Oral and Maxillofacial Side Effects of Radiation Therapy on Children

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SOMMAIRE

La radiothérapie de la tête et du cou entraîne fréquemment des changements sérieux et parfois inévitables aux structures orofaciales, surtout chez les enfants. Les complications graves et chroniques ont un impact considérable sur leur fonction buccale et leur qualité de vie. Cet article présente un aperçu général des effets secondaires de la radiothérapie sur les tissus buccodentaires des enfants, et il souligne les directives de prévention appropriées ainsi que les stratégies de gestion visant à minimiser ces complications.

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Radiation therapy, in conjunction with surgery or chemotherapy, has produced a significant increase in cure rates for many pediatric malignancies of the head and neck. However, this modality of treatment can produce adverse outcomes that manifest during or after the completion of therapy. Of the long-term survivors treated with head and neck radiation therapy, 77% to 100% have mild-to-severe radiation damage of soft tissues and bones.[1,2] The severity of disturbances varies with age, radiation dose and field sizes, and concomitant treatment such as chemotherapy.[1,3] To a large degree, salivary glands, oral mucosa, skin and bones are susceptible to changes that can result in constitutional complications such as dehydration, malnutrition and systemic infections. Implementation of oral care protocols before radiation therapy and frequent assessment of lesions during therapy can prevent or at least decrease the incidence and severity of these complications. In this review, the most common side effects seen in children after radiation therapy of the head and neck are detailed and their prevention or treatment discussed.

Treatment Side Effects

Based on the usual time of their occurrence, radiation-induced changes can be divided into 2 groups: early or acute side effects that are noted during or shortly after treatment, affecting mucosa, taste and salivary glands; and late side effects that develop months or years after the end of radiation therapy, affecting salivary glands, teeth, bone, muscles and skin.

The degree, progression and irreversibility of these changes are related to the radiation dose, the child's age at diagnosis, the irradiation field, the degree of hypovascularity and hypocellularity of tissues, and the healing capacity of the exposed epithelial cells.[4,5]

Mucositis

Mucositis is the most troubling acute side effect experienced by patients undergoing radiation therapy of the head and neck. Mucosal damage occurs because of decreased cell renewal in the epithelium, which causes mucosal atrophy and ulceration.[4] Sonis[6] describes the 4 serial phases of the development of mucositis as inflammatory-vascular, epithelial, ulcerative-

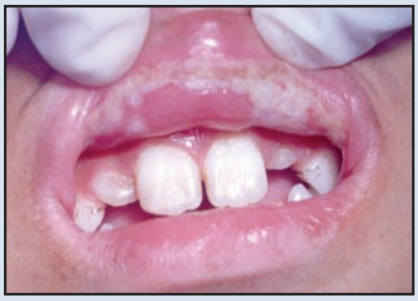

Figure 1: Extensive ulceration of the upper lip in a patient treated for nasopharyngeal carcinoma.

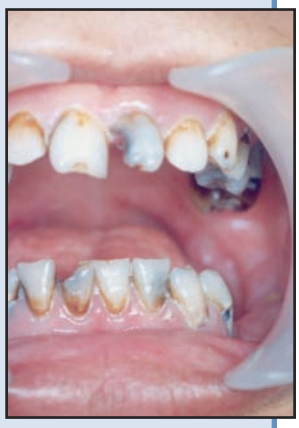

Figure 2: Intraoral view showing postradiation caries in a patient 7 years after she was treated for a nasopharyngeal carcinoma at the age of 11 years.

