Managing side effects of radiotherapy in head and neck cancer

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Curative radiotherapy for head and neck cancer causes very significant side effects. In addition to their considerable impact on the patient's quality of life, these effects can prejudice treatment outcome. This review looks at the management of the adverse effects of radiotherapy for head and neck cancer.

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Radiotherapy frequently cures head and neck cancer but at the expense of significant side effects caused by radiation-induced damage to normal tissues. These radiation reactions may be classified as early and late: early reactions occur during and/or shortly after treatment and may persist for up to 3 months; late reactions occur months to years after the treatment. However, this classification is not clear-cut. Certain predictable reactions (e.g. dry mouth) occur acutely and persist as a permanent late effect. Alternatively, an exaggerated acute reaction may fail to resolve and persist as a chronic consequential effect (Denham et al, 1999). The common acute and late effects of radiotherapy for head and neck cancer are listed in *Table 1*.

The importance of acute reactions is that they have a significant impact on the patient's quality of life (QoL) and may delay, or even prevent, delivery of a full curative radiation dose. Such changes to the normal time-course of radiation dose delivery can result in significant reductions in the likelihood of cure. In contrast, late reactions only evolve after treatment is completed, have a chronic, debilitating effect on the patient's QoL and may, on occasions, be life threatening. Therefore, in an attempt to reduce radiotherapy-induced side effects, strenuous efforts are made to limit the amount of normal tissue that is irradiated. However, in order to treat the tumour it is frequently necessary to risk a degree of normal tissue damage. Therefore, a certain level of risk for some potential complications must be accepted and discussed with the patient.

This review aims to give an understanding of the biological principles that govern the pathogenesis and management of acute and late toxicity. It looks at the common acute and late reactions seen in the clinical setting and discusses their management in the context of a multidisciplinary team.

TABLE 1.
Early and late side effects of radiotherapy

Early	Mucositis
	Desquamation
	Xerostomia
	Alopecia
	Loss of taste
	Lhermitte's phenomenon
Late	Xerostomia
	Osteoradionecrosis
	Fibrosis
	Soft tissue necrosis
	Neurological damage
	Second malignancy

RADIOTHERAPY-INDUCED TISSUE DAMAGE

The target of radiation in both cancerous and normal cells is DNA. Damage occurs either through a direct or an indirect effect. The direct effect is rare and is caused by a radiation beam depositing its energy directly in a DNA molecule. More commonly, the indirect effect results from a radiation beam depositing its energy in a water molecule to form free radicals (highly reactive molecules that can damage DNA). This DNA damage, if sufficiently severe, can trigger cell death. Actively dividing cells (e.g. skin, mucosa, hair follicles) are most sensitive to radiotherapy and their death causes the acute reaction. In contrast, non-dividing cells (e.g.

connective tissue, bone) do not manifest their accumulated DNA damage unless called upon to divide, dying a so-called 'mitotic death' at a later date. Cells contain scavenger molecules (e.g. glutathione) that can mop up free radicals and limit DNA damage. In addition, both normal and cancer cells can repair DNA damage, although it is hoped that malignant cells do this less effectively. By dividing a course of radiotherapy into 30–35 separate fractions over 6–7 weeks, this differential in the ability to repair DNA damage is magnified with the result that the tumour can be cured without completely destroying the surrounding normal tissues.

FACTORS AFFECTING RADIATION REACTIONS

The degree of radiation reaction can be influenced by treatment- and patient-related factors.

Treatment factors

Radiotherapy-induced toxicity is directly proportional to the total radiation dose delivered and the volume of tissue that is irradiated. In addition, the dose delivered per treatment fraction is important, especially for late reactions. It is this fact that underlies the use of protracted courses of small fractions of radiation over many weeks.

Different types of radiation deposit their dose at different depths within tissue. Low energy (superficial) X-rays (50–200 KeV) and electrons deposit a higher proportion of their dose at the skin surface compared to high energy X-rays and γ-rays (1–10 MV). Therefore, skin toxicity is reduced when high energy X-rays and γ-rays are used.

Patients with advanced head and neck cancer often receive concurrent chemotherapy and radiotherapy. This approach certainly increases acute reactions and may accentuate late reactions.

