Prevention and Treatment of the Consequences of Head and Neck Radiotherapy

A. Vissink[1]*
F.R. Burlage[2]
F.K.L. Spijkervet[1]
J. Jansma[1]
R.P. Coppes[2,3]

[1]Department of Oral and Maxillofacial Surgery and [2]Department of Radiotherapy, University Hospital, PO Box 30.001, 9700 RB Groningen, the Netherlands; and [3]Department of Radiation and Stress Cell Biology, University of Groningen, Ant. Deusinglaan 1, 9713 AV Groningen, the Netherlands; *corresponding author, A.Vissink@kchir.azg.nl

ABSTRACT: The location of the primary tumor or lymph node metastases dictates the inclusion of the oral cavity, salivary glands, and jaws in the radiation treatment portals for patients who have head and neck cancer. The clinical sequelae of the radiation treatment include mucositis, hyposalivation, loss of taste, osteoradionecrosis, radiation caries, and trismus. These sequelae may be dose-limiting and have a tremendous effect on the patient's quality of life. Most treatment protocols to prevent these sequelae are still based on clinical experience, but alternatives based on fundamental basic and clinical research are becoming more and more available. Many of these alternatives either need further study before they can be incorporated into the protocols commonly used to prevent and treat the radiation-related oral sequelae or await implementation of these protocols. In this review, the various possibilities for prevention and/or treatment of radiation-induced changes in healthy oral tissues and their consequences are discussed.

Key words. Radiotherapy, mucositis, xerostomia, caries, osteoradionecrosis, prevention, treatment.

Introduction

Radiation therapy plays an important role in the treatment of patients with head and neck cancer. Depending on the location of the malignancy (primary tumor, lymph node metastases), inevitably, the salivary glands, oral mucosa, and jaws have to be included in the radiation treatment portals. As a result, changes induced by exposure to radiation occur in these tissues. The resulting oral sequelae may cause substantial problems during and after radiation therapy and are major factors in determining the patient's quality of life (Vissink *et al.*, 2003). Acute exacerbation of focal infection, *e.g.*, periapical and periodontal infection, and severe mucositis occasionally may necessitate an adjustment or an interruption of the radiation treatment schedule. For all of these reasons, oral complications should be prevented or reduced to a minimum (Consensus statement, 1990; Jansma *et al.*, 1992; Epstein and Stevenson-Moore, 2001). Most preventive procedures described in the literature are based on clinical experience, since there is a rather small number of sound clinical trials reported in the literature, and there is a great diversity in supportive care treatment policies and preventive approach policies in daily practice (Jansma *et al.*, 1992; Scully and Epstein, 1996; Epstein and Stevenson-Moore, 2001; Schiødt and Hermund, 2002). In this review, the various possibilities to prevent or treat the radiation-induced changes in healthy oral tissues and their consequences are discussed.

Mucositis

Radiation mucositis is considered to be an inevitable but transient side-effect of therapeutic head and neck irradiation (Scully and Epstein, 1996; Karthaus *et al.*, 1999; Plevovà, 1999; Sonis *et al.*, 1999). Its occurrence and severity are strongly related to dose, fraction size, radiation portals, fractionation, and type of ionizing irradiation (Denham *et al.*, 1999). The use of various radiation treatment modalities and schedules of fractionation can play an important role in the prevention of mucositis. The use of high-energy photonbeams, with linear accelerators, provides a more homogenous dose distribution in and outside the target area compared with the orthovoltage technique. This is due to the higher penetration of high-energy beams. Consequently, the number of hot spots in the normal tissues is reduced. This has resulted in some decrease in the incidence and severity of mucositis. More recently, it has been claimed that new irradiation techniques like hyperfractionation and accelerated treatment improve local control in head and neck cancer (Horiot *et al.*, 1994; Russell, 2000; Vissink *et al.*, 2003). Trials, however, have shown that the median time to onset of pseudomembranous mucositis was more rapid for patients treated on, *e.g.*, an accelerated schedule, *viz.* 21 days for an accelerated schedule *vs.* 33.5 days for those treated with conventional fractionation (Denham *et al.*, 1999). Some clinicians even apply a split-course accelerated schedule to keep mucositis within a tolerable range (Maciejewski *et al.*, 1991). The

increase in early toxicity caused by these new techniques remains a matter of clinical concern. Thus, effective control of mucositis has gained importance with implementation of these new radiation schedules. Currently, chemoradiotherapy is also applied more frequently for advanced head and neck cancer and in organ-sparing strategies (Bensadoun *et al.*, 2001); consequently, the significance of effective mucositis prevention and treatment will further increase, since chemotherapy may induce an exacerbated local tissue reaction.

