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Radiotherapy and the Oral Environment – The Effects of Radiotherapy on the Hard and Soft Tissues of the Mouth and its Management

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Abstract - *Radiation therapy plays an important role in the care of patients with head and neck cancer. When the oral cavity and the salivary glands are exposed to high doses of radiation, there can be dramatic effects on the patient's oral health. The clinical consequences of radiation can include mucositis, hyposalivation, taste loss, osteoradionecrosis, radiation caries and trismus. This paper looks at the available literature regarding the effects of radiotherapy on the oral environment and outlines practical clinical approaches to prevent or reduce the adverse side effects of treatment.*

KEY WORDS: Radiation, Salivary Gland, Oral Health, Mucosa

INTRODUCTION

Radiation pays an important role in the care of patients with head and neck cancer. Most patients with head and neck cancer treated with curative intent receive a dose of between 50-70Gy. This is usually given in fractions of 2 Gy over a five to seven week period. Patients are typically seen five days a week. Unfortunately, in addition to the desirable anti-tumour effects of radiation, it can also cause damage to the healthy tissues located in the field of radiation. These changes may be classified as acute or transient, intermediate or late in timing and can also be classified as being direct changes or indirect changes. These changes affect the oral mucosa, salivary gland tissue, taste buds, the temporomandibular ligaments and muscles, the teeth and/or the mandibular/maxillary bone.

Mucositis

Radiation mucositis is defined as the reactive inflammation of the oral and oropharyngeal mucous membranes during radiotherapy in the head and neck region[1]. Historically, mucositis was believed to be a result of the mitotic death of epithelial cells[2]. It was believed that direct damage by radiation or chemotherapy to the basal epithelial cell layer led to loss of renewal capacity of the epithelium, resulting ultimately in cell death, atrophy, and consequent ulceration. More recently, morphological evidence provided by electron microscopy has demonstrated that endothelial and connective tissue damage precedes epithelial changes in irradiated oral mucosa[3] suggesting that endothelial injury is an early event in the development of radiation induced mucositis.

In 80% of patients undergoing head and neck radiotherapy, the onset of symptoms appears as early as the end of the first week and will continue for up to 3 weeks following the radiotherapy treatment[4]. Unfortunately, this results in very unpleasant symptoms including local discomfort as well as difficulties in eating, drinking, swallowing and speech. Some clinicians describe the appearance of mucositis as a white discoloration of the oral mucosa, which is hyperkeratinisation, followed by or in combination with erythema[5,6]. Others consider erythema to be the initial reaction[7,8]. Around the third week of radiation more severe symptoms of mucositis such as pseudomembranes and ulceration may appear. It may also coexist with candidal infection and gram -ve infections[9]. (Figure 1)

Unfortunately there is not an established preventive regimen for mucositis and controlled studies on this issue with a large number of patients are lacking. Therefore most recommendations are based on clinical practice.

Management

During radiotherapy, it is important that dentate patients achieve good plaque control to maintain oral health. However the discomfort of mucositis may hamper this. Therefore, mechanical plaque removal with the use of a soft bristled brush is advocated. Mouthrinses such as chlorhexidine gluconate (0.02%) have beneficial chemotherapeutic effects with respect to plaque control[10]. It has been shown that alcohol free mouthrinses cause less discomfort for the patient than those containing alcohol[11]. In addition to this, a recent review emphasized the potential importance of avoiding alcohol containing mouthwashes due to the increased risk of developing oral cancer[12]; although this is a matter of debate at present. Denture hygiene is also important for the health of the hard and soft tissues and therefore the prosthesis must be regularly cleaned and should be removed at night.

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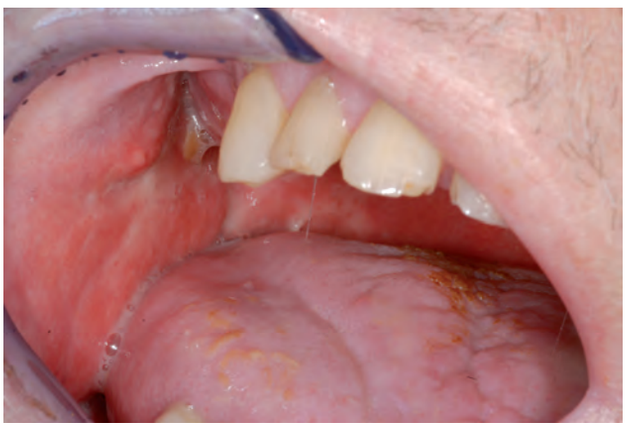

Figure 1.

