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Review Article

Oral management strategies for radiotherapy of head and neck cancer

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SUMMARY

Radiotherapy, often with concomitant chemotherapy, has a significant role in the management of head and neck cancer, however, radiotherapy induces adverse events include oral mucositis, hyposalivation, loss of taste, dental caries, osteoradionecrosis, and trismus, all of which have an impact on patients' quality of life. Therefore, it is necessary to implement oral management strategies prior to the initiation of radiotherapy in patients with head and neck cancer. Since 2014, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) have enumerated the "Principles of Dental Evaluation and Management (DENT-A)" in the section on head and neck cancers, however, oral management was not explained in detail. Oral management has not been achieved a consensus protocol. The aim of this literature is to show that oral management strategy include removal infected teeth before the start of radiotherapy to prevent osteoradionecrosis, oral care for preventing severe oral mucositis to support patient complete radiotherapy during radiotherapy, and prevent of dental caries followed by osteoradionecrosis after radiotherapy.

1. Introduction

Cancers of the head and neck cancer represent 5% of all cancers. In 2018, they accounted for an estimated 887,649 new cancer cases and 453,307 cancer-related deaths worldwide [1]. Head and neck cancer is a broad term that encompasses epithelial malignancies arising from the paranasal sinuses, nasal cavity, oral cavity, pharynx, larynx, and salivary glands. Almost all of these epithelial malignancies are squamous cell carcinomas of the head and neck, for which the most important risk factors are tobacco and alcohol consumption [2]. Although their incidence is rare, salivary gland tumors are head and neck cancers that include various histopathological subtypes.

Radiotherapy ('radiation therapy' or 'irradiation') is defined as 'the use of high-energy radiation from X-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors' [3]. Radiotherapy, often with concomitant chemotherapy, has a significant role in the 'curative' management of head and neck cancer. Primary chemo-radiation allows preservation of organ function, and is the treatment of choice for tumors arising in the oropharynx, nasopharynx, hypopharynx, and larynx [4,5]. In oral cavity cancers, the best cure rates are obtained using surgical techniques with adjuvant or post-operative radiotherapy (with or without chemotherapy) [6]. Radiotherapy also plays an important role in the palliation of symptoms in patients with advanced/incurable head and neck cancer, offering shrinkage of tumors, prevention of ulceration, prevention of bleeding, and pain control [7,8].

Radiotherapy to the head and neck region may cause undesirable radiotherapy-induced changes in the surrounding tissues [9]. Radiotherapy-induced adverse events include oral mucositis, hyposalivation, loss of taste, dental caries, osteoradionecrosis, and trismus, all of which have an impact on patients' quality of life. Therefore, it is necessary to implement oral management strategies prior to the initiation of radiotherapy in patients with head and neck cancer. Since 2014, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) have enumerated the "Principles of Dental Evaluation and Management (DENT-A) [10]" in the section on head and cancers. Kawashita et al. have also demonstrated the benefits of the use of the prophylactic bundle in oral management prior to initiation of radiotherapy [11]. In this review, we discuss the oral management strategies that are in use for head and neck cancer, both, prior to the initiation of radiotherapy and following treatment.

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2. Oral management strategies for head and neck cancer radiotherapy

2.1. Prior to radiotherapy

2.1.1. Tooth extraction before the start of radiotherapy to prevent osteoradionecrosis

Osteoradionecrosis (ORN) of the jaw is defined as a non-healing exposure of the bone with necrosis, which starts with a breach in the oral mucosa and persists for at least 3 months in a patient who has undergone previous radiotherapy. The necrosis, however, must be evidently different from a recurrent, vestigial, or metastatic tumor [12–14]. Prior to the well-known alterations of the "three–H concept" (hypoxia, hypocellularity, hypovascularity), that become apparent in the vascular system [15], radiogenic effects initially appear in osteoclasts [16,17]; reports suggest that microorganisms do not play any causative role in ORN, but have a contaminant role instead. The bone shows significant fibrosis with a loss of remodeling elements.

The aim of oral management before the start of radiotherapy is to prevent ORN. Although the incidence of ORN is low, it rarely cures spontaneously once it occurs; in patients with advanced lesions, surgical resection of the jaw becomes necessary [18]. Therefore, dental evaluation of the source of infection and the need for dental extractions need to be determined [10]. If necessary, extractions should be completed at least 2 weeks prior to the start of radiotherapy.

