Oral complications of radiotherapy

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Radiotherapy-induced damage in the oral mucosa is the result of the deleterious effects of radiation, not only on the oral mucosa itself but also on the adjacent salivary glands, bone, dentition, and masticatory musculature and apparatus. Biological response modifiers, cytoprotective drugs, salivary-sparing radiation techniques, and surgery have been introduced to combat and, more importantly, to prevent, the development of these complications. Radiotherapy-induced oral complications are complex, dynamic pathobiological processes that lower the quality of life and predispose patients to serious clinical disorders. Here, we focus on these oral complications of radiotherapy, highlight preventive and therapeutic developments, and review the current treatment options available for these disorders.

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Introduction

Treatment of head and neck cancer generally consists of a combination of radiotherapy and surgery, and, more recently, concomitant chemotherapy. About two-thirds of patients with head and neck cancer present with local or regionally advanced disease and are usually treated with both surgery and radiotherapy or with multimodality treatment (incorporating radiotherapy and chemotherapy). Surgery and radiotherapy for limited T1 or T2 non-metastatic disease, and chemotherapy with surgery or radiotherapy for advanced disease cause a plethora of short-term and long-term oral and oropharyngeal sequelae, which impair quality of life.

The oral cavity and oropharynx are common sites for radiation-induced adverse effects (figure 1). These events can be caused by several factors including: high cellular turnover rates of the oral mucosa, a diverse and complex microflora, and trauma to oral tissues during normal oral function. In 90–100% of patients whose irradiation fields include the oral cavity, some degree of oral complication will develop as a result.[1]

Effects of tumourcidal doses of radiation on healthy oral mucosa are divided into acute and chronic types (panel). Acute effects develop during the early phases of radiotherapy and continue into the immediate post-treatment period (2–3 weeks). Chronic or late effects of radiotherapy can manifest at any time thereafter, from weeks to years after treatment.[2] The acute effects range from merely uncomfortable to intensely painful, but generally resolve in time. However, severe and acute toxic effects on the oral mucosa can compromise the delivery of optimum cancer-therapy protocols and dose reduction or result in the need for treatment schedules to be modified so that oral lesions can resolve. In cases of severe oral morbidity, the patient might no longer be able to continue cancer therapy, after which treatment would have to be discontinued. However, supportive care with placement of a feeding tube (percutaneous oesophageal gastrostomy) can allow treatment to be continued in the presence of severe odynophagia.

Oral complications of radiotherapy in the head and neck region are the result of the deleterious effects of radiation, which affect not only the oral mucosa itself but also the adjacent salivary glands, bone, dentition, and masticatory musculature and apparatus. These radiation-induced conditions include mucositis; salivary gland damage resulting in decreased to absent salivary function; bacterial, fungal, or viral infection (especially in patients with neutropenia or who are immunocompromised); dental caries; loss or perversion of taste; and osteoradionecrosis of the jaw.

The radiation dose needed for cancer treatment is based on the location and type of malignant disease, and whether or not radiotherapy will be used on its own or in combination with other treatment options. Most patients with head and neck carcinomas, treated with a curative intent, receive a dose of 2 Gy per fraction delivered five times per week, up to a total dose of 64–70 Gy.[3] The severity of oral complications is related to the daily and total cumulative dose of radiation, the volume of irradiated tissue, and use of concurrent radiation-sensitising and mucositis-inducing chemotherapeutic drugs.[4–9]

Mucositis

Radiation-induced mucositis is one of the most troublesome acute reactions for patients receiving radiotherapy. The terms oral mucositis and stomatitis are often used interchangeably at examination, but do

