An update on the effects of radiation therapy and dental management of head and neck cancer patients

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ABSTRACT
Defects in the maxillofacial region may result in cosmetic, functional and psychological impairment which can have far-reaching effects on patients’ quality of life. Head and neck cancer may be treated with a variety of modalities including surgical resection, chemotherapy and radiation therapy. Ionising radiation destroys tumour cells, rendering them less able to divide, and thereby halting tumour progression, but also destroys many normal cells leaving patients with a number of oral and/or facial side effects, some of which develop quickly and others only becoming evident after some time. This paper will review these complications and the effects they have on patient functionality, aesthetically and psychosocially. It will also propose ways in which dentists can be part of the multidisciplinary team who try to prevent, reduce or manage post radiation sequelae, and help restore patients’ dignity, functioning and general quality of life.

“The topic of osseointegrated implants in irradiated bone is a much debated, complex and controversial issue. This will be addressed in a follow-up review.

INTRODUCTION
The face is the most prominent and visible part of the body and provides a sense of identity to a person. Functionally, it facilitates expression of emotion, communication and intellect and provides the essential access to the respiratory and gastrointestinal tracts. Cognitively, it carries the sole sensory regions of vision, hearing, taste and smell.

Defects in the maxillofacial region may result in cosmetic, functional and psychological impairment which can have far-reaching effects on patients’ quality of life.

Head and neck cancer may be treated with a variety of modalities including surgical resection, radiation therapy and chemotherapy. These may be implemented separately or in combination, depending on the staging and type of malignancy. Both the cancers and associated treatment regimens can have a number of adverse functional and aesthetic consequences that are difficult to manage. They can affect mastication, deglutition, verbal communication, respiration, facial expression and facial appearance. The resulting morbidity and deformity may impact on the physical, psychological and social wellbeing of affected individuals, leading many to lives of self-isolation, avoidance of social and work activities, limited personal interactions and ensuing depression. Patients with advanced malignant diseases that require multimodal treatment may experience the worst of these consequences due to the extensive surgery, large radiation doses, prolonged treatment and mental anguish relating to both survival and quality of life (QOL). Management needs to include therapy directed towards improving survival, as well as provision of rehabilitation to restore function and quality of life so that patients can resume some degree of normality and reintegrate into society.

This paper will focus on the adverse effects of radiation therapy in the orofacial region, and the impact on dental management and rehabilitation.

Overview of radiation therapy in the head and neck region
Radiotherapy (DXT) has a crucial role in the treatment of many head and neck cancers as either a first line therapy or sole treatment modality, in conjunction with surgery and/or chemotherapy, or as a palliative measure. Certain types of tumours may be controlled or reduced in volume with radiotherapy. However, advanced disease and non-responsive malignancies will show a poor response. A conventional DXT protocol involves delivery of a daily radiation fraction dose of 2 Gray (Gy) for 5 days per week, continued over 6-7 successional weeks. The cumulative dosage may reach 60 and 70 Gy for those having radical therapy.

The ionising radiation destroys tumour cells, rendering them less able to divide, and thereby halting tumour progression, but it also destroys many normal cells in the process. Patients can suffer from a number of side effects, some of which develop quickly and others only becoming evident after some time. The intensity, progression, potential for repair and regeneration, or subsequent permanency of the side effects are influenced by DXT planning (such as radical therapy with or without surgery and chemotherapy, accelerated hyperfraction intensity-modulated radiation therapy (IMRT) and proton beam
therapy), cumulative radiation dose and volume, degree of vascularity, repair potential, cellularity of the tissue being irradiated, tumour type, age of patient, concurrent use of drugs for chemotherapy and other contributing physical conditions or habits. 4,5

Oro-facial related complications of radiation therapy
Radiation therapy has a number of unavoidable immediate and delayed complications, some of which may resolve, but many are unfortunately permanent. The early effects are visible during or immediately after DXT and include oral mucositis, pain in the soft tissues and teeth, loss of taste or altered taste sensation, burning mouth, trismus and/or reduced oral opening, odynophagia, dysphagia and oral candidiasis. 6