The Consensus Development Panel of the National Institutes of Health (Consensus statement, 1990) stated that no drugs can prevent mucositis, an opinion that still holds true to date (Scully and Epstein, 1996; Zimmermann *et al.*, 1998; Karthaus *et al.*, 1999; Plevovà,1999; Sonis *et al.*, 1999; Sutherland and Browman, 2001). Consequently, prevention of mucositis is still limited to reduction of its severity by oral care programs, relief of pain and discomfort, and/or strategies to eliminate micro-organisms that are thought to be involved in the development or promotion of radiation mucositis.

Currently, most oral care programs aim at: removal of mucosal-irritating factors, cleansing of the oral mucosa, maintaining the moisture of the lips and the oral cavity, relief of mucosal pain and inflammation, and prevention or treatment of infection (Miaskowski, 1990; Scully and Epstein, 1996; Zimmermann *et al.*, 1998). Although it has been suggested that good oral hygiene may reduce the development and severity of mucositis, no controlled studies of large numbers of patients have yet been undertaken. This is also the case for the other recommendations mentioned in this paragraph, which are all predominantly based on clinical experience rather than on controlled studies. Nevertheless, these recommendations still are a part of most protocols aimed to reduce the oral sequelae of head and neck radiotherapy. To prevent iatrogenic mucosal damage, irritating factors such as sharp or rough fillings should be smoothened or polished prior to radiotherapy, and prosthetic appliances should be closely evaluated (Engelmeier and King, 1983). Plaque control and oral hygiene should be maintained (Borowski *et al.*, 1994; Scully and Epstein, 1996). Some authors recommend discouraging the wearing of dentures during radiotherapy (Curtis *et al.*, 1976; Beumer and Brady, 1978). Since denture surfaces may be colonized with *Candida* species, others recommend special attention to denture hygiene and removal of the appliance, at least at night (Lockhart, 1986; Epstein, 1990). In keeping with the aim of eliminating irritating factors, the use of tobacco, alcohol, and spicy and acidic foods should also be discouraged (Scully and Epstein, 1996).

For relief of pain and discomfort due to mucositis, several anaesthetics, analgesics, and mucosal-coating agents have been recommended (Scully and Epstein, 1996). In their meta-analysis of randomized controlled trials on the prophylaxis of radiation mucositis, Sutherland and Browman (2001) rated these agents as indirect (*e.g.*, benzydamine) or direct (*e.g.*, sucralfate) cytoprotectants. It has to be stressed, however, that these agents exert no therapeutic effect. Periodic rinses with topical anaesthetics such as viscous xylocaine (lidocaine) and benzydamine have been proposed (Dreizen *et al.*, 1977b; Lockhart, 1986; Scully and Epstein, 1996; Meredith *et al.*, 1997). For relief of pain and resolution of mucositis, encouraging results have also been reported with the use of sucralfate suspensions, which are believed to form a barrier on the oral mucosa (Makkonen *et al.*, 1994; Franzén *et al.*, 1995). However, this finding could not be reproduced (Meredith *et al.*, 1997; Lievens *et al.*, 1998), and therefore its clinical value is still questionable (Sutherland and Browman, 2001). (In)direct cytoprotectants, antibacterials have been used to prevent or reduce radiation mucositis (Sutherland and Browman, 2001). The potential beneficial effects of aqueous chlorhexidine rinses to control chemotherapy-associated oral mucositis have been reported (Scully and Epstein, 1996), but they are unable to control radiation mucositis (Spijkervet *et al.*, 1989b; Epstein *et al.*, 1992; Foote *et al.*, 1994; Scully and Epstein, 1996; Adamietz *et al.*, 1998). However, they still have value in plaque control in these patients.