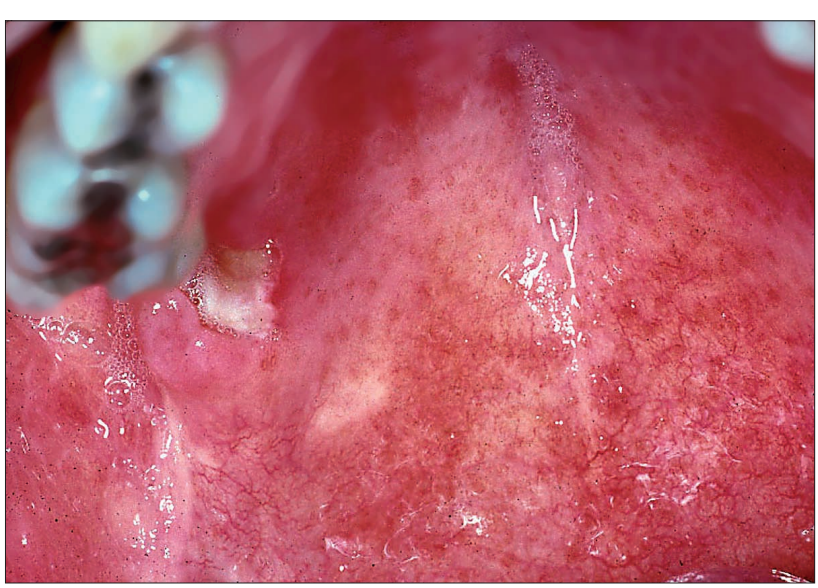

Figure 1: **Diffuse, radiation-induced early grade 2 mucositis with solitary ulcer at lateral aspect of palatal mucosa**

Panel: Oral complications of radiotherapy

Acute complications
Oral mucositis
Infection: fungal, bacterial
Salivary gland dysfunction: sialadenitis, xerostomia
Taste dysfunction

Chronic complications
Mucosal fibrosis and atrophy
Salivary gland dysfunction: xerostomia, dental caries
Soft-tissue necrosis
Osteoradionecrosis
Taste dysfunction: dysgeusia, ageusia
Muscular fibrosis, cutaneous fibrosis, or trismus
Infections: fungal, bacterial

not refer to identical processes. Oral mucositis describes inflammation of oral mucosa resulting from chemotherapeutic drugs or ionising radiation. Stomatitis is a general term that refers to any inflammatory condition of oral tissue, including the mucosa and periodontium. Stomatitis thus includes infections of oral tissues, including mucositis. Mucositis typically manifests initially as erythema, with ulceration developing later (figures 1 and 2).

Pathogenesis

Acute mucositis results from the loss of squamous epithelial 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.

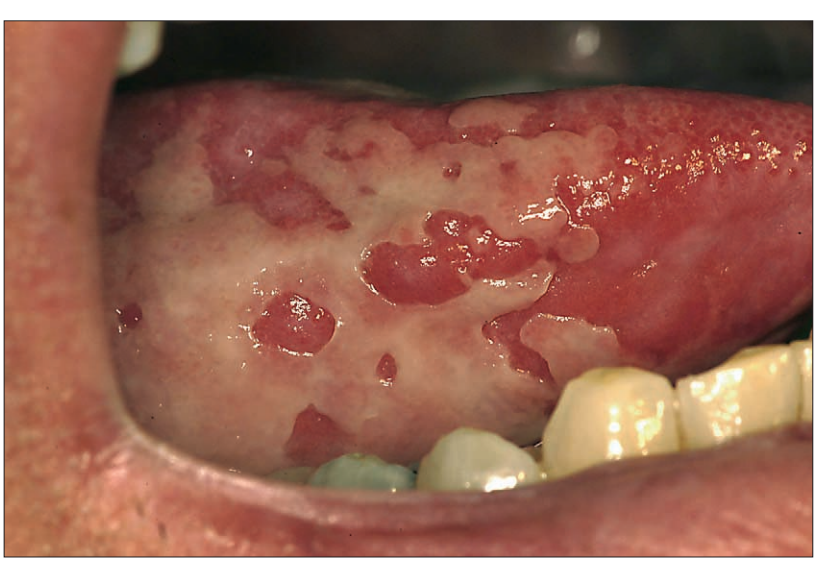

Figure 2: **Confluent, painful oral ulceration with thick fibrinous surface (grade 3 lesion)**
The patient's ulceration necessitated a change in diet, with corresponding restriction of function.

A study[10] in which the sequence of gene expression in irradiated oral mucosa was assessed showed a succession of affected genes that, taken collectively, suggested an intricate functional interaction. Furthermore, the biological endpoint of cell death leading to tissue injury could occur through routes mediated by nuclear factor κB (NFκB), P53, and through the ceramide pathway.