Patient factors

Some rare genetic disorders relating to the repair of DNA damage cause increased radiation reactions (*Table 2*). Acquired disorders that can affect patients with head and neck cancer include conditions that affect tissue repair (e.g. poor nutritional status, high alcohol intake, smoking). Reduced levels of scavenger molecules (in such conditions as human immunodeficiency virus infection or acquired immunodeficiency syndrome; HIV/AIDS) may also increase reactions (Costleigh et al, 1995; Formenti et al, 1995).

TABLE 2.
Genetic syndromes associated with increased sensitivity to radiation

Ataxia telangiectasia
Gardner's syndrome
Fanconi's anaemia
Severe combined immunodeficiency syndrome
Xeroderma pigmentosum

ACUTE SIDE EFFECTS

Mucositis

Mucositis occurs through death of stem cells in the basal layer of the non-keratinized epithelium of the upper aerodigestive tract. Because the stem cells renew the epithelium every 2 weeks or so, the acute reaction is not observed until the third week of treatment when the lack of replacement epithelial cells becomes apparent. There are four recognized phases (*Table 3*) and grades (*Table 4*) for mucositis. A representative example of a grade 3 mucositis of the soft palate is shown in *Figure 1*.

Management of mucositis: There are no effective means of preventing the occurrence of radiotherapy-induced mucositis (Symonds, 1998). Hence, care is taken during the planning process to ensure maximal shielding of mucosa from radiation beams, without compromising tumour coverage. Once present there is no established treatment to accelerate the resolution of mucositis, although several measures are recommended to alleviate symptoms.

TABLE 3.
The four phases of radiation-induced mucositis

The inflammatory phase	Cytokine release (mainly tumour necrosis factor-α, interleukin-1 and interleukin-6) by the epithelium and surrounding connective tissue causes tissue damage
The epithelial phase	Manifest by atrophy and ulceration as the damaged basal cell layer migrates to the surface and is exposed
The ulcerative phase	Fibrinous pseudomembranes cover areas of ulceration. There is colonization with Gram-negative organisms with endotoxin and cytokine release, causing more damage to the epithelium
The healing phase	The epithelium regenerates as the basal cell layer proliferates and the normal microflora is established

TABLE 4.
Grading of mucositis

Grade 0	No change over baseline
Grade 1	Hyperaemia
Grade 2	Patchy mucositis
Grade 3	Confluent mucositis
Grade 4	Ulceration, haemorrhage, necrosis

The mainstay of therapy is the use of oral analgesics which are prescribed according to the World Health Organization analgesic ladder (*Figure 2*). Although frequently prescribed, there is no convincing support for the use of mouthwashes (Feber, 1996). Normal saline and sodium bicarbonate are used, especially if there is extensive slough. Mouthwashes containing alcohol are avoided as they may increase local inflammation and cause pain. Likewise, the patient is advised to avoid alcohol and smoking during treatment.

Cytoprotectants: *Sucralfate:* This agent forms ionic bonds with proteins within an ulcer and acts as a protective barrier. It may also aid healing by increasing local prostaglandin E_2 release (Ferraro and Mattern, 1984).

Topical non-steroidal anti-inflammatory drugs: A large double-blind, placebo-controlled trial of benzydamine reported decreased pain scores for patients on the active compound (Epstein and Stevenson-Moore, 1989). Indomethacin given on the first day of treatment has also been shown to decrease the severity and onset of mucositis (Pillsbury et al, 1986).

Steroids: The role of corticosteroid mouthwashes is unclear. A few non-randomized trials suggest they may be useful (Abdelaal et al, 1989; Rothwell and Spector, 1990) but the risk of oral candidiasis that may accentuate mucositis must be considered.

Growth factors: Granulocyte-macrophage colony stimulating factor (GM-CSF) is an endogenous 14 KDa protein which acts on connective tissue, triggering release of fibroblast growth factor and interleukin-1 which stimulate the basal layer to proliferate. A small randomized trial of this agent administered subcutaneously in patients with larynx cancer demonstrated that it reduced mucositis of the upper aerodigestive tract (J McAleese, personal communication, 2002). An ongoing Radiation Therapy Oncology Group trial is addressing similar issues. Topical GM-CSF mouthwash has no role to play (Sprinzl et al, 2001).

Antimicrobials: Patients undergoing treatment may develop oropharyngeal candidal infections because of poor oral hygiene and reduced mucosal defence mechanisms. Candida is treated with nystatin mouthwash or oral fluconazole in cases of persistent infection. At present, there is no established prophylactic role for antifungal and antibacterial antimicrobials. Polymyxin E and tobramycin are active against Gram-negative organisms that frequently colonize and promote mucositis by endotoxin release. There is evidence that selective depletion of Gram-negative organisms by antibiotic lozenges can decrease mucositis (Spijkervet et al, 1991).