The delayed side effects tend to have more adverse consequences and include loss of salivary gland function due to direct damage and fibrosis of the glands as well as obliteration of their blood supply. The salivary glands are particularly sensitive to ionising radiation. A cumulative dose above 52 Gy can cause irreversible damage and dysfunction if the glands lie within the radiation field. 7,8 A reduction in stimulated salivary flow causes changes in the protein and electrolyte composition, and will impact on the many other functions of saliva. The reduced volume means a reduction in constituent protective elements such as immunoglobulins, ions, mucins and salivary proteins, which further reduces its protective and buffering capacity. Patients become more at risk for the growth of many pathologic microorganisms leading to associated oral and dental diseases such as periodontal disease and dental caries (radiation-induced caries). Other chronic sequelae include acute and chronic pain, mucositis, mucosal sensitivity, dry mouth, altered or reduced taste, mucosal or skin related to exposed bone in the previously irradiated area. Predisposing factors include tumour size and location, radiation dose, occurrence of local trauma, dental extractions, oral and dental infection, immune defects and malnutrition. While some of the side effects may resolve or improve with time, professional guidance and medication, others such as poor bone healing and the risk of ORN may remain for years after completion of therapy. 5,6 A better understanding of the underlying pathophysiology may improve the ability of the clinician to prevent the occurrence and help improve the prognosis of this complication. 15

The morbidity associated with all of these oral complications often also impacts on the rest of the body, both physically and psychosocially. Pain, lack of taste and difficulty swallowing make eating difficult and unpleasant. Patients either avoid eating or limit their diet to soft foods that are easy to swallow. This can lead to malnourishment, dehydration and weight loss. Patients with advanced lesions may also develop facial disfigurement, swallowing and mastication difficulties, unintelligible speech, limited oral function, unpleasant odour and poorer survival outcomes. These added consequences further limit their desire for social interaction and routine work, thereby drastically diminishing their QOL. Awareness, prevention or limitation, and management of these adverse sequelae is an essential role for all professionals involved in treatment and care of head and neck cancer patients. To this end they need to be knowledgeable about these issues and help devise coping strategies for the patients and their families. 6,10

Historical and histopathological perspectives in osteoradionecrosis (ORN)
As early as 1922, the first report about osteoradionecrosis of jaws after radiotherapy was published. 13 Since then many clinicians reported on this phenomenon, often using different names such as “radiation osteitis” and “osteomyelitis”. Its presence was always feared due to the devastating damage it caused and extreme difficulty in treatment. 14 Nearly 50 years later, Mainous (1975) advocated the use of hyperbaric oxygen therapy (HBO) to treat radiation-induced tissue injury. This led Marx to conduct extensive research into the field. In 1983 he published many position papers on therapy protocols that have been widely followed and implemented. He proposed the hypoxic, hypocellular and hypovascular theory to provide a better understanding of the pathophysiology of osteoradionecrosis. He believed that hyperbaric oxygen therapy could be used as an adjunct to surgery but not as a treatment modality on its own as it cannot resurrect dead bone or reverse radiation damage entirely. 15

Although there is no evidence that HBO cures mild or moderate ORN, it is reported to be useful for preventing late-onset radiation-induced tissue damage by improving mucosal healing, restoring bone continuity, decreasing wound dehiscence and increasing vascular perfusion to the soft tissue and, to a lesser extent, the underlying bone. It may also help improve or stabilise other symptoms such as xerostomia, pain, erythema and oedema. Despite these advantages, HBO therapy requires a considerable amount of equipment, is time consuming, expensive and some patients reported it to be claustrophobic. Moreover, in reality HBO is not practical, as it requires at least 20-30 sessions in a compression chamber, each lasting 90 min, and often further follow-up “dives”. 16

Over the years HBO therapy has come in and out of favour, leading others to seek more predictable and better alternatives. Delanian and Lefax in 2004 considered the damage seen in ORN to be due to radiation-induced fibrosis of the normal tissues and bone. 17 However, this theory can be discounted if the histopathological features

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of ORN are to be considered. Radiation-induced changes in the tissue result in hypocellularity and hypovascularity leading to tissue hypoxia. Initially the damage is seen in the smallest of vessels causing hyperaemia followed by endarteritis, thrombosis and, finally, total obliteration. This hampers the tissue’s ability to repair itself, and even routine physiological remodelling and repair decrease or cease. If this compromised tissue is then faced with increased repair requirements as a result of traumatic, ischaemic death and collagen lysis will exceed synthesis and cellular replication, resulting in a non-healing wound in which the energy, oxygen and metabolic demands exceed the supply. It furthermore makes the bone more susceptible to infection.