As the source of infection in the jaw, pre-radiotherapy periapical foci were reported to be an independent risk factor for the development of ORN [19]. Since most cases of ORN occur in the molar region of the lower jaw, the mandibular molar, with the periapical focus, may need to be extracted. Furthermore, tooth extraction after radiotherapy has also been found to significantly correlate with the development of ORN. Therefore, teeth that cannot be preserved for a long time should be extracted before the start of radiotherapy. Periodontal diseases are required extraction before radiotherapy to avoid future dental extraction and to reduce the development of ORN [20,21]. The German Society of Dental, and Oral and Craniomandibular Sciences show criteria for tooth removal before radiotherapy are periodontal probing depth equal or greater than 5 mm and furcation involvement. Another important risk factor for the development of osteonecrosis is the radiation dose to the bone, particularly to the less vascular mandible [22,23]. A radiation dose of 50 Gy or higher to the mandible significantly increased the risk of ORN [24,25].

2.1.2. Preparation of spacers to prevent serious oral mucositis

Radiotherapy for head and neck cancer is broadly classified into two types, namely, external irradiation and brachytherapy. External irradiation is most commonly employed. It generally involves the use of linear accelerators that direct X-ray and/or electron beams from outside the body into the tumor. Any existing dental metals produce an electronic backscatter, which may damage the surrounding soft tissue [26]. Backscatter effects on the surface of dental materials cause an increase of up to 170% of the radiation dose, measured without materials. It has also been reported that the extent of the backscatter effect reaches maximal levels within a distance of 4 mm. Therefore, in some cases, a spacer retainer, also known as a spacer, is placed as appropriate. The thickness of the spacers are typically 3 mm, reaching up to 5 mm for cases with metal restorations [11].

Recently, high-precision radiotherapy, such as intensity modulated radiotherapy (IMRT) is being widely used owing to the superior efficacy of IMRT in avoiding side effects compared with three-dimensional conformal radiotherapy (3D-CRT). IMRT has the advantage of allowing more precise dose delivery to the tumor site, while simultaneously reducing the exposure of normal tissues to radiation. Therefore, more accurate and reproducible patient fixation is considerably more important in IMRT than in 3D-CRT.

In radiotherapy treatment plans, the target volumes to be irradiated are clearly defined as the gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV). The GTV is the tumor volume, which is generally delineated by diagnostic images, inspection, and/or palpation of both the primary and metastatic lesions. The CTV is the tissue volume that encompasses the GTV and any regions of subclinical disease, including lymph node areas designated for prophylactic irradiation. In radiotherapy for head and neck cancers, usually a 5- to 10-mm (or greater) margin is added around the GTVs. In view of internal organ motion and variations in daily setup (set-up margin), the PTV is expanded between 5 and 10 mm around the CTVs. In high-precision radiotherapy such as IMRT, it is important to decrease the PTV margin accounting for organ movement and set-up errors. Therefore, ready-made patient immobilization spacers are employed in head and neck IMRT to decrease rotation, flexion, and extension of the head.

2.2. During radiotherapy

Acute adverse events associated with radiotherapy include oral mucositis, xerostomia, and loss of taste. Radiation-induced oral mucositis is considerably unpleasant and is more pronounced in patients undergoing chemoradiotherapy. In extreme cases, lesions are characterized by large and painful ulcers that have a significant impact on the patient's quality of life, and may considerably restrict activities such as eating, speaking, and even swallowing saliva [27]. Oral mucositis involves breaks in the tight junction between cells, which allows the development of bacterial infections [28,29]. The aim of oral management during radiotherapy is to prevent severe oral mucositis and related secondary infections; it also intends to control pain and support ingestion.

Oral mucositis management should involve a defined preventive oral care regimen that includes aggressive implementation of oral hygiene procedures including brushing, flossing, and the use of bland rinses. Although these methods do not prevent mucositis or impact the severity of the lesions per se, they provide essential support to the oral cavity and may indirectly improve treatment compliance by decreasing the risks of infection [30].

