1998). Nystatin rinses are the most widely prescribed treatment for oral fungal infections, despite a lack of proven efficacy. Nystatin has an unpleasant flavour and may cause nausea and vomiting, (Feber, 1995) and its high sucrose content is a major concern in dentate patients. For more severe infections, the use of a systemic antifungal medication such as fluconazole (Diflucan) or amphotericin B is recommended. (Carl, 1993) Systemic amphotericin B must be used with caution because of its potential to cause liver toxicity. (Simon and Roberts, 1991) Topical antifungals to consider include clotrimazole, ketoconazole and chlorhexidine. Chlorhexidine gluconate (0.12%; Peridex), an antimicrobial rinse, has both antifungal and antibacterial properties in addition to antiplaque effects; however, its value is still unconfirmed. Its tendency to stain teeth and its alcohol content, which can irritate inflamed tissues, are drawbacks (Epstein *et al*., 1998). If chlorhexidine is used, it is important to note that nystatin and chlorhexidine should *not* be used concurrently, because chlorhexidine binds to nystatin, rendering both ineffective; (Feber, 1995) furthermore, chlorhexidine should be used atleast 30 minutes before or after the use of any other topical agents with which it may bind. For cancer patients with viral infections, such as Herpes simplex 1, acyclovir (Zovirax, GlaxoSmithKline) orderivatives are recommended for both prophylaxis and treatment (Carl, 1993; Epstein *et al*., 1993). Penciclovir (Denavir, GlaxoSmithKline), a newer topical antiviral with increased tissue penetration, is now available.

Post radiotherapy

Xerostomia

Xerostomia is probably the most common persistent oral sequela for patients who receive therapeutic doses of radiation for head and neck cancer. The disorder becomes evident as saliva becomes scant, sticky, and viscous as a result of changes in its composition during the course of radiotherapy. Xerostomia causes oral discomfort and pain, an increased risk of dental caries, oral infection, difficulty speaking, and dysphagia, and has a detrimental effect on patients'quality of life. Recovery, if it occurs at all, could take years. (Cooper *et al*., 1995) Various radiotherapy regimens result in varying degrees of xerostomia. Mantle, unilateral, and bilateral fields of radiation can be associated with a fall in salivaryflow of 30–40%, 50–60%, and 80%, respectively. In patients with head and neck cancer whose major salivary glands were within the treated fields of radiotherapy, the prevalence of xerostomia after the procedure varies between 94–100%. (Kies *et al*., 2001) So various ways to manage xerostomia starts with salivary-gland-sparing techniques such as three-dimensional intensity-modulated radiotherapy. Another way includes use of sialogogues. Untreated or unaffected residual salivary tissue is the target for sialogogues. Salivary stimulants can be characterised as gustatory, tactile, or pharrmacological. (Vissink *et al*., 2003) Gustatory stimuli, especially acidic substances, are used as sucking sweets (hard-boiled sweets) to increase salivary secretion. Bitter substances also stimulate salivary secretion, whereas sweet substances stimulate salivary flow to a reduced extent and can exacerbate the sensation of a dry mouth. A combination of tactile and gustatory stimuli can be found in (sugarless) chewing gum. (Vissink *et al*., 1988) Pharmacological sialogogues are typically agonists of the muscarinic M3 receptor and include pilocarpine and cevimeline. (Ship and Hu, 2004) Of these drugs, pilocarpine has been most extensively investigated. The use of pilocarpine to stimulate residual salivary tissue after completion of radiotherapy has restricted efficacy, because the functional gain ceases with drug withdrawal. (Niedermeier *et al*., 1998) The effect of pilocarpine is more persistent when it is used before and continued during radiotherapy, and then stopped 3 months after radiotherapy. (Zimmerman *et al*., 1997) Adverse effects of non-selective cholinergic agonists include perspiration, increased bowel and bladder motility,and flushing. (Vivino *et al*., 1999) Patients with a history of asthma, severe chronic obstructive pulmonary disease, congestiveheart disease, and narrow angle glaucoma should avoid these drugs. Cevimeline is a quinuclidine analogue of acetylcholine that has a high affinity for M3muscarinic receptors of lacrimal and salivary glands, but a low affinity for equivalent M2 receptors on cardiac and lung tissue. (Porter *et al*., 2004) Thus, cevimeline can enhance salivarysecretions while keeping adverse effects to a minimum on pulmonary and cardiac function. Cevimeline is being investigated for treatment of radiotherapy-induced salivary hypofunction. (Ship and Hu, 2004) It could also have clinical application in management of xerostomia secondary to irradiation, but additional data are clearly needed (Porter *et al*., 2004) Artificial saliva or saliva substitutes preparations (oral rinses containing hyetellose, hyprolose, or carmellose) are purely palliative substances that relieve the discomfort of xerostomia by temporarily wetting the oral mucosa.