Silver nitrate: This agent stimulates cell division in normal mucosa. There are conflicting data on its role in managing mucositis (Maciejewski, 1991; Dorr et al, 1995).

Modulators of oxidative stress: Gluthathione and amifostine work by mopping up free radicals. Therefore, they may reduce the acute radiation reaction. There are very limited data relating to their effect in preventing mucositis.

Figure 1. Grade 3 radiation mucositis affecting the soft palate. This is a direct view into the oral cavity with a tongue depressor (bottom of picture) in place. Confluent mucosal reaction can be seen over the soft palate with evidence of a yellow/white pseudomembrane and increased vascularity (small dilated blood vessels are seen at the margin of the reaction). The tongue, which is seen at the bottom of the picture bulging either side of the tongue depressor, has significant overlying slough.

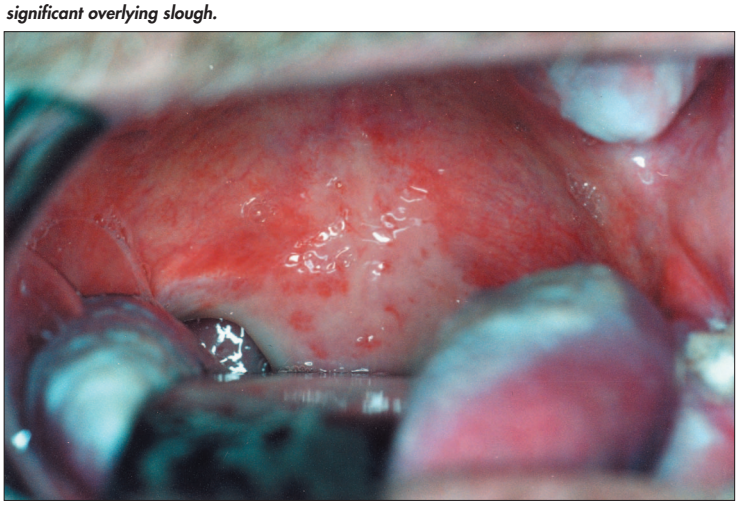
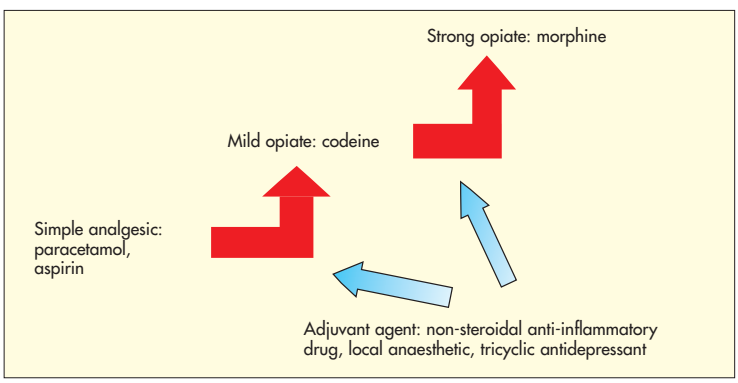


Figure 2. Analgesia for mucositis: The World Health Organization analgesic ladder.



Xerostomia

The major salivary glands produce up to 90% of saliva. The position and size of the parotid gland means that it is frequently included in the radiation treatment field for head and neck cancer. The serous acini (which produce watery saliva) are more sensitive to the effects of radiotherapy than the mucous acini, resulting in the production

of thick, tenacious saliva. The decrease in the quantity and quality of saliva may lead to a change in oral flora and accelerated dental caries.

The free radical scavenger amifostine accumulates preferentially in salivary tissue. It has been shown to reduce acute and chronic xerostomia without adversely affecting the antitumour effects of radiotherapy. Amifostine is expensive and may cause nausea, vomiting, hypotension and rarely allergic reactions (Schuchter, 1996). More recently, there has been significant progress in the use of intensity-modulated radiotherapy as a means of sparing the parotid gland from receiving high radiation doses in patients with head and neck cancer. Otherwise, the management of xerostomia is palliative. Patients should sip water regularly or use artificial saliva. In severe cases, oral pilocarpine can improve symptoms (LeVeque et al, 1993), although unpleasant cholinergic side effects are often limiting.