The mandible is at an increased risk of ORN compared to other bones in the craniofacial skeleton which receive their blood supply from vessels that enter the bone via direct muscular attachments, periosteal perforators and intramedullary vessels. The mandible is a denser bone that receives far less perfusion from these sources making it more susceptible to the development of osteoradionecrosis.

Prevention and management of osteoradionecrosis (ORN)

It is recommended that dental extractions and any elective oral and/or dental surgical procedures should be avoided during and immediately after radiation therapy due to the poor wound healing and risk of ORN. If extractions are unavoidable, they must be as atraumatic as possible and the clinician must ensure there is no remaining sepsis, bleeding or open sockets. Patients must be advised to report early symptoms or clinical signs of pain, swelling or non-healing lesions so they can be attended to immediately.

Martos-Fernández et al (2018) reviewed the literature on the fibro-atrophic theory of ORN along with the use of a combination drug therapy regime of pentoxifylline, tocopherol (PVe) and clodronate (PENTOCLO®) to prevent ORN. The theory is based on fibroblast activation and dysregulation. In the onset and progression of ORN, there is an early “prefibrotic phase” with an intermediate “organised phase” and a final remodelling “fibroatrophic phase”. Thus drug therapies that have been proposed offer targeted approaches to different aspects of the fibroatrophic model. The free radical scavenger tocopherol protects cell membranes against peroxidation of lipids, thereby reducing ROS generation from oxidative stress. Tocopherol can also inhibit tumour necrosing factor alpha (TNF) and downregulates procollagen gene expression, which also reduces fibrosis. In combination with this, pentoxifylline, a methylxanthine derivative with an anti-TNFα effect, has an inhibitory effect on fibroblast activation as well as increasing collagenase activity.17,22,24 Martos-Fernández et al (2018) found limited data, and no consensus on the efficacy, optimal therapeutic doses or suggested treatment time for this proposal.

More recently, investigations have been carried out with various bisphosphonate drugs. Clodronate is a first-generation, non-nitrogenous oral bisphosphonate which is not associated with drug-induced osteonecrosis and can reduce osteoclast activity, decrease fibroblast and macrophage proliferation, and promote bone formation by osteoblasts. Its enhanced antifibrotic effect may make it beneficial in the treatment of ORN. As seen by the number of studies in this field, there is no consensus and much controversy about the ideal therapy for prevention and treatment of ORN. It is widely agreed that a multimodal approach is needed, with some researchers suggesting additional antibiotic and anti-inflammatory treatment prior to starting antifibrogenic drugs, to resolve osteitis and achieve a greater healing effect.25

The role of the dentist in treating irradiated patients

The management of patients receiving DXT to the head and neck region should be based on early intervention and preventative care, initiated prior to radiation therapy. Ideally patients should be seen by a multidisciplinary team at the initial consultation and treatment planning session. Thereafter, the general dentist should carry out a thorough examination of hard and soft tissues together with appropriate radiographs to evaluate the oral health status and, at the same time, consider future rehabilitative needs. Initiation of radiation therapy should be delayed until periodontal and crucial dental procedures have been completed and there is clinical and radiographic evidence of healing. Any invasive dental procedures should ideally be completed at least 3–4 weeks prior to starting DXT. Oral hygiene instructions and tailor-made programmes are necessary to motivate patients on the importance of dental hygiene. This is especially needed as they often avoid meticulous brushing and flossing due to pain and limited mouth opening. Additionally, dietary counselling is fundamental to their wellbeing and healing post-therapy. It may also be necessary to prescribe adjunctive aids such as salivary stimulants, artificial saliva, analgesic or antibacterial mouth rinses, and dietary supplements though some sialogogues may elicit unwanted gastrointestinal side effects. Patient education with regards to the disease process, its prevention and management is vital.

