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Research Article

AN INSIGHT TO CUMULATIVE COROLLARY OF RADIATION THERAPY

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ABSTRACT

Patients undergoing radiotherapy for head and neck cancer are prone to dental complications. Radiotherapy to the head and neck region causes xerostomia and salivary gland dysfunction which dramatically increases the risk of dental caries and its sequelae. Radiation therapy (RT) also affects the dental hard tissues increasing their susceptibility to demineralization following RT. Postradiation caries is a rapidly progressing and highly destructive type of dental caries. Counseling of the patients before and after radiotherapy can be done to make them aware of the complications of radiotherapy and thus can help in preventing them. This review summarizes the side effects of radiation therapy for head and neck cancer and also the preventive measures and treatment modalities for the same.

INTRODUCTION

The malignant tumors of the upper airways and digestive passages have a high incidence rate of occurrence in the world.[1] The choice treatment for these malignancies is surgery, associated or not to radiotherapy.[2]Head and neck cancers (HNC) are often treated with radiation therapy (RT), a technique that utilizes ionizing radiation and exerts therapeutic effect by semi selectively damaging the genetic material of vulnerable malignant cells, either directly or through the production of free radicals, resulting in cell death. Adverse effects of radiation therapy arise by the same mechanism damaging normal cells, especially those that are rapidly dividing, or otherwise less capable of repairing radiation induced damage.[3,4] In the oral cavity these can be cells of the mucous membrane, underlying soft tissue, tooth, periosteum, bone, glands and vasculature resulting in specific radiation syndromes. Such syndromes include xerostomia and dysgeusia from salivary gland damage, mucositis from epithelial damage, pathological alterations in the normal flora alterations, radiation caries, reduced mouth opening from changes in collagen structure and osteoradionecrosis of the jaw (ORN) from reduced bone healing capacity.[5,6] Management of oral health is especially important for the HNC patient as oral complications are common both during and after radiation. While the majority of oral complications are unavoidable consequences of ionizing radiation (deterministic), some are preventable. The incidence of some complications is associated with treatment factors, such as in the case of osteoradionecrosis and dental extractions.[7] As oral complications are common, potentially preventable and have iatrogenic factors, it is essential that those working with HNC patients be aware of the prevention and management of radiotherapy-related oral complications. In this article we aim to highlight the current understanding and management of the dental needs for patients who have or will undergo radiation therapy.[8]

Biological aspects of radiotherapy

Radiotherapy is a treatment option for malignant tumors whose therapeutic agent is ionizing radiation. Ionizing radiations are

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divided into the corpuscular and electromagnetic ones. Corpuscular radiations are represented by electrons, protons and neutrons; electromagnetic radiations are called photons, being represented by X rays and by gamma rays. In the clinical practice, most radiotherapy treatments are done through the use of photons.[9]Ionizing radiations act on the nuclear DNA leading to death or loss of its reproductive capacity. Since DNA content duplicates during mitosis, those cells with a high degree of mitotic activity are more radiosensitive than those with low mitotic rate.

Radiation action can be direct or indirect. On the direct action, the DNA molecule is cleaved, interfering in the duplication process. On the indirect effect, water is dissociated into its two elements, H+ and OH; the latter reacts with the basis of DNA, interfering in the duplication process. Since water represents most part of cell content, the indirect effect is proportionally more important than the direct one.[10] Due to the fact of being in a continuous multiplying process, malignant cells can suffer the radiation effects. However, the multiplying ability varies according to cell type.[11]

Radiotherapy can be administered in short duration schemes up to extremely long schemes, lasting for several weeks. The justification for applications in small daily fractions is based on radiobiology "5 Rs": reoxygenation, redistribution, recruitment, repopulation and regeneration.[12] Most patients on radiotherapy receive a total dose of 50-70 Gy as curative dose. These doses are fractioned during a period of 5-7 weeks, once a day, 5 days a week, with a daily dose of approximately 2Gy. On the concomitant treatment, 45c Gy are used on the pre-operative stage and 55-60 Gy on the post-operative.[13]