Altered sense of taste

Dysgeusia occurs because of radiotherapy-induced damage to the circumvallate and the fungiform papillae of the tongue. The taste buds mediating bitter or sour taste are affected more than those for sweet or salty taste. The extent of sensory disturbance is directly related to the volume of the tongue that is irradiated (Fernando et al, 1995). Complete or partial recovery is usual but can be very slow and may take months to resolve. This symptom can be very distressing to the patient and is rather poorly understood.

Maintaining nutrition

Mucositis, xerostomia and dysgeusia all contribute to a decrease in oral intake. Many patients with head and neck cancer have a pre-existing poor nutritional state. Management of this problem involves a multidisciplinary team including the oncologist, dietician, pain control team and gastroenterologist. In some circumstances, a nasogastric or percutaneous endoscopic gastrostomy tube is required to maintain nutrition while the acute reactions settle.

Acute skin reactions

Normally, attempts are made to limit the acute radiation effects in the skin by using high energy X-rays or γ-rays that deposit their maximal dose 1–2 cm below the skin surface (the so-called skin-sparing or build-up effect). However, certain

sites (e.g. back of pinna, skin over laryngeal promontory) are particularly prone to acute skin reactions because of loss of a normal skin-sparing effect. In addition, in order to immobilize patients and ensure day-to-day reproducibility during radiotherapy, a personalized perspex shell is used which has the effect of negating the skin-sparing effect and increasing the dose that is delivered to the skin. The perspex shell can be cut out in areas that do not compromise the tumour dose to prevent skin soreness. Other types of radiation, such as electrons, are often used and deposit a higher percentage of their dose at the skin surface. Skin reactions can be graded as in *Table 5* and are managed as shown in *Table 6*. Typical dry and moist desquamation reactions are depicted in *Figures 3* and *4* respectively.

Figure 3. Radiation-induced skin reaction. There is erythema (grade 1) affecting the skin from the level of the mandible to the mid-neck below the thyroid promontory. In addition, there are areas of dry scaling of the skin (dry desquamation – grade 2) especially affecting the area of skin below the ear lobe.

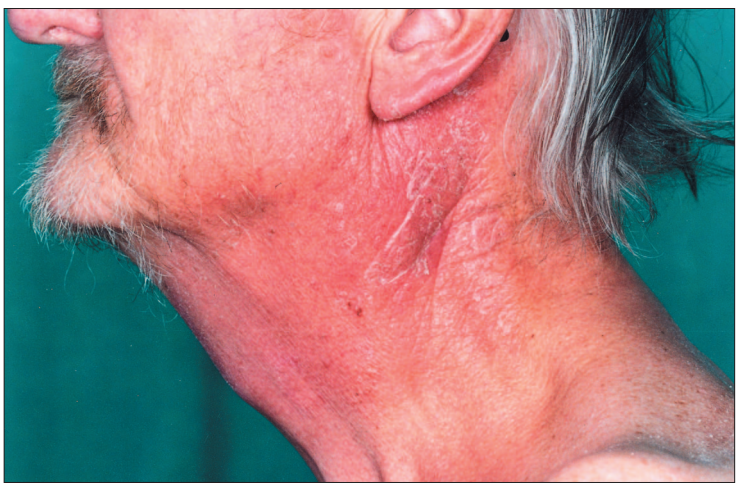
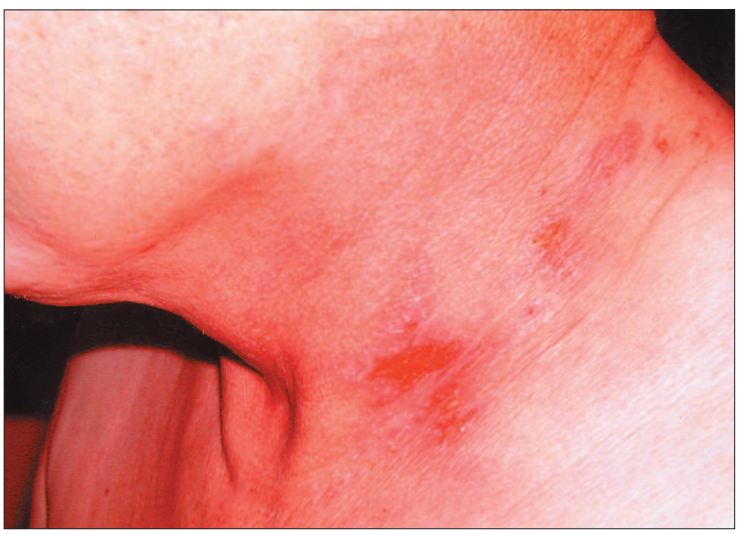


Figure 4. A patient with moist desquamation (grade 3) in the skin of the left side of the neck. Areas of superficial ulceration are seen which tend to weep and can become secondarily infected.