2.2.1. Use of pilocarpine hydrochloride

Salivary gland dysfunction is a predictable side effect of radiotherapy to the head and neck region [31]. Salivary glands are sensitive to radiation, and even low doses result in a rapid decline in function [32,33]. This develops soon after the initiation of radiotherapy, progresses during treatment (and for some time after treatment), and it essentially permanent in cases where cumulative doses exceed 30 Gy [32]. Patients develop xerostomia (subjective symptoms of dryness) and hyposalivation (objective reduction in salivary flow). Hyposalivation may further aggravate inflamed tissues, increase the risk of local infection, and make mastication difficult. Many patients complain about the thickening of salivary secretions owing to a decrease in the serous component of saliva. In healthy people, the average salivary flow rate is approximately 1.0 ml/min. This rate dramatically declines to well below 0.5 ml/min within 1–2 weeks of initiating radiotherapy [33].

Pilocarpine is a parasympathomimetic agent that functions primarily as a muscarinic agonist, causing pharmacological stimulation of exocrine glands in humans; this results in salivation [34]. As per the Cochrane Collaboration, pilocarpine hydrochloride is more effective than placebo and is at least as effective as artificial saliva [35]; the response rate ranges from 42% to 51% with a time to response of up to 12 weeks. The overall side effect

rate has been found to be high, with side effects being the main reason for withdrawal in study patients (6%–15% of participants taking 5 mg thrice a day had to withdraw). The side effects usually result from generalized parasympathomimetic stimulation and include sweating, headaches, urinary frequency, and vasodilatation. Dose dependence has not been noted in response rates, but in the rates of side effects. Study patients with side effects have been administered a dose of 2.5 mg 4 times daily [36]. Pilocarpine is contraindicated in patients with obstructive pulmonary disease, severe ischemic heart disease, stricture of the gastrointestinal tract or the bladder neck, Parkinson's disease, and iritis.

2.2.2. Oral care

Patients usually receive professional oral care by a dental hygienist at least once a week until completion of radiotherapy [11]. Modalities for oral care typically include the removal of dental plaque using professional mechanical tooth-cleaning methods and the gentle removal of mucosal debris using a wet sponge to keep the oral cavity as clean as possible.

For palliation of a dry mouth, it is advisable to sip water as needed to alleviate mouth dryness [37]. Several supportive products including artificial saliva are also available. In addition, it is also advisable to rinse the mouth with a solution made from ½ a teaspoon of baking soda (and/or ¼ or ½ a teaspoon of table salt) in 1 cup of warm water several times a day to clean and lubricate the oral tissues and to buffer the oral environment.

Chlorhexidine and povidone-iodine are 2 of the most commonly used antiseptic agents in this setting [38]. Chlorhexidine and povidone-iodine have different mechanisms of action and different spectrums of efficacy. Chlorhexidine damages the outer layers of the microbial cell membrane, upsetting resting membrane potentials, whereas povidone-iodine uncouples iodine, which is absorbed by microbes, resulting in the inactivation of key cytoplasmic pathways [39]. Povidone-iodine is useful for the prevention of oral infections. However, the MASCC/ISOO (Multinational Association of Supportive Care in Cancer in Cancer and International Society of Oral Oncology) Clinical Practice Guidelines for oral mucositis suggest that chlorhexidine mouthwashes should not be used to prevent oral mucositis in patients receiving radiation therapy for head and neck cancer [40].

Oral viscous lidocaine is useful for the treatment of symptoms related to inflamed oral mucosa, including radiation- or chemotherapy-induced mucositis [41]. Since the patient is instructed to spit out the solution after each use, the number of daily treatments with viscous lidocaine mouthwash are not restricted. However, particular attention must be paid to aspiration and to any biting of the buccal mucosa or tongue.

2.3. Pathogenesis of oral mucositis

Radiotherapy for head and neck cancer almost always induces oral mucositis. The pathophysiologic progression that results in mucositis may be described in 5 phases: initiation, upregulation and message generation, signaling and amplification, ulceration, and healing [37,42].

2.3.1. Initiation of tissue injury

Radiation and/or chemotherapy induce cellular damage, which results in the death of the basal epithelial cells. The generation of reactive oxygen species (free radicals) by radiation or chemotherapy is also believed to exert a role in the initiation of mucosal injury. These small highly reactive molecules are byproducts of oxygen metabolism and may cause significant cellular damage.