Pre-radiotherapy dental assessment

The benefit of a multidisciplinary team (MDT) approach to assessing, diagnosing and managing head and neck cancer patients is widely acknowledged and as such, every patient with head and neck cancer should be managed in this environment.[14,15] Given the oral and dental implications related to treatment, a dental practitioner with experience in HNC should be included at the minimum. The assessment includes consideration of the diagnosis, prognosis, proposed treatment, individual patient factors and pre-existing oral health. Immediate management involves extractions of unrestorable teeth or those with gross periodontal disease prior to treatment, irrespective of fields. All healthy teeth as well as deeply impacted teeth without pathology are left in situ. Extractions are undertaken with as little trauma as possible and minimal flap surgery. Depending on financial eligibility, patients are then referred back to their general dentist with a thorough plan or continued to be seen at the clinic. In general, we advise routine three-monthly check-ups, daily fluoride and bicarb rinses and restorations as required. General dental practitioners should be aware of their local MDT and clinics where HNC patients are seen and refer patients who present with complications. The cancer diagnosis should include tumour type and staging, location within the oral cavity and proximity or involvement of adjacent structures.[16] Human Papilloma Virus (HPV) status is an important prognostic factor;16 however, a review of the literature does not reveal an increased risk of radiotherapy associated complications such as ORN, mucositis, candidiasis or xerostomia. Important treatment factors include the anticipated radiation dose, field size and location. Specific areas receiving doses over 60 Grays should be flagged as higher risk for complications, especially if the major salivary glands are included. The use of surgery or chemotherapy should be known. It is practical to have a rough timetable for treatment and follow-up appointments. A full medical and dental history should be taken, as with all patients. Factors likely to increase the risk of oral complications should be noted, and the opportunity should be taken to discuss risk factor modification, such as smoking and alcohol cessation.[17] The patient should be assessed for motivation, and whether they are able to manage expected dental hygiene regimens. Motivation is of paramount importance but difficult to assess. Current dental hygiene habits and prior engagement with dental professionals may be of some use. If there are significant concerns with motivation, additional appointments with an experienced hygienist could help prevent complications. Finally, the oral cavity itself should be examined, and relevant radiographic images obtained, such as bitewings and periapicals if indicated. The patient's general dentition, as well as a tooth-by-tooth assessment should be recorded. If the patient wears dentures they should be advised to avoid using them until treatment is completed.[18]

Oral complications of radiotherapy

1. Factors affecting adverse reactions of radiotherapy include
2. The volume and area being irradiated,
3. The total dose,
4. The fractioning,
5. The age of the patient
6. The patient's clinical conditions and on the associated treatments.

A small increase on tumor dosage is enough for a significant increase on the complications incidence. Acute reactions happen during the treatment and most of the time, they are reversible. Late complications are normally irreversible, leading to permanent incapability and to a worsening of quality of life, and they vary on intensity, being normally classified into mild, moderate and severe.[19]

Many head and neck cancer patients are submitted to high doses of radiotherapy on large areas of radiation including the oral cavity, maxilla, mandible and salivary glands. Thus, anti-cancer therapy is associated with several adverse reactions. These reactions can occur in an acute stage (during or at the weeks right after treatment) or in a chronic stage (months or years after radiotherapy). The severity of acute oral complications will depend on the inclusion degree of these structures on the radiated area. [20]

Xerostomia

Xerostomia, or "dry mouth", can result from some diseases or it can be an adverse reaction to some drugs. Among radiated patients in the head and neck area, it is one of the most frequent complains. Chencharick and Mossman[21] noticed that 80% of radiated patients complain of xerostomia. However, the relation between the individual perception of dry mouth and the real values of salivary flow have not yet been completely defined. In some situations, there is a co-relation between reduced salivary flow and xerostomia complaint.[22] However, in many

cases there is not a relation between xerostomia and objective findings of salivary gland dysfunction - that is to say, patients without alterations of salivary flow may complain of mouth dryness. Patients with xerostomia complain of oral discomfort, taste loss, speech and swallowing difficulties.[23] Saliva also suffers qualitative alterations resulting from radiotherapy with decrease of amylase activity, buffer capacity and pH, with consequent acidification. There are also alterations of several electrolytes such as calcium, potassium, sodium and phosphate. Thus, individuals who were radiated are more susceptible to periodontal disease, rampant tooth decay and oral infections by fungus and bacteria. [24]