To avoid mucosal irritation, the patient should be advised to avoid tobacco, spicy, acidic or hard foods and alcohol. Any pain experienced during function can be palliated using available oral solutions. There are solutions available that contain local anesthetics such as diphenhydramine, viscous xylocaine, lidocaine, benzydamine or dyclonine hydrochloride. A double-blind randomized trial compared the efficacy of a) viscous lidocaine with 1% cocaine b) dyclonine c) kaolin-pectin plus diphenhydramine and d) saline, or placebo[13]. The results suggested the dyclonine to be more effective, but failed to demonstrate a significant difference between the four solutions

Benzydamine hydrochloride is an agent with anti-inflammatory, analgesic, anesthetic and antimicrobial capabilities. It may therefore be useful for relieving mucositis symptoms. Recent studies have shown that benzydamine also inhibits the production and effects of pro-inflammatory cytokines particularly tumour necrosing factor[14]. This suggests anti-inflammatory effects as the main mode of action. Other studies have shown that topical benzydamine reduces the frequency and severity of ulcerative oral lesions and decreases pain in radiation induced mucositis[15,16,17].

A variety of agents have been used as mucosal barriers or coating agents such as Sulcralfate, Gelclair and Oromagic. Sucralfate is a sulfated disaccharide which when taken by mouth is only 3-5% systemically absorbed, but binds electrostatically to ulcer bases, acting as a barrier to irritants and promoting healing[18]. Although it is questionable whether this can prevent mucositis, it has been shown to decrease, oropharyngeal pain[19].

Gelclair is a more recently available preparation which forms a bioprotective coating that provides almost instant comfort and effective pain relief and therefore can potentially improve a sufferer's ability to eat and drink[20]. Palifermin is a form of recombinant human keratinocyte growth factor-1. It has shown to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies who are undergoing stem-cell transplantation; however, use in non-stem cell transplant patients should be discouraged until more data is available[21].

Amifostine is an antioxidant that is also heralded to be preventative by protecting the normal cells from radiation injury preferentially to cancer cells. However, studies have shown it to have only a small benefit in preventing and reducing the severity of mild mucositis[22,23].

Honey has antibacterial and wound healing properties and has been shown to be effective at reducing the prevalence of severe mucositis in one study, although there was bias noted in the study[24]. This would obviously only be worth considering in an edentulous patient.

Taste loss

Alteration in taste is an early response to radiation to the mouth and often precedes mucositis[25]. However, there has been very little systematic research in this area to assess the course of taste loss and recovery following radiation. Most patients experience partial or complete loss of taste during radiotherapy and this is often transitory[3,4].

Taste loss has been reported 2-3 days after the onset of radiation with doses as low as 20-30Gy[26]. Direct radiation damage to the taste buds or the innervating nerve fibres have been reported to be the cause of taste loss[27]. Perception of bitter and acid flavours is reported to be more impaired than the perception to sweet and salt[28]. Taste sense gradually returns to normal or near normal levels within 1 year after radiation although it has been documented as taking up to 5 years[29]. The recovery time depends on the dose of radiation received.

There has been little systematic research in this area to assess the course of taste loss and recovery following radiation.

Mossman and Henkin (1978) showed in an uncontrolled study that following the administration of zinc sulphate to patients who had radiation induced taste dysfunction, it helped improve taste impairment in some patients[30].

Hyposalivation

Radiation induced hyposalivation starts in the first week of treatment; 50-60% reduction in the salivary flow occurs and after 7 weeks of conventional radiotherapy, salivary flow reduces to approximately 20%[31].