In addition to direct tissue injury, the oral microbial flora is thought to contribute to radiotherapy-induced mucositis.[11] Although the exact mechanism is unknown, one hypothesis proposes that endotoxins produced by gram-negative bacilli are potent mediators of the inflammatory process. Resident bacteria on ulcerated surfaces provide a rich source of cell wall products that amplify mechanisms, which enhance local injury.[12] Mucosal-barrier injury associated with mucositis promotes adherence and invasion by oral commensal organisms and, in conjunction with floral changes, leads to the presence of, or an increase in, pathogens such as α-haemolytic streptococci.[13]

Symptoms of radiation-induced mucositis include intense pain, dysphagia, and odynophagia with resulting anorexia and difficulty speaking. The pain from mucositis is often so intense that it can prevent oral intake, necessitating the use of parenteral analgesics that can greatly affect quality of life and interrupt therapy. Signs of radiation-induced mucositis might include erythema, ulceration, necrosis, and bleeding. The differential diagnosis of mucositis could include viral and fungal infections and graft-versus-host disease. Viral infections differ clinically from mucositis, because they are typically cropped and localised and affect keratinised mucosa, and often coincide with fever at onset.[14]

Grading of the severity of mucositis has little standardisation or validation, with no system being universally accepted. Nevertheless, the ability to assess and convey the severity of mucositis is very important. One study[15] found that the most commonly used grading system for mucositis was the WHO classification, followed by the the Radiation Therapy Oncology Group scale, the European Organisation for Research and Treatment of Cancer (EORTC), and the National Cancer Institutes Common Toxicity Criteria (NCI-CTC; table).[16]

Management of radiation-induced mucositis is directed toward prevention (whenever possible) and treatment. Regimens for the prevention of radiation-induced mucositis include the use of anti-inflammatory drugs, antimicrobial substances, biological response modifiers, and cytoprotective compounds. Unfortunately, many studies assessing interventions for the prevention of oral mucositis have been small, single-centre studies, few have used detailed mucosal assessment scales, and many have done varying comparisons of treatments.[12] Several drugs have been investigated in the prevention of mucositis; unfortunately, their efficacy is still in question.

In 1990, The National Institute of Health Consensus Conference on Oral Complications of Cancer Therapies[17] recommended that all patients with cancer should have an oral examination before treatment, and, if needed, treatment of oral disease in an effort to reduce the risk of complications during treatment. The cost-effectiveness of this approach has been questioned, with no consensus about which patients would benefit from dental intervention. High-risk patients, such as those receiving radiation to the oral mucosa or high-dose chemotherapy with bone-marrow transplantation or peripheral stem-cell transplantation, are the most likely to benefit.

The treatments for radiation-induced mucositis include avoidance, the use of mucosal-coating drugs, cleansing devices, lubricants, emollients, and pain management strategies. These approaches have not generally been effective. Various substances have shown to be potentially effective in chemotherapy-induced but not radiotherapy-induced mucositis.[18] Systemically delivered treatments of mucositis such as antioxidants (β carotene, azelastine), immunomodulatory drugs (indometacin), anticholinergic drugs, pentoxifylline, cytokines, antiviral drugs, and glutamic acid are being used with varying success.

Pain control

Patients with oropharyngeal pain often need systemic analgesics, adjunctive drug treatment, physical therapy, and psychological therapy in addition to oral care. In general, mucositis should be treated conservatively to avoid further tissue irritation and damaging of the remaining regenerative epithelial cells. Plaque control and oral hygiene should be maintained. The efficacy of chlorhexidine as an adjunct to oral hygiene measures is uncertain in management of mucositis. Findings suggest that the drug's value is no greater than that of sterile saline. In patients who have received radiotherapy, some data[14] suggest that chlorhexidine worsens the condition. Prophylactic rinsing with saline or chlorhexidine might provide indirect benefits, by controlling plaque amounts, gingivitis, and oropharyngeal candidiasis.