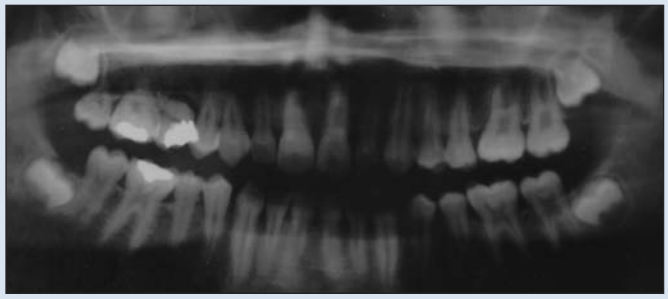

Figure 3: Representative panoramic radiograph showing abnormalities of root morphology, microdontia and arrested development of the second premolar. The patient received orbital radiation (right lateral field 46 Gy) for retinoblastoma of the right eye at the age of 4 years.

bacteriologic and healing. Each phase is interdependent and is the consequence of a series of actions mediated by cytokines, direct effects of therapy on the epithelium, changes in oral bacterial flora and the status of the patient's bone marrow.[6]

Clinically, mucositis presents as erythema, mucosal atrophy and ulceration with or without pseudomembranes (**Fig. 1**). These changes in the oral mucous membrane become evident during the first week after a 2-Gy daily fractioned radiation therapy program, and heal completely 2 to 3 weeks later.[4,7] The reaction to radiation, however, is highly individual: some patients are affected early in the course of their treatment; others are affected very little. The major clinical problem for patients developing oral mucositis is pain. Its adverse consequences include a decreased ability to eat, speak and sleep. A high concentration of the endogenous oral flora may lead to further mucosal damage.[8] The loss of the integrity of the oral mucosa also predisposes patients to systemic infections with bacteria, yeast and viruses.

Current care for patients with mucositis, which is essentially palliative, includes appropriate oral hygiene, dietary modifications and mucosal protectants. Special attention should be given to plaque control and oral hygiene. To maintain oral moistness and decrease pathogenic flora, the use of antiplaque rinses (isotonic saline or sodium bicarbonate solution) and some antimicrobial agents (nystatin, amphotericin B) is recommended. Antimicrobial agents must be considered for either fungal or bacterial infections.[7,9] Analgesic mouth rinses such as 2% viscous lidocaine are used to relieve pain, unless the pain requires systemic analgesic drugs. In clinical practice, additional measures such as other antimicrobials, growth factors, coating agents and cytokine-like agents are frequently used.[7,10] In severe cases, management of mucositis may require placement of a feeding tube, hospitalization and intensive supportive care.

Salivary Gland Dysfunction

Radiation treatment of tumours of the head and neck commonly damages the salivary glands, decreasing the salivary flow rate and changing salivary composition.[11] Several mechanisms cause salivary gland dysfunction after irradiation. Early changes result from damage to the plasma membrane of acinar cells or disturbances in intracellular signalling; late damage may be the result of a lack of proper cell renewal because of damage to the DNA of progenitor cells and stem cells.[12] The extent of radiation-induced salivary dysfunction depends on the dose of radiation, the volume of irradiated gland tissue and the nature of the salivary glands being irradiated.[11] The duration of depressed salivary function varies among patients. Recovery of adequate saliva may be gradual over several months; certain irradiation doses, however, may result in permanent glandular changes that cause irreversible loss of ability to secrete saliva.[11,12] The functional impairment of salivary glands results in impeded oral functioning, a burning sensation, cracked lips, and increased susceptibility to oral infections and dental caries.[8,9] Radiation therapy also changes the composition of saliva, increasing its viscosity, reducing its buffering capacity, altering its concentration of electrolytes, and changing its nonimmune and immune antibacterial systems.[8,9,11]

For relief from discomfort due to salivary dysfunction and associated oral symptoms, several moistening agents and saliva substitutes are recommended. Prophylactic treatment with specific cholinergic receptor agonists (e.g., pilocarpine) temporarily protects salivary-gland cells from acute radiation damage, reducing symptoms of xerostomia and mucosal toxicity.[12,13] Administration of medications that are known to induce xerostomia (e.g., anorectic agents, antiemitics and antihistamines) should be carefully considered.