Xerostomia treatment can be done through the use of mechanic/taste stimulants, saliva substitutes or systemic agents. Alternative methods, such as acupuncture, had also been mentioned as treatment options for xerostomia. Generally speaking, stimulants and saliva substitutes only reduce xerostomia, without altering salivary flow. On the other hand, systemic agents besides reducing xerostomia, also decrease oral problems associated with salivary glands hypo function, through the increase of salivary flow. Thus, the treatment of choice for radiotherapy-induced xerostomia, should be through the use of systemic agents, and pilocarpine is the most studied one among them. Besides, studies show that systemic agents, such as pilocarpine, are more effective when used during radiotherapy. This has also been recently showed for betanechol, when the drug used concomitantly with radiotherapy is able to increase salivary flow at rest, right after the end of the radiotherapy treatment, besides decreasing the subjective complaint of dry mouth.[25]

Post-radiotherapy management: hygiene and radiation caries following radiation, chemical and microbial changes in the oral cavity result in a cariogenic environment. Over half of all patients will demonstrate dental deterioration over time with an incidence risk of 6% per month. Radiation caries occurs even in teeth not exposed to radiation, and if not managed can progress to full dental loss over a period of as little as three years.34 Incidence is related to radiotherapy dose, with an odds increase of 2–3 at 30–60 Gy, and 10 at over 60 Gy. The proposed mechanism is that the salivary glands withstand doses up to 30 Gy and sustain maximal damage between 30–60 Gy. The additional risk is due to direct radiation effects on the tooth structure, which weakens dentine-enamel bonds and results in shear fracturing. Radiation caries occur at different locations than in common dental decay. The sites most affected post-radiotherapy are the labial surfaces of the cervical, cuspal and incisor areas. These areas receive compression, torsion and shearing forces and are the regions most resistant to caries in non-irradiated patients.[26] Prevention is key. Use of fluoride in medicament carrier trays dramatically reduces the risk of dental deterioration, and prescription fluoride should be used at least once daily. In one study, each additional daily use of fluoride per week resulted in a 14% reduction in moderate or severe dental deterioration. Additional preventive techniques include dental hygiene measures such as regular rinses, brushing, flossing and the management of xerostomia. Rinses should be either non-acidic fluoride preparations or bicarbonate preparations, and brushing and flossing should be gentle and thorough.

Dental management during radiotherapy induced Xerostomia

Radiation damage to the salivary glands, especially the parotids, results in gland dysfunction through cell death and fibrosis. The result is hypo salivation and increased salivary viscosity experienced as xerostomia.

Mucositis

Mucositis is defined as a mucosal irritation.[27] Anti-neoplastic-therapy-induced mucositis is a significant adverse reaction that may interfere on the radiotherapy process altering the tumor local control and therefore, the patient's survival.

Mucositis is believed to occur in four stages

1. Inflammatory/Vascular,
2. Epithelial,
3. Ulcerative/Bacteriologic
4. Healing.

Due to oral mucosa damages, patients will complain of pain, what may lead to the need of using painkillers during treatment. The pain intensifies whenever the patient tries to eat or drink. Mucositis is even worse when chemotherapy is used in association with radiotherapy in cancer treatment.[27]

The most used scale to measure oral mucositis is the one by the WHO, which classifies mucositis into four degrees.
Degree 0 is when there are no signs or symptoms.

1. Degree 1 is when the mucosa is erythematose and painful.
2. Degree 2 is characterized by ulcers, and the patient can eat normally.
3. Degree 3 is when the patient has ulcers and can only drink fluids.
4. Degree 4 is when the patient cannot eat or drink.

The oral basal epithelium has a rapid cellular turnover and is therefore at higher risk of radiation damage. Cell death and the inability of the mucosa to repair lead to oral mucositis (OM), typically presenting as atrophy, swelling, erythema, ulceration and pseudomembrane formation, frequently accompanied by colonization with gram-negative organisms and candida species. OM can cause considerable pain, as well as functional difficulties including eating, drinking and speech.