Trismus

5–38% of patients develop trismus after treatment for head-and-neck cancer. (Thomas *et al*., 1988; Steelman and Sokol, 1986) Patients who have been previously irradiated, those who receive both surgery and radiotherapy, and those who are being treated for a recurrence, seem to be at higher risk of trismus than are those receiving their first treatment. Whenever

possible, the dose of radiotherapy to the temporomandibular joint and to the mastication muscles should be reduced. Physicians should be proactive in identifying early signs of trismus. One simple test is the so-called three finger test, in which the patient is asked to insert three fingers into the mouth. Management of trismus includes physiotherapy with a range of simple and inexpensive devices. These instruments include aggregated tongue blades or forced opening with finger pressure several times per day, as well as the use of more elaborate dynamic opening systems. Pentoxifylline, a methylxanthine derivative used to treat vascular diseases such as intermittent claudication, has been reported to have effects against TNF_ (tumournecrosis factor), increase erythrocyte flexibility, vasodilate, and inhibit inflammation. Clinical reports of pentoxifylline as the only substance for radiation-induced fibrosis and trismus seem to be contradictory; findings need to be confirmed by randomised placebo-controlled studies. Endogenous tocopherol can scavenge reactive oxygen species generated during oxidative stress. In events of established or late evolving trismus, the use of pentoxifylline with concomitant use of tocopherol for several months has proven effective. (Chua *et al*., 2001)

Extraction

The first 4 months after radiotherapy represent a time of tissue recovery without the accumulation of the three H tissue effects. It offers a short but useful period in which to accomplish necessary oral surgery procedures without the need for HBO. After 4 months, development of the three H tissue will begin to affect healing. After this time, the standard protocol of HBO is recommended for elective surgery in irradiated tissues. That protocol consists of 20 sessions at 2.4 atmospheres of absolute pressure (ATA) for 90 minutes on 100% oxygen prior to surgery and 10 sessions after surgery. Daily sessions are conducted 5 or 6 days per week. Specifically related to tooth extraction years after radiotherapy, this protocol has shown a dramatic reduction in the development of osteoradionecrosis. This protocol is also indicated when any other surgery is performed on irradiated tissue. Even vascularized or pedicled vascular flap surgery requires this protocol. Althoughthe flap may be vascular, the tissue into which it is placed is not. Frequent dehiscences, tissue necrosis, and infections occur adjacent to vascularized flaps that have been placed into irradiated tissues unsupported by HBO. Today, this protocol has also allowed the placement of osseointegrated dental implants in irradiated patients without a significant incidence of osteoradionecrosis. (Marx First edition)

Osteoradionecrosis

Established osteoradionecrosis with exposed bone represents an advanced radiation tissue injury. A specific protocol using hyperbaric oxygen combined with selective surgeries when required has proven effective in resolving osteoradionecrosis. This protocol is recommended by the Undersea and Hyperbaric Medicine Society and endorsed by the National Cancer Institute through a consensus conference. It uses 30 sessions of hyperbaric oxygen at 2.4 ATA for 90 treatment minutes of 100% oxygen followed by 10 sessions after an assessment or surgery. This protocol not only uses hyperbaric oxygen to develop a capillary angiogenesis in the three H tissue, but uses the individual's response to it as a guideline to select the correct degree of adjunctive surgery. The focus of hyperbaric oxygen in the treatment of osteoradionecrosis is not on the dead bone; it is on the radiation injured tissue that is not yet dead. Only surgical removal can manage the dead bone. Osteoradionecrosis that presents with a pathologic fracture, an oro cutaneous fistula, or osteolysis to the inferior border of the mandible represents an advanced stage (stageIII). Other individuals with osteoradionecrosis are placed into stage I of the protocol. In stage 1, individuals receive an initial 30 sessions of hyperbaric oxygen. After 30 sessions, the wound is assessed for a response. A stage I responder will evidence granulation tissue and a softening of the exposed bone. At this time, the soft exposed bone is debrided and the final 10 sessions of hyperbaric oxygen are completed. If successful, exposed bone will become covered with mucosa over the following 1 to 2 months. If the exposed bone is unchanged after 30 sessions of hyperbaric oxygen and no granulation tissue is present, the individual represents a stage I non responder and proceeds to stage II. In stage II, the exposed bone is surgically removed with minimal reflection of the vascular periosteum over vital bone. If the exposed bone is a tooth socket, the bony excision is an alveolectomy. If the exposed bone is buccal or lingual cortex, the bony excision takes the form of a decortication. A primary closure over the remaining bleeding viable bone should be achieved. After this surgery, the individual goes on to complete the final 10 sessions of hyperbaric oxygen therapy. Stage II responders will heal to resolution of their osteoradionecrosis without a dehiscence and without further exposed bone. Stage II nonresponders will develop dehiscences and further exposed bone indicative of a greater amount of dead bone than was clinically or radiographically evident. Stage II nonresponders are advanced to stage III. Because of nonresponse in stage II, individuals in stage III usually will have received their complete 40 sessions of hyperbaric oxygen. These individuals are then directly treated with stage III surgery. Individuals in stage III who present with a pathologic fracture, an orocutaneous fistula, or an osteolysis to the inferior border of the mandible undergo their first 30 sessions of hyperbaric oxygen prior to stage III surgery. Stage III surgery consists of a continuity resection back to bleeding bone margins. The bony edges of the host bone should be rounded to prevent penetration through thin tissues, and there should be minimal reflection of the vascular periosteum on the remaining host bone. If a soft tissue defect is present, soft tissue flaps such as myocutaneous or free vascular flaps are accomplished at this time. The defect is best stabilized with a rigid titanium reconstruction plate or with external pin fixation. If the individual has not received the full course of 40 hyperbaric oxygen sessions, the final 10 sessions are performed in the postoperative phase. Once the tissues have healed and matured (about 3 to 4 months), bony reconstruction can be accomplished without the need for additional hyperbaric oxygen. Such individuals can then undergo dental rehabilitation if required with split thickness skin graft vestibuloplasties\ and/or dental implant placement. (Marx First edition)

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