Benzydamine, an anti-inflammatory drug, reduces concentrations of tumour-necrosis factor and is effective in reducing the intensity and duration of mucosal damage.[19] Systemic drugs for pain relief, including opioid analgesics, have been used in patients receiving radiotherapy.[20,21] Several locally applied drugs have also been investigated to prevent or treat mucositis, which include sucralfate, vitamin E, chlorhexidine, anti-inflammatory substances, cytokines, alprostadil and dinoprostone, multidrug topical mouth rinses, folinic acid, and allopurinol.[1] Most of the studies addressing the use of topical drugs pertain to the use of sucralfate and chlorhexidine, also with conflicting results.

Sucralfate, a non-absorbable aluminum salt of sucrose and octasulfate, adheres to ulcer bases and creates a surface barrier in the gastrointestinal tract. The drug has some antibacterial activity[22] and binds to epidermal growth factor, which might accelerate healing.[23] Sucralfate is thus a direct cytoprotectant, which was initially thought to prevent or control radiation-induced mucositis,[24,25] but double-blinded studies have not confirmed its efficacy. However, even though sucralfate does not prevent mucositis, reduced overall oropharyngeal pain was recorded in one study.[26]

	Clinical features	Functional or symptomatic features
1: Mucosal erythema	Mild symptoms	Normal diet
2: Patchy ulceration	Symptomatic	Modified diet
3: Confluent ulcers or pseudomembrane ease of bleeding	Symptomatic	Unable to aliment orally
4: Tissue necrosis, spontaneous bleeding	Life-threatening consequences	Symptoms associated with life-threatening consequences
5: Death	..	Death

Data from ref 16.

Table: **Grading of mucositis severity**

Antimicrobial treatment

Radiotherapy effectively changes the healthy oral microbial flora with a striking increase in oral gram-negative enterobacteria and pseudomonads. This shift in flora is thought to contribute to mucositis. However, the role for antibacterial therapy in the control of radiation-induced mucositis has not been established. Conflicting outcomes of interventional studies with antibiotic therapy casts some doubt on the hypothesis that bacteria are major drivers of mucositis in patients who have not received myeloablation.

Biological response modifiers, cytoprotective drugs, and low-energy lasers have been introduced for mucositis treatment. Cytoprotective drugs act mainly as free-radical scavengers or antioxidants, which include amifostine, prostaglandins, glutamic acid, N-acetylcysteine, and vitamin E. Biological response modifiers offer the potential to lower the sensitivity of epithelial cells to the toxic effects of cancer therapy or to stimulate tissue repair. Drugs that have been introduced recently or are under investigation include: palifermin, interleukin 1 and interleukin 11, and transforming growth factor β (TGFβ).

The colony-stimulating factors molgramostim and filgrastim have also been investigated. Molgramostim used concurrently with conventional fractionated radiotherapy was assessed in a consecutive series of patients and was associated with reduced mucositis, which suggested that it protected the mucosa during radiotherapy.[27] Both the pineal hormone melatonin and the cytoprotector amifostine have been postulated to have activity in prevention of mucositis.[28,29] Palifermin has been introduced to reduce oral mucositis related to cytotoxic therapy for haematological cancers and has yielded encouraging results, which raises the possibility for controlled studies of similar compounds in patients undergoing radiotherapy to the oral cavity or head and neck region.[30]

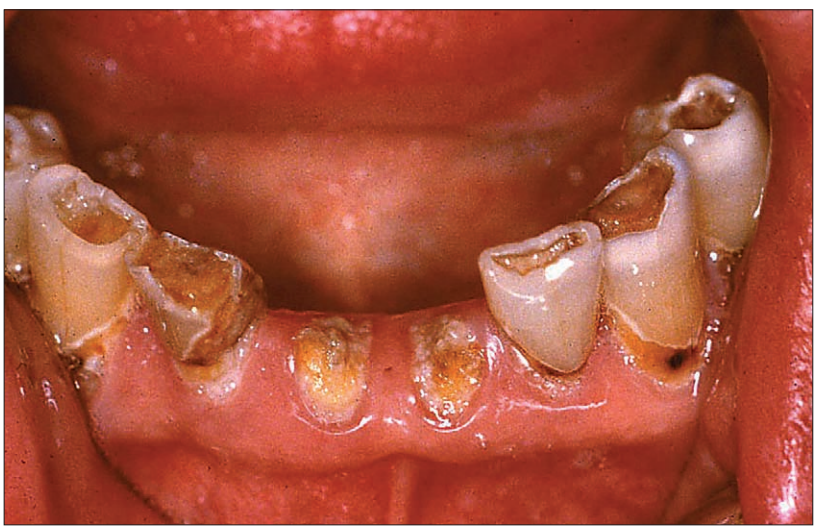

Figure 3: **Severe radiation-related dental caries caused by xerostomia and inadequate dental treatment**