Radiation therapy complications in children

While childhood malignancies are relatively uncommon, they do occur. Treatment that involves radiation therapy to the head and neck region in children is more aggressive than in adults and carries a high risk of cranio-facial disfigurement and asymmetry of skeletal structures. If given during the period of tooth formation, it may result in numerous types of tooth or root aberrations. Retinoblastoma is the most common primary malignancy in childhood. Surgical enucleation is the treatment of choice; however, in bilateral cases radiotherapy and chemotherapy may be used to try to preserve the possibility of vision in at least one eye.

The congenital absence or acquired loss of the globe during childhood is both cosmetically and psychologically debilitating. In addition, normal socket and facial development is dependent on orbital growth. Thus loss of the eye, combined with scarring and radiation damage, will further compromise the development of the orbital region. The resulting socket becomes progressively and comparatively reduced in size as the rest of the face develops. It may also develop hypoplastic soft tissue and shortening of the eyelid rim and subsequent facial asymmetry. This makes the prosthetic rehabilitation especially challenging in young children and adolescents.

Management of dentate and partially dentate patients

In dentate patients, a tooth by tooth analysis will determine which teeth are sound, which are salvageable if restored.
and which are not viable to treat. The aim should be to preserve as many healthy teeth as possible for both psychological and functional reasons. In addition to their use in maintaining nutritional requirements and social interactions, they may also be needed as abutments for future prostheses. Conservative restorations for carious teeth should be carried out wherever possible and as per necessity, along with procedures that may prevent future trauma such as smoothing sharp edges of chipped teeth or crowns, and addressing crowns with inadequate marginal seals. Periodontal therapy and endodontic treatment should only be carried out on teeth where there is a relatively good prognosis for improvement to avoid the need for later extractions. Fabrication of custom fluoride trays and prescription of a neutral fluoride gel is essential to help prevent development of post radiation caries. Teeth with a poor prognosis should be extracted in a low traumatic manner to limit damage to the bone and surrounding tissues. Thereafter it is recommended to wait at least two weeks before commencing with the radiation therapy. Patients with existing crown and bridge work need to have these restorations examined closely. Poorly-adapted margins and pontic sites can be a source of plaque accumulation and need to be addressed. Similarly, those with existing implants need clinical and radiographic examination to ensure there are no signs of infection or peri-implantitis. They should also be placed on an implant maintenance programme as removal of failing implants post-radiation therapy carries as much risk for ORN as extraction of teeth.

**Management of edentulous patients**

Patients with existing full or partial dentures should be examined for areas of mucosal trauma. Ill-fitting and fractured dentures should be adjusted, repaired or relined wherever possible. Stability and occlusion should be assessed to prevent traumatic interferences from developing. If their condition and cleanliness is poor the patient must be advised to discontinue use, and rather have a replacement denture made. It is, however, advisable to delay new denture fabrication as the surgical resection and/or radiation changes may alter the alveolar shape. This can create defects that will affect the denture bearing tissues thus compromising the fit, retention and stability of the new dentures. This may also predispose the patient to denture-induced trauma and the development of ORN if bone is exposed.

**Preventative dental prostheses used during radiation therapy**

The number and severity of complications associated with radiotherapy has prompted clinicians to develop various radiotherapy prostheses aimed at reducing or preventing complications, or improving the effectiveness of the radiation delivery. Early examples of these date back to the 1930s where materials like rubber, wax and modelling compounds were used to fabricate these devices. As the years progressed, these were replaced with acrylic resins and lead plates. The prostheses have varying names associated with different functions i.e. spacers, shields, tissue protectors and radiation carriers. They are custom made for each patient and may incorporate channels through which the radiation material is delivered, as well as lead plates to protect the healthy underlying or adjacent tissues. These stents and shields have contributed to better treatment results and fewer complications allowing for rehabilitation to begin earlier and more safely in the post radiotherapy phase.