Because of the high carriage rate of Gram-negative bacilli found in many high-dose radiotherapy patients (Rice and Gill, 1979; Spijkervet *et al.*, 1989a; Martin and van Saene, 1992; Martin, 1993), it has been postulated that selective elimination of these oral Gram-negative bacilli has a prophylactic or ameliorating effect on the development of radiation mucositis (Spijkervet *et al.*, 1990). Several authors have studied the radiation-mucositis-reducing effect of polymyxin E/tobramycin/amphotericin B (PTA)-containing lozenges, pastilles, or paste (Spijkervet *et al.*, 1990, 1991; Symonds *et al.*, 1996; Okuno *et al.*, 1997; Wijers *et al.*, 2001; El-Sayed *et al.*, 2002). The results have been very encouraging, in that eradication of Gram-negative bacilli (selective elimination of oral flora) was associated with at least some reduction of mucositis. This was also the conclusion of the Sutherland and Browman (2001) meta-analysis, which showed that only narrow-spectrum antibiotic lozenges have some benefit in the prophylaxis of radiation mucositis.

There is also a significant amount of preliminary research indicating that the administration of growth factors (granulocyte-macrophage colony-stimulating factor, keratinocyte growth factor) has a potential to reduce the development of radiation mucositis and can significantly promote healing (Nicolatou *et al.*, 1998; Farrell *et al.*, 1999; Mascarin *et al.*, 1999; Wagner *et al.*, 1999; Makkonen *et al.*, 2000). The reduction of mucositis and promotion of healing by growth factors are most likely due to the stimulation of surviving stem cells (Dörr *et al.*, 2001), but this needs further study, because these therapies may affect tumor response. This consideration is also applicable to the administration of the radioprotective agent amifostine during radiation treatment (Antonadou *et al.*, 2002; Buntzel *et al.*, 2002). A major flaw of most of the preliminary growth factor and radioprotector studies is that their trial design is at least questionable and the outcomes subject to debate (Sutherland and Browman, 2001). Nevertheless, the results of these preliminary studies are promising and may finally lead to modification of current oral care programs that are of limited efficacy in preventing and treating radiation mucositis. Clearly, high-quality randomized, placebo-controlled clinical trials are needed.

In summary, although there are major similarities in the etiopathogenesis of radiation mucositis and mucosal toxicity resulting from chemotherapy, radiation mucositis is more difficult to prevent and/or treat. Various agents have been shown to be potentially effective in the prevention and/or treatment of mucositis induced by chemotherapy, but not radiation mucositis (Worthington *et al.*, 2002). Only the administration of antibiotic lozenges has been shown to be of some use in the reduction of the severity of radiation mucositis. Results with the administration of growth factors and radical scavengers are promising and need further study, focused not only on the prevention of mucositis but also on the potential effects of these therapies on tumor response.

Taste Loss

Alteration of taste sensation occurs as a result of the direct effect of radiation on the taste buds and due to changes in the saliva (Mossman, 1986; Spielman, 1998). In most instances, taste gradually returns to normal or near-normal levels within one year after radiotherapy (Tomita and Osaki, 1990). Because of this transitory aspect, there is usually no need for treatment.

Prevention of taste loss can best be accomplished through direct shielding of healthy tissue or placement of these tissues outside the radiation field by means of shielding or repositioning prostheses. Recently, a cytoprotection against the loss of taste was reported by the administration of amifostine during a course of radiochemotherapy (Buntzel *et al.*, 2002). However, the design of the latter is questionable, because a wide variety of treatment protocols was used. Since taste loss can result in weight loss, the importance of dietary counseling should be stressed (Lees, 1999; Erkurt *et al.*, 2000). Food with pleasing taste, color, and smell and substitution of food aromas for the sense of taste may improve food intake. Dietary counseling is also of great help in adapting to the taste of food, since in many patients the perception of the various flavors does not change to the same extent. Consequently, food that was enjoyed by the patient before radiation treatment can often have a less pleasant taste after treatment (Vissink *et al.*, 2003). Thus, a basic meal plan including the addition of supplementary feedings should be started at the beginning of therapy and followed, with modifications, during at least the total period of treatment. As the taste perception, mostly gradually although not completely, returns to normal, dietary counseling often has to be continued until the complaints subside or the patient has adapted to the new situation. Attention also has to be paid to the level of hyposalivation, since insufficient moistening and lubrication of the oral tissues and food have a major negative impact on food intake and the ability of a patient to eat (Epstein *et al.*, 1999a).