2.3.2. Upregulation of inflammation via generation of messenger signals

In addition to causing direct cell death, free radicals activate second messengers that transmit signals from receptors on the cellular surface to the inside of the cell. This leads to upregulation of pro-inflammatory cytokines, tissue injury and cell death.

2.3.3. Signaling and amplification

Upregulation of proinflammatory cytokines such as tumor necrosis factor- alpha (TNF-α), produced mainly by macrophages, causes injury to mucosal cells, and also activates molecular pathways that amplify mucosal injury

2.3.4. Ulceration and inflammation

Mucosal ulcerations are associated with a significant inflammatory cell infiltrate, partly related to the metabolic byproducts of the colonizing oral microflora. The secondary infection also further upregulates the production of pro-inflammatory cytokines.

2.3.5. Healing

The healing phase is characterized by epithelial proliferation and cellular and tissue differentiation, restoring the integrity of the epithelium.

2.4. Clinical course of oral mucositis

The lesions of radiation-induced oral mucositis are limited to tissues within the field of radiation, with the involvement of non-keratinized tissue being more common. The initial clinical signs of oral mucositis include mucosal erythema and superficial sloughing, which may occur with cumulative radiation doses of 20−30 Gy, at which, the intact mucosa begins to break down; this is followed by ulceration [43]. The ulcerations are typically covered by a white fibrinous pseudomembrane. The clinical severity is directly proportional to the dose of radiation administered. Most patients who receive more than 50 Gy to the oral mucosa develop severe ulcerative oral mucositis [44]. The lesions typically heal within approximately 2–4 weeks after the last fraction of radiotherapy.

2.5. Evaluation of oral mucositis

A wide variety of scales have been used in clinical practice and research to record the extent and severity of oral mucositis (Table 1) [45,46]. The World Health Organization (WHO) Oral Toxicity Scale and the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) system are two most commonly used scales (Table 1). The WHO Oral Toxicity Scale is a simple and easy-to-use tool that is suitable for wide implementation in both, research and clinical practice settings. To assign a grade, this scale combines objective mucosal changes (such as erythema and ulceration) with functional outcomes (such as the ability to eat) [47]. The NCI-CTCAE, a longstanding empirically developed system, has similar impact and applicability as the dedicated WHO Oral Toxicity Scale. In terms of the specific criteria for grading radiotherapy-related oral mucositis in head and neck cancer, differences have been observed in terms of subjective variables such as pain, dysphagia, and eating behavior in version 4.0; version 3.0 (clinical exam) mainly assessed oral mucositis based on objective signs including erythema, ulceration, and bleeding [48]. The NCI-CTCAE v5.0 is currently available [49].

2.6. Prevention and treatment of oral mucositis

A systematic review has showed that non-opioid interventions, including topical mouthwashes: doxepin, amitriptyline, diclofenac,

Table 1
Definition of oral mucositis by grading scales.

Grading Scale	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
World Health Organisation (WHO)	Soreness, erythema	Ulcers but able to eat solid foods	Oral ulcers and able to take liquids only	Oral alimentation impossible	–
NCI-CTCAE v3.0 (clinical exam)	Erythema of the mucosa	Patcy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequenced	Death
NCI-CTCAE v3.0 (functional/symptomatic)	Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function	Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL	Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL	Symptoms associated with life-threatening consequence	Death
NCI-CTCAE v4.0	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicate	Sever pain; interfering with oral intake	Life-threatening consequences; urgent intervention idicated	Death
NCI-CTCAE v5.0	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicate	Sever pain; interfering with oral intake	Life-threatening consequences; urgent intervention idicated	Death

and benzydamine, provided relief of pain due to radiotherapy-induced oral mucositis with or without chemotherapy for head and neck cancer [50]. However, these topical mouthwashes are not readily available in Japan. Low-level laser therapy has been suggested for the prevention of oral mucositis in patients undergoing radiotherapy without concomitant chemotherapy. However, the impact of low-level laser therapy on tumor behavior and response to treatment remains unclear [51]. Orally administered systemic zinc supplements may offer benefit in the prevention of oral mucositis in patients receiving radiation therapy or chemoradiation for oral cancer. Currently, there is no consensus-based protocol for the prophylaxis and treatment of chemoradiotherapy-induced oral mucositis in patients with head and neck cancer [52–55].