When the salivary glands are within the field of radiation, it affects both the acinar and the vascular tissue, thereby leading to reduced resting and stimulated salivary flows[32,33]. The serous acini are more readily affected by radiation than mucous acinar and ductal cells[34] and therefore the parotid salivary glands are particulary susceptible to damage[20,35]. Above the total dose of 25-40Gy, the parotid gland function becomes irreversibly reduced[36,37].

As well as reduced amount, the saliva becomes very viscous in consistency and may become coloured white, yellow or brown[38]. The oral protective functions are reduced (buffering capacity and antibacterial systems) and the electrolyte levels are altered. Whole saliva bicarbonate concentration is lowered and the pH reduces from about 7.0 to 5.0[39,40]. In response to this, the microflora becomes altered with an increase in acidogenic and cariogenic micro-organisms such as Streptococcus mutans, Lactobacillus *spp* and Candida *spp*[41,42].

Some recovery of the salivary gland function is possible up to 12-18 months after radiotherapy, depending on the dose and the volume of radiotherapy received by the salivary gland tissue[43].

For the patient, the symptoms of oral dryness are unpleasant. Oral clearance, mastication and deglutition becomes very difficult and the dentition may suffer from radiation caries as a consequence.

Management

The symptomatic management of xerostomia includes the use of salivary substitutes and salivary stimulants[44]. Salivary substitutes can be categorised as solutions based on mucin, carboxymethylcellulose (CMC) and linseed. Mucin based salivary substitutes such as Saliva Orthana and Glandosane have been shown to be more effective and better tolerated than the carboxymethylcellulose based ones[45,46]. Saliva Orthana also has a neutral pH, an electrolyte composition similar to that of natural saliva and contains fluoride. However the mucin in Saliva Orthana is derived from porcine gastric mucosa and therefore this product may not be suitable for some ethnic or religious groups. Carboxymethylcellulose based saliva substitutes such as Luborant have been widely used and in a recent study CMC based artificial saliva demonstrated significantly better effects in patients with severe xerostomia whose functional salivary gland capacity was severely compromised[47]. The linseed polysaccharide based substitute has been reported to reduce the complaints of hyposalivation in about 75% of patients who had Sjogrens syndrome[48]. Some patients prefer frequent water sips or the application of a fine water spray to control the symptoms.

Salivary stimulants such as ascorbic acid, malic acid, sugar free chewing gum, parasympathomimetic drugs such as pilocarpine and other substances such as sugar free mints and nicotinamide have been used with varying success. Unfortunately most of the commercially marketed salivary stimulants have significant side effects. Malic acid and ascorbic acid can cause demineralization of teeth[49].

Pilocarpine hydrochloride, a parasympathomimetic drug is effective in the management of radiation induced xerostomia[50,51]. The recommended dose is 5mg three times a day although some patients appear to respond only to higher doses (10mg). However, a significant number of patients do not respond to the drug (49-52%)[52]. According to the SIGN guideline 90, the administration of oral pilocarpine (5-10mg three times a day) may be recommended to patients to improve radiation induced xerostomia with evidence of some intact salivary function unless there are contraindications for its use[53].

In addition to the above there are products on the market that mimic the salivary peroxidase system and which contain antibacterial enzymes. They are Biotene Oral Balance system and BioXtra system. They contain hydroxyethylcellulose, polyglycerylmethacrylate, lactoperoxidase, glucose oxidase and xylitol as active components and also contain lactoferrin, lysozyme and monofluorophosphate. In a double blind evaluation comparing the two products in 20 patients, the study demonstrated that both systems were effective in alleviating post radiation xerostomia although BioXtra seemed to have longer lasting lubricating effect[54].

Radiation Caries

Following radiotherapy to the head and neck region, generalised dental caries of rapid onset and progression may occur[55]. Caries may become evident as early as three months after radiotherapy with the resulting lesions having quite a different clinical appearance to standard carious lesions. Based on clinical appearance, radiation caries is observed as three different lesions as described in Table 1[56,57]. At any one time it appears that all types of lesions may be present in a patient who has undergone radiotherapy. (Figure 2).

The distribution of these lesions is atypical as they are usually present on tooth surfaces which would otherwise be relatively immune to dental caries due to protection from the salivary glands[33,58].