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 (figure 3), 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.[31] Various radiotherapy regimens result in varying degrees of xerostomia. Mantle, unilateral, and bilateral fields of radiation can be associated with a fall in salivary flow 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%.[32–34] With salivary-gland-sparing techniques such as three-dimensional intensity-modulated radiotherapy, this effect has fallen sharply.[35]

Saliva is important for lubrication, and thus important for comfort of the mouth and oropharynx, but it is also needed to modulate the oral microbial flora, remineralise teeth, maintain the mucosal immune system, and prepare the food bolus during mastication. Saliva is hypotonic to plasma, with concentrations of sodium and chloride ions being less than those of plasma. The greater the secretory flow rate, the higher the tonicity of the saliva. Saliva consists of two components that are secreted by independent mechanisms: a fluid component that includes ions and is produced mainly by parasympathetic stimulation, and a protein component generated by secretory vesicles in acini and released mainly in response to sympathetic stimulation.[36] The major salivary glands (parotid, submandibular, and sublingual) produce up to 90% of salivary secretions. The average output of saliva in healthy individuals ranges between 620 mL[37] and 1000 mL[38] per day.

Radiation portals designed for the management of oral and head and neck cancer often include the parotid and submandibular glands, and, in some cases, many minor salivary glands. The acinar (fluid-producing) salivary gland cells are highly radiosensitive. Laboratory data[39] have suggested that irradiated serous salivary glands undergo interphase cell death by apoptosis, resulting in an increased intensity of degenerative changes with dose and time in serous acinar cells that produces two types of damage: apoptosis at low doses and necrosis at high doses.[40] However, more recent findings[41,42] have suggested that cell-membrane damage by radiation impairs receptor-cell signalling, which in turn leads to compromised and incomplete function.

Damage also occurs in the parenchyma of the salivary gland, and radiation-associated inflammation, vascular changes, and oedema contribute to the overall extent of damage.[31] This induced damage to the salivary glands leads to decreased salivary flow, changes in electrolyte and immunoglobulin composition of saliva, reduction in salivary pH, and repopulation of cariogenic bacteria in the mouth.[43] The extent of glandular change is generally directly related to radiation dose delivered to the salivary glands, with the most severe and irreversible forms of salivary dysfunction resulting from damage to or loss of salivary acinar cells.[44] In addition to direct cellular damage, an absence of wetting medium reduces the ability of chemoreceptors on the tongue and palate to accept stimuli in foods or liquids, resulting in a failure of the salivary gustatory response. This thickened mucinous saliva forms a barrier to dietary, thermal, and mechanical stimulation of the taste buds, which in turn affects the salivary-centre feedback pathway of salivary gland stimulation and ultimate secretion.

Functional impairment correlates with the volume of salivary gland parenchyma exposed and the total radiation dose. Clinically, xerostomia has been reported in association with as little as two or three doses of 2 Gy each. Doses greater than 30 Gy generally lead to permanent or semipermanent xerostomia.[45,46] Both resting and stimulated salivary flow are inhibited. However, a compensatory hypertrophy of the unirradiated salivary-gland tissue occurs after a few months and up to 1 year, which lessens the sensation of xerostomia; however, little further improvement can be expected after this period.[36]

If all major salivary glands are included in the radiation field, salivary function often falls by 50–60% in the first week, with basal salivary flow reaching a measurable minimum 2–3 weeks after use of 23 Gy of fractionated radiotherapy.[44] Radiation to a salivary-gland tumour could be restricted to the ipsilateral gland and thus might not cause severe xerostomia, whereas radiation to the nasopharynx usually affects both parotid glands, causing severe and permanent xerostomia. Radiation fields used to treat oral-cavity cancer usually

circumvent some of the parotid beds, thus producing less xerostomia.[47]

Management of xerostomia

Aggressive preradiation oral care could keep the severity of xerostomia to a minimum. Assessment, ideally 2–3 weeks before treatment, by a dental team experienced in oral oncology is essential to determine oral health status, undertake necessary dental and oral interventions, and allow for healing from any invasive procedures needed. Good oral hygiene and detection of oral abnormalities coupled with appropriate nutritional intake are important pretreatment strategies. Specific factors that might need attention before radiotherapy is started include management of mucosal lesions, dental caries and associated periapical inflammatory disease, periodontal disease, dental prostheses, impacted or unerupted teeth within the planned radiation field, orthodontic appliances, temporomandibular dysfunction, and pretreatment salivary dysfunction.