Alopecia

Alopecia occurs because the stem cells in the hair follicles are sensitive to radiotherapy. The pattern is confined within the boundaries of the radiation fields but beam exit sites can also be affected. In treatment of head and neck cancer, alopecia is usually transient but it may be permanent in areas of high dose.

Neurological side effects

Lhermitte's phenomenon is manifest by tingling in the arms and legs, especially when the neck is flexed. It is thought to be caused by transient radiotherapy-induced demyelination and is self-limiting.

LATE SIDE EFFECTS

Osteoradionecrosis

Osteoradionecrosis occurs when bone cells are called upon to divide in response to trauma (e.g. dental extraction) weeks, months or even years after radiotherapy. The cells then express their DNA damage and fail to heal the wound, resulting in bone necrosis. Osteoradionecrosis predominantly affects the mandible and maxilla (being 24 times commoner in the former). The

TABLE 5.
Grading of skin reactions

Grade 0	No reaction
Grade I	Faint erythema
Grade II	Moderate/brisk erythema, dry desquamation
Grade III	Moist desquamation
Grade IV	Skin necrosis, full thickness ulceration

TABLE 6.
Management of acute skin reactions

Avoid irritants	Strong soaps, sunlight
Avoid local trauma	Non-abrasive towels, loose-fitting clothing
Dry desquamation	Keep skin moisturized with aqueous cream
	1% Hydrocortisone cream
Moist desquamation	Proflavine
	Geliperm dressings (Geislich Sons Ltd, Chester, UK)
	Treat secondary infections

pathogenesis is one of hypocellularity, hypoxia and hypovascularity. The incidence is related to the total dose received and the dose per fraction.

Prevention and management of osteoradionecrosis: In order to reduce the risk of osteoradionecrosis, patients are advised to have all preventative and restorative dental work carried out before radiotherapy. Good oral hygiene needs to be maintained during and after completion of radiotherapy. If dental work needs to be carried out, it must be performed by an experienced dental surgeon. Once present, osteoradionecrosis poses a difficult management problem. In most cases, healing will eventually take place with conservative measures (good hygiene, adequate nutrition and prolonged courses of antibiotics), although this can be extremely slow. Debridement of bony sequestra is sometimes required. In these situations, there may be a role for adjuvant hyperbaric oxygen.

Soft tissue fibrosis and necrosis

Fibrosis of soft tissue is common problem after radiotherapy for head and neck cancer. The tissue becomes progressively thicker and woody hard, limiting movement and causing disfigurement. There may be a role for the use of oxypentifylline which has been used to treat fibrosis at other sites. Necrosis manifests as an ulcer that fails to heal. It is sometimes difficult to distinguish clinically from recurrent disease and biopsies may be necessary. The management is conservative, keeping the area clean to prevent secondary infection.

Second malignancy

As well as treating cancer, radiation may cause second malignancies. The most common types of second malignancies are skin cancers and sarcomas. The increased risk is estimated at approximately 1% per decade.

Late radiation-induced neuropathy

The tolerance of peripheral nerves for radiotherapy is higher than for the central nervous system and acute side effects are not commonly seen. Late-onset neuropathies are caused by a combination of demyelination, fibrosis and vascular degeneration.

CONCLUSIONS

Radiotherapy is an important curative treatment for head and neck cancers but comes at the price of significant early and late side effects. Careful management of these side effects improves the tolerability of treatment. Multidisciplinary approaches to treating these side effects gives the best chance of prompt resolution of acute effects and reduction in the risk of late effects. HM

Conflict of interest: none.

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KEY POINTS

- Toxicity to normal tissue governs the dose that can be safely used to treat head and neck cancer.
- Acute side effects have a significant impact on the patient's quality of life.
- Late effects may be debilitating and sometimes life-threatening.
- Attempts to reduce the acute reaction offer the prospect of improving the tolerability of radiotherapy.
- Attempts to limit late reactions may offer the promise of increasing the dose that can be delivered safely and, thus, improving treatment outcome.
- The effective management of side effects of radiotherapy requires a multidisciplinary approach.