Dental management during radiotherapy induced mucositis

Methods used to prevent and treat mucositis include good dental hygiene such as frequent brushing with a soft, regularly replaced toothbrush, regular flossing, four-hourly non-medicated oral rinses, adequate hydration and the avoidance of oral irritants such as alcohol and tobacco. Symptomatic treatment includes tooth mousse and topical barrier gels. The Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO) updated guidelines recommend that sucralfate, chlorhexidine and antimicrobial lozenges not be used for the prevention of radiotherapy induced oral mucositis, but do state that benzydamine has a role for patient receiving moderate dose RT.28 Other agents that have been investigated include aloe vera gels and honey products, which may be beneficial for some patients. In patients with metal fillings, the use of dentalprotective stents to prevent scattering may reduce the incidence of local mucositis. We recommend that patients

receive appropriate analgaesia for their pain, and are screened by a dietician to assess their oral intake.

Candidiasis

Radiated patients are more prone to developing oral infections caused by fungi and bacterias.[15] Studies have showed that patients submitted to radiotherapy have a higher number of microbial species, such as Lactobacillus spp., Streptococcos aureus and Candida albicans.[9] Oral candidiasis is a common infection in patients being treated for upper airways and digestive tract malignancies. Colonization of oral mucosa can be found in as many as 93% of these patients, whereas Candida infection can be found in 17-29% of patients submitted to radiotherapy. The increased risk for oral candidiasis is likely to be the result of the drop in salivary flow as a consequence of radiotherapy. Besides, a possible explanation for a higher predisposition of irradiated patients to candidiasis is a reduced phagocytic activity of salivary granulocytes against this micro-organisms.[28]

Clinically, candidiasis can be seen both in its pseudomembranous and erythematous forms. The latter can be of difficult diagnosis, and it may be confused with irradiation induced mucositis. Patients complain more of pain and / or burning sensation.[28]

Several studies have already analyzed which Candida species were involved in colonization and infection of radiated patients. Previous studies[28] showed that Candida albicans was the most prevalent micro-organism. However, other species had been identified recently. C. glabrata e C. krusei micro-organisms had already been seen in patients submitted to radiotherapy.[21] Recent studies found a relation between oral candidosis and C. dubliniensis species. In this study, the authors suggest that the species C. albicans and C. dubliniensis probably act together in the infections that affect radiated patients.[22,23] Besides, it is known that the non-albicans species distribution varies according to geographical location. Thus, in North America, the predominant species is C. glabrata. Whereas a study done in Brazil showed that the predominant species is C. tropicalis.

Oropharyngeal candidiasis (OPC) is caused by both albicans (>80%) and non-albicans species, and is a frequent infection after radiation therapy to the head and neck. Although candida is a normal oral commensal that occasionally causes infection in healthy patients, radiotherapy related hyposalivation alters the oropharyngeal environment and signifi- cantly increases the risk of colonization and infection. While it may be regarded as benign, it can be a significant cause for morbidity and decreased quality of life. OPC typically affects the tongue, oral cavity and labial commisure, and presents in three forms: pseudomembranous, erythematous/atrophic and cheilitis. The usual appearance is that of removable white lesions overlying an erythematous and atrophic patch. Symptoms may be absent or include burning pain, difficulty in swallowing, dysgeusia and halitosis.

Dental management during radiotherapy

OPC is treated when symptomatic and focuses on local therapy unless the presentation is severe, disseminated candidiasis is suspected, the patient is high risk (i.e. immunosuppressed) or fails to respond to local methods. Prevention is through regular dental hygiene, saliva substitutes and smoking and alcohol cessation. First line treatment includes topical miconazole, fluconazole or nystatin, available in several forms such as creams, suspensions or lozenges. When systemic therapy is indicated, the first line drug is oral fluconazole.

Dysgeusia

Dysgeusia affects patients from the second or third week of radiotherapy onwards, and it may last for several weeks or even months. It occurs because the taste buds are radiosensitive, with the degeneration of their normal histological architecture. The increase of salivary flow viscosity and the saliva biochemical alteration creates a mechanical barrier of saliva which makes it difficult the physical contact between the tongue and foodstuff. The recovery until reaching almost normal levels generally takes place around 60 to 120 days after the end of the radiation. Studies show that dysgeusia is a complaint by approximately 70% of patients submitted to radiotherapy, also implying in the loss of appetite and weight, being the most uncomfortable complication for most radiated patients.[29]