Protectants

Classic free-radical generation has been associated with radiation-induced damage to salivary tissue; because of this relation, antioxidants and free-radical scavengers have been used to lessen some of the toxic effects of radiation in healthy cells. This hypothesis is still important and is now being reconsidered for research.[42]

Since the mid 1900s, researchers have realised that radiation-induced inactivation of biological substances could be modulated by some aminoacids, glutathione, and ascorbic acid. On the basis of these observations, Patt and colleagues[48] investigated the effect of rats given the thiol-containing aminoacid cysteine, before delivery of 8 Gy of whole-body radiotherapy. Thiol-containing compounds, including amifostine, are thought to scavenge free radicals and help create local tissue hypoxia by competing with oxygen. Amifostine, an inactive prodrug, is activated to its selective tissue-protective metabolite in healthy tissue but not in neoplastic tissue.[49] Trials have been undertaken to assess the ability of amifostine to protect against mucositis and xerostomia. In 1994, McDonald and colleagues[50] showed that amifostine, given concurrently with every fraction of radiotherapy for 6–7 weeks, was tolerated and improved overall salivary gland function. A large, multicentre randomised study[51] established the role of amifostine as a protector against xerostomia during standard fractionated radiotherapy. Since then, Wasserman and colleagues[52] have stated that amifostine treatment during radiotherapy for the head and neck reduces the severity and duration of xerostomia 2 years after treatment. Adverse effects (sometimes serious),[53] the need for daily injections, and cost concerns have restricted wide acceptance; however, subcutaneous treatment, although not licenced as a delivery method, seems to be equally effective and is associated with few toxic effects.[54]

Salivary-sparing radiation techniques

Three-dimensional radiotherapy planning and dose-delivery techniques, such as intensity-modulated radiotherapy, have been used to restrict radiation exposure to healthy structures adjacent to the radiation targets. The use of an inverse-planning algorithm allows selective sparing or dose reduction to adjacent healthy tissues without compromising dose delivery to the tumour. Other potential uses for intensity-modulated radiotherapy and recent tomographic modes of delivery allow use of increased doses to target tissues and reduced doses to non-targeted tissues, thus increasing the therapeutic ratio. With this technique, substantial dose reductions have been achieved to contralateral parotid and submandibular glands, resulting in retention of salivary output and amelioration of xerostomia. This approach accords with results of several studies,[55–57] in which a radiation dose of 26 Gy was found to be the threshold for preserved stimulated saliva flow when parotid-sparing techniques were used. Roesink and colleagues[46] also showed a dose-dependent loss of acute function in irradiated parotid tissue.

Submandibular gland transfer

The usual radiation ports in the treatment of head and neck cancer deliver 60–65 Gy to the major salivary glands. However, the submental region is regularly shielded or can be beyond the treatment field and receives only scatter radiation amounting to 5% of the total dose (3·00–3·25 Gy).

Surgical techniques developed to spare salivary glands from head and neck radiotherapy were introduced in the early 1980s.[58] This idea has been revived with the Seikaly-Jha procedure. This technique is the transfer of a single submandibular salivary gland into the submental space, while pedicled on the facial artery, facial vein, and submandibular ganglion.[59] The method is given only to patients with clinically negative cervical lymph nodes, using the gland on the contralateral side of the primary tumour and is therefore not appropriate for all patients. For individuals treated in this way, follow-up data after radiotherapy indicate fewer complaints of xerostomia and few surgical complications.[60]

Sialogogues

Untreated or unaffected residual salivary tissue is the target for sialogogues. Salivary stimulants can be characterised as gustatory, tactile, or pharmacological.[61] 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.[62] Pharmacological sialogogues are typically agonists of the muscarinic M3 receptor and include pilocarpine and cevimeline.[63–65] Of