Oral mucositis should be treated with anti-inflammatory drugs. Rugo et al. showed dexamethasone mouthwash reduced the incidence and severity of oral mucositis in patients receiving chemotherapy for breast cancer [56]. Radiotherapy-induced oral mucositis is more severe than chemotherapy-induced oral mucositis. Therefore, radiotherapy-induced oral mucositis might be treated with steroid ointment which can adhere to oral membranes allowing for longer contact. Steroid ointment therapy for radiotherapy-induced oral mucositis has been used in Japan since the 1980s. Dexamethasone, triamcinolone acetonide, and beclomethasone dipropionate ointments were suggested to be useful for radiotherapy-induced oral mucositis. A multicenter phase II randomized controlled trial showed that a combination of adequate oral hydration, optimal oral cleanliness and hygiene, and topical dexamethasone therapy was effective for preventing severe oral mucositis caused by radiotherapy alone but not chemoradiotherapy [57]. Steroid ointments of medium potency (dexamethasone) may not prevent severe oral mucositis caused by chemoradiotherapy for head and neck cancer. However, strong or very strong topical steroid therapy may prevent severe oral mucositis.

2.7. *Oral fungal infections*

The risk for oral infections increases during and after therapy for oropharyngeal cancer because the oral microbial flora is altered by myelosuppression, and the oral cleansing property of saliva is diminished owing to the reduced salivary flow [58].

Candida is a normal oral commensal in healthy individuals, and hence candidiasis is one of the most frequent oral infections during therapy for oropharyngeal cancer [59]. Oral candidiasis usually presents as a removable white pseudomembrane or erythematous patch on the tongue, palate, and labial commissures. It causes alterations in taste, mucosal soreness, and an oral burning sensation [58]. The diagnosis of oral candidiasis is largely based on clinical features. However, occasionally, confirmatory laboratory investigations are required. Topical antifungal therapy is very effective in controlling oral candidiasis [60]

3. After radiotherapy

The goals of post-treatment dental management include the prevention and treatment of dental caries, and the prevention of post-radiation osteonecrosis [10]. Radiotherapy to the head and neck induces xerostomia and hyposalivation. This induces the development of severe dental caries and the introduction of infections in the jaw. The status of oral health after radiotherapy has been found to be a significant risk factor for the development of ORN. Radiation-related dental caries prevention programs are therefore crucial in the control of ORN [19,61,62].

Resistance to dental caries may be enhanced by the application of topical fluorides [63,64]; fluoride toothpaste has been demonstrated to provide significant benefit in preventing and remineralising root caries in patients undergoing radiation for head and neck cancer [65]. The efficacy of fluoride in these patients may be limited by the lack of calcium and phosphate secondary to hyposalivation [66]. Remineralization cannot occur if the saliva lacks sufficient levels of calcium and phosphate relative to tooth minerals. Exogenous calcium and phosphate may hypothetically improve dental outcomes by allowing remineralization of dental surfaces. It has been observed that after radiotherapy-induced hyposalivation, the colony counts of microorganisms in the oral microflora demonstrate a shift with an increase in cariogenic bacteria including *Streptococcus mutans* and *Lactobacillus* species [67,68]. Therefore, reductions in the rates of dental caries should involve the reduction of colony counts of cariogenic bacteria. Chlorhexidine suspensions have been shown to reduce colonization by cariogenic flora in patients undergoing radiotherapy to the head and neck. Unfortunately, the effects are not sustained and cariogenic bacterial counts have been noted to rapidly recover. This suggests the need for ongoing therapy to control the oral flora and reduce the risks of caries [69]. The use of topical fluorides and chlorhexidine mouth rinses may have an impact on the prevention of dental caries [58].

In conclusion, it is essential that the dental care provider motivates patients to adopt stringent plaque control. In addition, medications should be prescribed to stimulate salivary flow, and nutritional counseling should be offered to limit cariogenic diets. These measures are essential in the reduction of radiotherapy-induced dental caries, and will serve to improve the quality of life in head and neck cancer survivors [58].

Conflict of interest

The authors declare that they have no competing interests.

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