**Dental management after irradiation in the head and neck region**

Ideally dentists will have had an opportunity to consult with patients prior to their radiation therapy. Often their first encounter is only during or after treatment when a patient seeks help for symptoms or side effects that have developed due to their radiation. The first step is to elicit when the treatment commenced, date of completion, the type, mode and site of therapy, and the total cumulative dosage received. Any signs of bony exposure, oral/skin fistulas or swellings of the soft tissues require immediate attention, and are best referred to a maxillofacial surgeon for further management. The dentition should also be examined for the presence of tooth mobility, which could indicate underlying pathology. Pain, anaesthesia or dysesthesia must be viewed with suspicion and, if needed, investigated further and treated accordingly.

Oral hygiene and nutritional reinforcement is often needed as the mucositis, pain, discomfort and xerostomia hamper both and can result in ulceration, caries and reduced quality of life.

Wearing of dentures post radiation has not been shown to increase the risk of ORN provided that the dentures are well-fitting; however, there does appear to be an increased risk for soft tissue trauma. Furthermore, the discomfort from mucositis and xerostomia can make denture wearing uncomfortable and patients being unable to use them irrespective of how well the dentures previously fitted and functioned. This is primarily due to poor retention and difficulty forming a food bolus, chewing and swallowing as a result of the xerostomia.

Sialagogues (pilocarpine 5mg t.d.s. taken half an hour before meals) can help if there is residual gland function; however, if the major salivary glands have been included in the radiation field this will be of limited value. Patients may rather experiment with artificial salivary replacements, or frequent small sips of water. Sucking on sugar-free sweets and chewing gum may help stimulate flow, but there is a risk of radiation-induced caries developing if they develop a habit of sucking on sugary or acidic sweets. The progression of caries and predisposition to bacterial and fungal infections is exacerbated by the lack of saliva and its associated cleansing, buffering and antimicrobial action. Use of a neutral topical stannous fluoride gel (0.4%) in custom made fluoride trays may help protect the teeth. Limited use of non-alcohol antiseptic mouth rinses (chlorhexidine 0.12%), antifungal topical oral gels (Miconazole 2%w/w) or lozenges (Miconazole 10mg, t.d.s for 7-10 days) and analgesic mouth gels (Xylocaine 5% lidocaine) can be prescribed if indicated.

**Patient maintenance**

The main goals of patient maintenance are to prevent any future dental extractions to limit the chances of ORN developing, maintain a healthy oro-facial environment, and offer patients support and assistance during this time of adaptation. Mucositis, pain and discomfort slowly lessen but damage to salivary glands, bone and certain other tissues may be irreversible. A maintenance programme is important to ensure that oral hygiene remains optimal, and patients’ mouths are kept plaque- and caries-free. This also allows clinicians to check the surgical sites for any evidence of
dehiscence and infection and, more importantly, to monitor for any recurrence of the cancer.

Simultaneously, a holistic approach is needed. Clinicians are at times so focused on trying to rehabilitate the patient by restoring their lost function and appearance that they forget the psychological impact that cancer has on the patients, their dignity and their families. A deeper level of understanding, empathy and support will help those affected to come to terms with their diagnosis of cancer and be more prepared for the consequences that may follow. Counselling will help prepare them for the possibility of disfiguring surgery, side effects of adjunct chemotherapy and radiation and of having to adapt to a prosthesis. It is imperative that a clinical psychologist, dietician and physiotherapist be part of the multidisciplinary treatment team.

Patients may suffer from losses in strength, vision, dexterity, muscle strength and energy which will affect their ability to look after their own oral and general hygiene. A caregiver or family member may need to be educated on helping patients clean their defects and also with attachment, removal and cleaning of their extra oral prostheses. Physical therapy can help relieve oedema, soften and stretch fibrous tissue, increase the range of joint motion, restore circulatory efficiency, increase muscular strength and retain muscular agility. Custom made mouth opening devices and exercises are useful for those who have developed trismus due to damage to their temporomandibular joints or who have limited mouth opening due to muscular and soft tissue fibrosis. They also assist the patient in increasing the mouth opening for speech, mastication and oral hygiene.

Maintenance and cleaning of any intra- or extraoral prosthesis is important for hygienic purposes, to prevent them from becoming contaminated with microorganisms and to prolong their longevity. As healing occurs the defects change in size and shape due to scar tissue contracture, decreased swelling, tissue remodelling or recurrent tumour growth. This affects their fit, seal, retention, stability and performance.