Their effects can be extremely debilitating functionally, aesthetically and psychologically for the individual. Sudden fracture resulting in crown amputation is common in response to the demineralisation of the tooth structure under the sometimes clinical appearance of an "arrested" lesion.

Despite the specific clinical appearance of radiation caries, the pattern of demineralisation as observed using polarised light microscopy appears to be similar to that of ordinary caries[59]. They seemed to have the same morphological and demineralization pattern such as presence of demineralised dentin, translucent zone, reparative dentin deposition when examined histologically under polarised microscope.

Whether radiation caries is a direct or indirect effect of radiation has been debated over the years. In summary, it would appear to be mainly due to an indirect effect of radiotherapy caused by reduced salivary flow rate and its consequences and change in dietary habits due to mucositis[60]. However direct effects may take place rendering the teeth more susceptible to decalcification due to dentinal changes caused by radiation[61].

Table 1. *Three types of radiation caries lesion*

1. Starts bucco-cervically on anterior teeth, spreads circumferentially and then inwards.
2. Generalised superficial defect.
3. Generalised brown/black lesion of entire tooth with incisal/ occlusal wear.

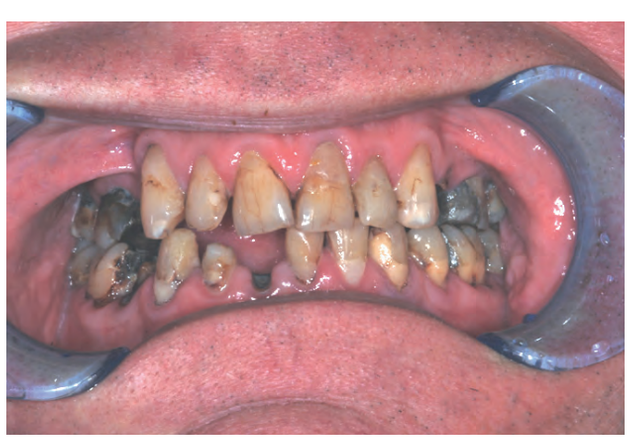

Figure 2.

Management

Flouride is universally recognised as being a major agent to prevent caries initiation and progression. It can be delivered as a paste, gel or mouthwash at various concentrations. Fluoride in toothpaste at a concentration of 1450ppm will reduce caries by 24% (Type I Cochrane review)[62] . Within the range 1000 to 2500ppm F, every 500ppm fluoride decreases caries by another 6%[63]. A concentration of 5000ppm fluoride has also been shown to be superior to 1100ppm F in arresting root surface caries over a six month period[64].

The current standard protocol of professionally applied topical fluoride is based on the study by Dreizen and colleagues, involving daily application of 1.1% neutral sodium fluoride gel (5000ppm) in a custom tray for the duration of the xerostomia[65].

In addition to the application of topical fluoride media, calcium based demineralising systems may be of great use in patients with very little salivary secretion. These systems are advocated because fluoride ions only promote remineralisation by the formation of fluorapatite in the presence of calcium and phosphate ions[66]. Such systems are based on casein phosphopeptide, amorphous calcium phosphate (CPP ACP) – (Recaldent, GC Toothmousse, Trident advantage gum), Unstabilised amorphous calcium phosphate (ACP) – Enamelon and bioactive glass containing calcium sodium phosphosilicate (Novamin).

Casein phosphopeptide amorphous calcium phosphate technology (CPP-ACP)

This is based on a nano-complex of the milk protein casein phosphopeptide (CPP) with amorphous calcium phosphate (APP). It is a water based sugar-free cream (available in 5 fruity flavours – melon, strawberry, mint, vanilla and tutti frutti) which neutralises an acidic environment. It binds to biofilms, plaque, bacteria as well as tooth structure and therefore is best to use immediately after cleaning of the teeth.

The casein phosphopeptides aims to stabilise high concentrations of Ca and PO_4 onto the tooth surface while still allowing it to diffuse down a concentration gradient[67].