Dysfunctional Taste and Malnutrition

Alteration in taste is a direct effect of radiation on the fungiform papillae and the taste buds of the tongue. Patients can develop altered taste (dysgeusia), partial loss of taste (hypogeusia) or complete loss of taste (ageusia). These alterations can lead to aversion to food, reduced intake of food and nutritional deficits, ultimately resulting in weight loss and, in severe cases, malnutrition, weakness, cachexia and susceptibility to infection.[8] Early intervention with a nasogastric feeding tube or parenteral nutrition is required to maintain normal growth and development, and to prevent nutritional deficiencies. Zinc supplements accelerate the recovery of taste sensations in these patients.[14]

Dental Disturbances

Changes in the chemical composition of saliva and increased amounts of cariogenic oral bacteria result in rapid decalcification of dental enamel. Aggressive and extensive caries, commonly known as radiation caries (**Fig. 2**), tends to spread to all dental surfaces, changing their translucency and colour. Radiation caries is not caused directly by irradiation, but results from the sequelae of xerostomia and a cariogenic shift in microflora. Ultimately, the carious process causes increased friability and the breakdown of teeth.

Irradiation may also induce disturbances in odontogenesis (**Fig. 3**). Abnormally small teeth (microdontia), short or blunted roots, small crowns, malocclusion, incomplete calcification, enlarged pulp chambers (taurodontism), premature closure of apices and delayed or arrested development of teeth have been reported.[1,2,15] The most severe disturbances in odontogenesis are seen when exposure to irradiation occurs in the preformative and differentiation phases rather than in the mature stages.[8] These changes in the primary teeth can cause significant malocclusion and may adversely affect facial development.

To prevent or at least minimize radiation caries, treatment of xerostomia-related complaints, meticulous oral hygiene, change of diet, control of cariogenic flora and application of topical fluoride are recommended. Intensive home care and antiseptic mouth rinses are helpful for eliminating debris and controlling microbial flora. Topical daily application of 1% neutral sodium fluoride gel with custom-made fluoride carriers reduces postradiation caries.[16] Treatment with prophylactic fluoride is initiated at least 1 week before radiation therapy and continued indefinitely. Dietary instructions about noncariogenic foods should be given.

Changes in Bone

Exposure to high levels of ionizing radiation can markedly affect the bone matrix. Changes in bone result from injury to the remodelling system (osteocytes, osteoblasts and osteoclasts), causing atrophy, osteoradionecrosis and pathological fractures.[8,17] Currently, the pathogenesis of osteoradionecrosis is thought to arise from a fibroatrophic process rather than from vascular alterations;

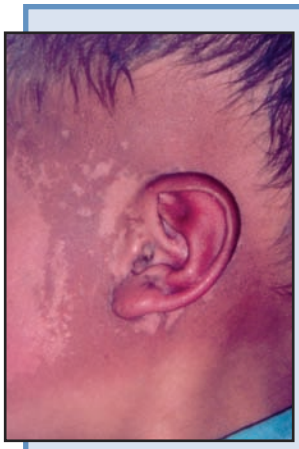

Figure 4: Acute radiation dermatitis after therapy for a primitive neuroectodermal tumour of the parotid gland.

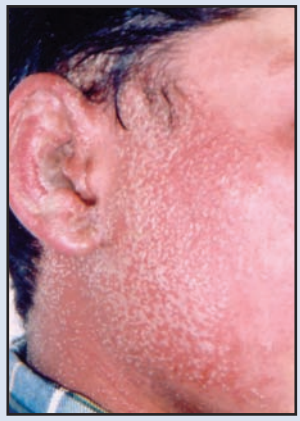

Figure 5: Severe radiation dermatitis with staphylococcal co-infection increasing erythema in a patient treated for nasopharyngeal carcinoma.

vascular dysfunctions help to generate the initial prefibrotic phase.[18] Tooth extraction and dental disease in irradiated regions have long been recognized as major risk factors for the development of osteoradionecrosis.[17] The mandible is much more susceptible to osteoradionecrosis than the maxilla. Nonhealing bone may become secondarily infected.