Extraoral prostheses may be retained mechanistically, with attachments and osseointegrated implants*, or with medical adhesives. The latter are generally water soluble and relatively easy to remove from the fitting surface of the silicone and the skin. However, the daily application and removal can easily tear and distort the thin margins and lead to skin irritation. Over time, the colour also fades, along with the deteriorating fit. Frequent follow-up visits are needed to re-stain or remake appliances and also to allow the dentists to monitor the tumour site for early signs of infection, necrosis or cancer resurgence.

Similarly, frequent replacement of obturators and intraoral prostheses is necessary to accommodate tissue changes, and ensure adequate retention, extension and border seal. Retentive elements such as housings, ball abutments or implants will also require technical maintenance and be periodically replaced*.

Denture wearing in the early days after surgery/radiation should be discouraged due to the friable nature of the underlying tissue as well as the frequently encountered xerostomia which compromises denture retention. The dry mucosa is also more prone to trauma if the dentures are rough, ill-fitting or move about too much. Patients who have existing dentures should limit their use during the first year while the tissues are still compromised. The general dentist can help limit mucosal damage by smoothing sharp edges, repairing fractures or placing soft reline material into the fitting surface. Note: The use of the latter carries an additional duty on the dentist to monitor their condition, and replace these frequently as the material is prone to hardened and distorted with time. They are also porous and easily become contaminated with bacterial and fungal organisms which is further hazard to the already compromised oral tissues. These materials also have reduced wettability, which increases the drag on the dry mucosa during function, further increasing the risk of soft tissue trauma. They must be used with caution and care.21, 27 If the patient suffers from xerostomia, the clinician must ensure that oral tissues are lubricated prior to taking impressions or carrying out any of the subsequent clinical stages of denture fabrication to prevent iatrogenic trauma to the mucosa. The use of salivary substitutes may be needed clinically and recommended for home use as well.21

A further consideration is that patients with severely fibrosed tissues, or who have had extensive resective surgery, may not have enough sulcus depths or ridge heights left to support or retain a denture. A vestibuloplasty may be required, but must be carried out with as low trauma as possible, and sufficient healing time allowed prior to fabricating the new denture.

CONCLUSION AND RECOMMENDATIONS

Evidence-based practice and sound principles should be used when deciding on the best and most appropriate treatment for a patient with head and neck cancer. However, individual patient circumstances, needs, desires and preferences must also be considered. The treatment planning and execution should ideally be performed by a multidisciplinary team where all the oral health care providers communicate and work together to provide comprehensive care for the patient. Practitioners need to have a holistic approach, realising that the initial diagnosis of cancer is usually shocking and emotionally disturbing to the sufferer as well as their friends and family. Their interventions should not be based solely on eradication of a disease, but must also encompass an understanding of how this will impact on the patient's quality of life and psychosocial interactions. In addition, they have a duty to try to educate patients on lifestyle habits such as smoking and alcohol cessation, good oral hygiene practices and avoidance of risk factors for oral cancers. Ideally, they should consult newly diagnosed cancer patients prior to commencement of any surgery or radiotherapy where they can carry out a pre-radiation dental assessment, provide surgical stents or radiation shields, carry out emergency dental work and institute early oral hygiene programmes. They should also prepare patients for the imminent radiation-induced side effects, and emphasise the need for regular
recall visits to help them deal with these, and to prevent the development of more sinister complications.

It is important to take into account the mental anguish experienced by clinicians treating patients with head and neck cancers and their subsequent defects, and the psychological impact it can have on their lives. Perhaps the profession needs to consider the wellbeing of both the patients and the clinicians as equally important. To this end, as clinicians we owe it to ourselves and our colleagues to provide more information, resources and help on how to “care for the care-givers”.

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CPD questionnaire on page 222

The Continuing Professional Development (CPD) section provides for twenty general questions and five ethics questions. The section provides members with a valuable source of CPD points whilst also achieving the objective of CPD, to assure continuing education. The importance of continuing professional development should not be underestimated, it is a career-long obligation for practicing professionals.