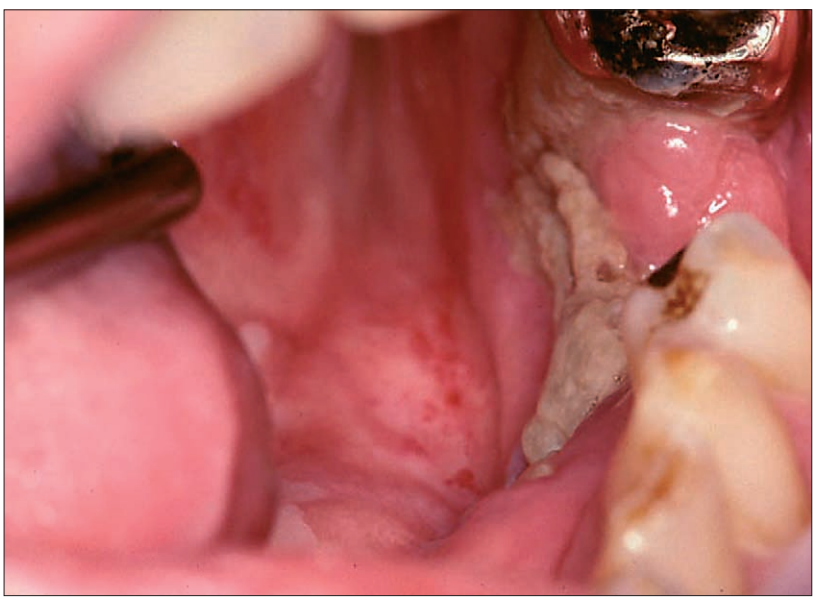

Figure 4: **Exposed, painful mandibular bone characteristic of osteoradionecrosis**

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.[66] The effect of pilocarpine is more persistent when it is used before and continued during radiotherapy, and then stopped 3 months after radiotherapy.[67]

Adverse effects of non-selective cholinergic agonists include perspiration, increased bowel and bladder motility, and flushing.[68] Patients with a history of asthma, severe chronic obstructive pulmonary disease, congestive heart disease, and narrow angle glaucoma should avoid these drugs. Cevimeline is a quinuclidine analogue of acetylcholine that has a high affinity for M3 muscarinic receptors of lacrimal and salivary glands, but a low affinity for equivalent M2 receptors on cardiac and lung tissue.[36] Thus, cevimeline can enhance salivary secretions while keeping adverse effects to a minimum on pulmonary and cardiac function. Cevimeline is being investigated for treatment of radiotherapy-induced salivary hypofunction.[65] It could also have clinical application in management of xerostomia secondary to irradiation, but additional data are clearly needed.[36]

Saliva substitutes

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

Inflammation of the pterygomasseteric sling often heralds the onset of trismus. This event occurs secondary to insult to the pterygoid muscles, mandible, or masseter muscle. When the interincisal distance on full opening is less than 18–20 mm, oral alimentation is difficult. Notably, patients with clinically significant trismus who undergo general anaesthesia usually need transnasal fibreoptic intubation or an awake tracheotomy. 5–38% of patients develop trismus after treatment for head-and-neck cancer.[69,70] 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.

Pathogenesis

The direct effect of radiation on muscle ultimately results in fibrosis and contracture,[71] with a gradual onset noted at about 9 weeks after treatment is completed. The damage progresses for the next 9 months at a rate of 2·4% loss of interincisal opening per month, with a more protracted loss of opening in later years. At 4 years, the reduction in mean interincisal opening has been measured at 32%.[72] Although the most apparent signs of trismus are damage and fibrosis of the muscles of mastication, trismus will probably also cause degenerative problems in the temporomandibular joint. These degenerative changes could mimic arthritic changes, and could be accompanied by inflammation and pain. If the symptoms are left untreated, degenerative processes could continue and ultimately become permanent.

Clinical characteristics

Trismus manifests as a slowly evolving inability to open the mouth to enable normal function. Interincisal opening will be restricted, painless, and could be noted most readily during the first year after treatment. Speech articulation will not be adversely affected in most instances, although eating is often made difficult because of the restricted range of motion in all excursive jaw movements. Restrained mouth opening can result in compromised oral hygiene, which is particularly important in patients who also have radiation-induced xerostomia.