Radiation caries

Even patients who had not experienced tooth decay for some time, may develop radiation caries when submitted to radiotherapy.[30] The main factor for the development of such injuries is the decrease of saliva amount and its qualitative alterations besides, radiation has a direct effect on teeth, making them more susceptible to decalcification.[30]

Osteoradionecrosis

Osteoradionecrosis (ORN) is a bone ischemic necrosis caused by radiation, being one of the most serious consequences of radiotherapy, causing pain as well as possible substantial loss of bone structur. Due to anti-cancer therapy, bone cells and the vascularization of bone tissue may suffer irreversible injuries. ORN may occur spontaneously or more commonly, after trauma (generally dental extractions). In 95% of cases ORN is associated with soft tissue necrosis and subsequent bone exposure. Mandibles are more affected than maxillas and patients with their natural teeth have greater chances of developing ORN. Spontaneous bone exposure occurs approximately one year after finishing radiotherapy and the risk of developing this complication remains indefinitely. Besides, studies show that approximately 60% of patients complain of pain, ranging from mild pain, controlled with drugs, to extremely painful conditions. However, the presence of these symptoms does not appear to be related to the extension of the process. ORN may also result in edema, suppuration and pathological fractures, which may occur in 15% of patients, always experienced together with pain.[31]

Post-radiotherapy management: extractions and osteoradionecrosis Osteoradionecrosis is a serious and typically late complication following radiation therapy to the head and neck, whereby irradiated bone is exposed and undergoes necrosis. The exact pathophysiology is unclear and a number of proposed mechanisms exist, from Marx's 'three Hs' theory through to the current fibroatrophic theory. A great number of staging systems exist for ORN (Table 1).49 One of the first methods was Marx's system where stage was based on response to the Wilford Hall hyperbaric oxygen protocol, with

potential to directly enter a higher stage if the initial presentation was severe. More contemporary systems such as Kagan and Schwartz's three stages classify ORN based on clinical presentation, and then treatment is decided according to the stage.[31] A simple system is presented based on clinical presentation.[32] Staging systems have focused on the mandible, as the maxilla is unlikely to develop ORN. Preventive measures are vital to avoid the need for dental intervention such as extractions and may have led to a significant decline in rates of ORN over the last few decades. However, even with adequate care, the extraction of diseased teeth may become inevitable. A minimal trauma technique is especially indicated in the irradiated patient and therefore experienced clinicians should perform the procedure. In addition, investigators have proposed that the number of teeth removed in a single session should be limited,

Post-radiotherapy management: treatment of osteoradionecrosis- For the patient who develops ORN, prompt referral should be made to a tertiary maxillofacial unit for further management. Treatment of ORN ranges from conservative methods such as saline rinses through to debridement, sequestrectomy, resection and free flaps, with or without the use of adjuncts such as HBO or pentoxyphylline, tocopherol and clodronate.

Soft tissue necrosis

Another possible consequence of radiotherapy is soft tissue necrosis, which may be defined as an ulcer located in the radiated tissue, without the presence of residual malignancy. The occurrence of soft tissue necrosis is related to dose, time and volume of the radiated gland, when the brachytherapy is used, the risk is higher. Soft tissue necrosis is a normally painful condition and good oral hygiene together with the use of painkillers and often times, antibiotics, are necessary to manage the condition. Since ulcerations are often seen on the tumor primary site, regular evaluations are necessary until the necrosis retreats, therefore excluding the possibility of recurrence. Besides, soft tissues may suffer fibrosis after radiotherapy, becoming pale, thin and without flexibility. When fibrosis affects chewing musculature (temporal, masseter and pterygoid muscles) trismus can happen. In the most serious cases, trismus may interfere with eating and dental care.[33]

CONCLUSIONS

Radiotherapy has been widely used in treating malignant lesions on the head and neck, with improvement in patient survival rates. However, this therapy is still associated with several adverse reactions that affect patient quality of life significantly, and may even affect the progress of the treatment. Taking into account that the occurrence of head and neck cancer rates are probably going to be the same as last decades, it is extremely important that health professionals are familiarized with the complications that may result from anti-neoplastic treatments. Multidisciplinary treatment, including medical team, dental surgeons, speech therapists, nutritionists and psychologists, is the best option in order to minimize or even prevent such complications.

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