In a randomised double blind trial in 2003, Reynold *et al* showed that CPP was present up to 3hrs in supragingival plaque after chewing gum[68]. Another double blind randomised cross over trial demonstrated that lozenges are a suitable vehicle to deliver CPP ACP to promote enamel remineralisation[69]. There has also been an in vitro study showing that following exposure of enamel to 0.2% citric acid for 1 hr, Tooth mousse and Proenamel offered significantly reduced enamel loss compared to distilled water[70]. Therefore, CPP ACP technology has been shown to decrease the progression of coronal caries and remineralise enamel subsurface lesions[71].

Enamelon™ (ACP) technology

This is based on unstabilized ACP, where a calcium salt and a phosphate salt are delivered separately intra-orally. As they mix with saliva they release calcium and phosphate ions which in the presence of fluoride will form a stable, insoluble fluoroapatite. In a study by Papas *et al* in 2008, they showed that Enamelon provided a significant benefit in preventing and remineralising root caries in high caries risk radiation patients[72].

Osteoradionecrosis

This is a long-term and the most serious side effect of radiotherapy. It is defined as necrotic soft tissue and exposed bone in an irradiated field that fails to heal spontaneously[73]. Some studies have not commented on the length of exposure, while others have suggested a period of up to 6 months[74,75,76].

The incidence of osteoradionecrosis (ORN) is greater in the mandible than the maxilla and is estimated to occur in 2% - 22% of irradiated patients[77,78]. The predilection for the mandible may be because of its reduced vascularity and/or because it has more compact bone than the maxilla and therefore absorbs more radiation. The incidence of ORN is very low when the total radiation dose is less than 60Gy. However, it is more common when brachytherapy is used as the mode of delivery with the mandible in the area of treatment instead of or in addition to external beam therapy. Recent studies have shown when chemotherapy is used in conjunction with radiation the incidence of ORN may increase[79,80]. In contrast, the use of intensity modulated radiotherapy may reduce the incidence of ORN.

Predisposing factors for ORN include size and site of tumour, radiation dose, fraction size, local trauma, dental disease, dentoalveolar surgery, immune defects and malnutrition. It may also occur spontaneously, unrelated to trauma[81].

Marx in 1983, proposed the 3 Hs (hypoxic-hypocellular-hypovascular) theory to understand the patho-physiology of ORN[38]. Radiation of bone leads to endarteritis obliterans with thrombosis of small blood vessels, fibrosis of periosteum and mucosa, and damage to osteocytes, osteoblasts and fibroblasts. Therefore there is breakdown of tissue driven by persistent hypoxia that can cause a chronic non-healing wound (a wound in which metabolic demands exceed supply) [38].

There has been a lot of work and research on the pathophysiology of ORN and the current theory proposes radiation-induced fibrosis, which can affect normal tissues as well as bone after radiation[82]. Therefore when ORN occurs in the jaw bone there is reduction in bone matrix and its replacement with fibrous tissue.

Management

Management of ORN is essentially conservative with pain relief and treatment of infection. If the patient is dentate, preventative measures such as a good oral hygiene regime, frequent topical fluoride application and 0.02% aqueous chlorhexidine gluconate mouthwashes should continue with advice on diet and nutrition. Small wounds may be debrided superficially and any loose necrotic bone removed. Systemic antibiotics should be reserved for symptomatic cases of established ORN where there is clinical evidence of infection and pus, including a discharging sinus[83]. (Figure 3)

Hyperbaric oxygen (HBO) regime has been shown to be effective in promoting healing in ORN[84,85]. Marx's (1983)

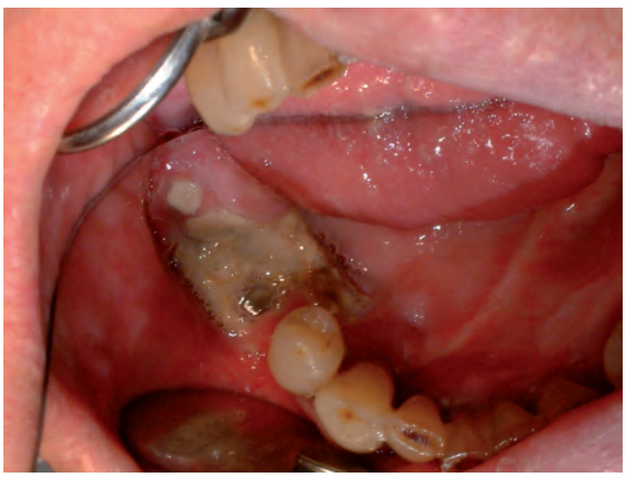

Figure 3.