Prevention and management

High-energy radiography beams and sophisticated multiple-field techniques should be used whenever possible to reduce the dose of radiotherapy to the temporomandibular joint and to the mastication muscles. 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 passive and active 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 (TheraBite®) thought to be more efficient.

Pentoxifylline, a methylxanthine derivative used to treat vascular diseases such as intermittent claudication, has been reported to have effects against TNFα (tumour necrosis factor α), 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.[73]

Search strategy and selection criteria

We identified data for this review by searching computerised bibliographic databases (MEDLINE, EMBASE, Current Contents) without language restrictions from 1966 to 2005 using the Cochrane Collaboration search strategy, which aims to identify all randomised controlled trials. The search terms "oral complications", "radiation therapy", and "head and neck cancer" and specific oral complications "xerostomia", "trismus", "osteoradionecrosis", "hyperbaric oxygen therapy" were used. Reference lists from relevant articles were searched. Only papers published in the English language between 1978 and 2005 were included. Studies that involved oral complications due solely to chemotherapy cancer treatment and work based on case studies and small case series were excluded.

Osteoradionecrosis

Osteoradionecrosis is not a common complication of radiotherapy. The incidence of the disorder varies greatly, ranging from 1% to 37·5%. However, these data are based on small sample sizes and short follow-up assessments. In a 30-year retrospective study of 830 patients, a collective rate of 8·2% was recorded, which is probably most representative.[74] One study[75] has shown an overall reduction in the incidence of osteoradionecrosis during the past 20 years.

Pathogenesis

The basis of this tissue alteration resides with radiation-related generation of free radicals and corresponding damage to endothelial cells within the treatment field. Over time, this occurrence leads to hypovascularity, tissue hypoxia, destruction of bone-forming cells, and marrow fibrosis.

Clinical characteristics

A wide range of presentations can be seen, from small asymptomatic regions of exposed bone that remain stable over time to full-blown osteonecrosis that is characterised by severe pain and a foul smelling necrotic jaw bone (of a green-grey colour) with suppuration (figure 4).

Management

If osteoradionecrosis is diagnosed early, local debridement, antibiotic treatment, and ultrasonography can be successful.[76] In patients with established disease, the use of hyperbaric oxygen coupled with resection of necrotic bone is indicated, although the value of hyperbaric oxygen in this circumstance has been challenged.[77]

Prevention

Late-onset radiation injuries could lead to cellular depletion, reduction of vascular density, involution of small vessels followed by fibrosis, and hypocellularity of bone-marrow elements. All these factors result in hypoxia, a major component of delayed wound healing secondary to decreased fibroblast activity and reduced efficiency of collagen production. Finally, secondary infection, injury, and surgery contribute to worsening late morbidity.[78]

Hyperbaric oxygen stimulates angiogenesis, fibroblast and osteoblast proliferation, and collagen formation in irradiated tissues, and increases cellular oxygen concentrations.[79,80] The benefit of hyperbaric oxygen use as a routine treatment in the management of dental extractions in the irradiated jaw is controversial. Studies have abandoned the previously established dogma based on the earlier work of Myers and Marx,[81] who postulated that exposure to high oxygen concentrations at raised atmospheric pressure results in production of a hyperoxic or normoxic hypercellular environment. However, Sulaiman and colleagues[82] have shown that careful dental extractions and meticulous follow-up can reduce rates of osteoradionecrosis in the absence of hyperbaric oxygen therapy. Furthermore, in established osteoradionecrosis of the mandible, a study[77] showed that hyperbaric oxygen was not beneficial.

Conclusions

Radiotherapy can greatly damage the head and neck region as a result of cancer treatment. A complex and dynamic pathobiological process ensues that diminishes patients' quality of life and often leads to serious clinical sequelae. Therefore, radiation-induced damage should be anticipated and prevented whenever possible and managed early. The introduction of biological response modifiers, cytoprotective drugs, tissue-sparing radiation techniques, and surgical advances should help control these complications.

Conflict of interest

We declare no conflicts of interest.

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