In addition to histologic changes in bone, children undergoing radiation therapy may experience abnormalities in the growth and maturation of craniofacial skeletal structures.[3,19] These changes are secondary to the effects of radiation on cartilaginous growth centres located in the condyles of the mandible and on the sutural growth centres of the maxilla. Craniofacial and dental abnormalities can cause severe cosmetic or functional sequelae, necessitating surgical or orthodontic intervention.

To minimize the risk of developing osteoradionecrosis, optimal precautions should be adopted. These include complete removal of the nonrestorative teeth as soon as possible to maximize the healing period. When osteoradionecrosis results in small lesions of the bone, daily saline irrigations and antibiotic coverage are recommended. For advanced presentations of osteoradionecrosis (pathologic fracture, fistula, full-thickness devitalization of bone), segmental mandibular resection with free vascularized-bone grafting become the standard of care.[18] If osteoradionecrosis is of fibroblastic origin, treatment with antioxidants and antifibrotic drugs may be promising.[18] Growth hormone supplements can prevent cartilaginous deviations in children treated for intracranial tumours at an early age by stimulating the growth of the condylar cartilage.[19,20]

Cutaneous Changes

Morphologic changes of the skin in the irradiated field usually start halfway through irradiation and persist for

Table 1 Guidelines for the oral management of pediatric patients receiving head and neck radiation therapy

Phase of treatment	Component of care
Before therapy	Detailed clinical history Complete dental examination Radiographic examination Instructions about personal hygiene Treatment of dental infections Application of fluoride
During therapy	Maintenance of good oral hygiene Antimicrobial rinses Mucositis management (e.g., antiseptic rinses, anesthetic, analgesics, coating agents) Xerostomia management (sialagogues, artificial saliva) Management of infectious complications (antibacterial, antifungal, antiviral agents) Management of dysfunctional taste (zinc sulfate supplements) Dietary measures Jaw-opening exercises to reduce trismus
After therapy	Daily use of topical fluorides and scrupulous oral hygiene Early repair of caries Antibiotic coverage for essential extractions Frequent follow-up appointments

some time afterwards (**Fig. 4**). An inflammatory reaction generalized in the skin, followed by desquamation of the epidermis, can lead to either the lesion healing or radionecrosis.[21] Scarring and atrophy of the epidermis increase the rigidity of tissues, making them less supple and less resistant to injury. The role of *Staphylococcus aureus* and its toxins has been overlooked in the pathogenesis of acute radiation dermatitis (**Fig. 5**).[22] **When the masticatory muscles** and the temporomandibular joint are included in the irradiated field, musculoskeletal fibrosis can cause trismus and mandibular dysfunction. **Limited opening of the jaw** interferes with adequate oral hygiene, fluoride application, speech, nutrition and dental treatment.[8]

Because treatment of trismus can be very difficult, preventive management with daily jaw-opening exercises and a prosthetic appliance to increase the range of motion of the mandible helps decrease muscle rigidity. Skin changes in the field of radiation are a temporary reaction and usually heal within a couple weeks of the completion of treatment. Severe cutaneous reactions may require topical and oral antibiotic therapy in conjunction with topical corticosteroids to eradicate infection and repair the skin's barrier function.[22]

Other Side Effects

Other side effects, including damage to nerves, delayed intellectual achievement, hearing loss, psychosocial sequelae and, rarely, radiation-induced malignancy or brain hemorrhage, can occur.[1,2] Although these side effects are rare, they can cause considerable distress.

Conclusion

The overall effect of radiation therapy on oral tissues and craniofacial skeletal growth, a spectrum of minor to major complications, should be considered for all pediatric patients undergoing such treatment. Prevention or reduction of these effects is possible and should be an integral part of treatment for head and neck cancer (**Table 1**). Treatment of potentially existing oral infections and frequent assessment of oral hygiene should be carried out before radiation therapy. In addition, application of fluoride is an important adjunct for preventing caries. Frequent dental follow-up should be scheduled throughout the treatment period to deal with complications and reinforce the importance of continued oral hygiene at home. After radiation therapy, continued surveillance of the oral cavity and early management of late complications are of utmost importance in the long-term care of the irradiated child.

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