Table 2. *Marx Protocol for HBO therapy*

Pressure	2.4 Atmospheres
Duration	90 mins
Prophylactic	20 dives pre-op; 10 dives post-op
Active ORN	30 dives pre-op; 10 dives post-op

protocol for HBO is shown in Table 2[86]. Marx's initial study compared HBO treatment to antibiotic administration (penicillin) in a randomized trial and showed that only 2 of 37 patients in the HBO group and 11 of 37 in the penicillin (control) group, developed osteoradionecrosis[87]. These results suggested the use of HBO to prevent ORN is beneficial compared to antibiotics. However, more recent studies including a prospective randomized controlled study by Annane *et al* showed no benefit of HBO over placebo[88]. Therefore, this is still a controversial area at present.

New treatment regimes with pentoxifylline, a vasodilator that also inhibits fibrosis and tocopherol (Vitamin E) to reduce the damage caused by free radicals[89] are in use in some units. These two drugs act synergistically as potent antifibrotic agents.

TMD and trismus

Trismus is a late complication following radiation for head and neck cancers[90]. Generally the onset of trismus is noted 3-6months after radiation treatment and is usually a lifelong complication[91]. The reported incidence varies from 5% to 47% in those with head and neck cancer[92] and depends on the total radiation dose, fractionation and treatment techniques.

It is caused primarily due to radiation to the temporomandibular joint and/or masticatory muscles or by the invasion of these tissues by the tumour[93]. It is a result of fibrosis of the ligaments around the temporomandibular joints and the adjacent soft tissue as well as scarring of the pterygomandibular raphes[94].

Management

First line treatments include physical therapy with manual jaw exercises, tongue depressor therapy or use of mechanical mouth stretching devices such as Therabite[95,96]. Buchbinder (1993) in his study compared the use of Therabite to tongue blade therapy in patients whose mouth opening was less than 30mm. He showed that the Therabite combined with unassisted exercise improved mouth opening by 13.6mm after 10 weeks of therapy. At week 6 and thereafter, the net increase in Therabite group (13.6 mm [±1.6 mm]) was significantly greater than tongue depressor group (4.4 mm [±2.1 mm]).

Other non surgical regimes include microelectric current and pentoxifylline therapies; but are not widely used as results from these studies were not promising[97,98].

Surgical management is usually advocated after the non invasive lines of treatments have failed. In a study by Bhrany *et al* (2007), coronoidectomy was carried out in 18 patients with inter-incisal opening of less than 20mm after failing physical therapy for 3 months. They demonstrated that that post-coronoidectomy, inter-incisal opening was maintained up to 35mm; although the study lacked a control population[99].

Periodontium

The direct and indirect effects of radiation on the periodontium can result in a decreased capacity for repair and can lead on to an increase in attachment loss, and even an increased risk of developing osteoradionecrosis[100, 101,102,103]. Morphologic and histological changes are noted in the periodontium; decreased vascularity and cellularity of the periodontal membrane and disorientation of the Sharpeys fibers and widening of the periodontal ligament space have been reported[104,105]. Hyposalivation caused due to radiation can also predispose patients to an increase risk of periodontal disease. This could be due to an increased plaque accumulation and a shift in oral microflora[106,107]. Marques and Dib (2004) showed that there was about 70% clinical attachment loss in their patients 6-8 months following radiation to the head and neck region[108] illustrating the importance of thorough pre and post radiation treatment planning and preventative regime.

DISCUSSION

The consequences of early and late radiation effects in the head and neck region have a tremendous impact on the quality of the life for patients. Radiation induced side effects can be reduced to some extent with preventative regimes as outlined in this paper. With an increasing number of ageing dentate patients, prevention is the key. The role of multidisciplinary care is essential in managing these patients and the role of specialist dental input has been widely recognized[109,110].

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