Some patients may be left with residual hypogeusia after radiotherapy. Zinc supplements are reported to be helpful in increasing taste acuity in such patients (Ripamonti *et al.*, 1998; Matsuo, 2000). It is probably of more benefit in the acceleration of taste improvement in the post-radiotherapy period than in the preservation of taste during radiotherapy.

Hyposalivation

The most effective intervention for reduced salivary gland function is its prevention (Cooper *et al.*, 1995), because once chronic hyposalivation occurs, treatment essentially relies upon stimulation of the residual secretory capacity of the salivary glands (Johnson *et al.*, 1993; LeVeque *et al.*, 1993; Blom *et al.*, 1996; Johnstone *et al.*, 2001), the use of saliva replacements if the result of stimulation of the residual salivary flow is insufficient (Vissink *et al.*, 1987; Sreebny *et al.*, 1995; Van der Reijden *et al.*, 1996; Epstein *et al.*, 1999b; Momm *et al.*, 2001), or possibly, in future, by gene transfer to repair hypofunctional gland parenchyma or to produce secretory transgene products (Delporte *et al.*, 1997; Baum and O'Connell, 1999; Atkinson and Baum, 2001; Vitolo and Baum, 2002). Surgical transposition of the submandibular salivary glands outside the treatment portals has also been described as a successful method for the prevention of hyposalivation (Jha *et al.*, 2000), but its indications are limited.

At present, prevention of radiation damage to salivary glands is best accomplished by meticulous treatment planning and beam arrangement designed to spare as much of the parotid and submandibular glands as possible (Hazuka *et al.*, 1993; Cooper *et al.*, 1995; Jones *et al.*, 1996; Nishioka *et al.*, 1997; Wu *et al.*, 2000; Eisbruch *et al.*, 1999, 2001; Henson *et al.*, 2001; Roesink *et al.*, 2001). Changing a conventional schedule of fractionated radiotherapy into a schedule of continuous, hyperfractionated, accelerated radiotherapy (CHART) results in some sparing of salivary gland function (Leslie and Dishe, 1991, 1994), but the effect is insufficient to be of clinical significance. A better option might be to attempt to spare one of the parotid glands by three-dimensional treatment planning and conformal dose-delivery techniques. This has been shown not only to reduce the radiation-induced impairment of salivary gland function, but also, concomitantly, to improve the xerostomia-related quality of life when compared with conventional radiotherapy (Henson *et al.*, 2001).

Second to meticulous treatment planning and beam arrangement, the greatest potential to prevent salivary glands from post-radiotherapy functional loss comes from sialogogue studies (Greenspan and Daniels, 1987; Joensuu *et al.*, 1993; Johnson *et al.*, 1993; LeVeque *et al.*, 1993; Epstein *et al.*, 1994; Rieke *et al.*, 1995; Niedermeier *et al.*, 1998; Horiot *et al.*, 2000). Of the sialogogues, pilocarpine has been most extensively studied. Administration of pilocarpine or pure cholinergic sialogogues to stimulate any residual function of the salivary gland post-radiotherapy is worthwhile to a limited extent, because the functional gain ceases as soon as the administration of the sialogogue is stopped. That means that the patients have to use these sialogogues, with all their side-effects, for the rest of their lives. Probably, a significant part of the beneficial effect of pilocarpine on post-irradiation xerostomia can be attributed to stimulation of the minor salivary glands, since the minor palatal glands have been shown to have a greater resistance to and ability to recover from irradiation than serous parotid glands (Niedermeier *et al.*, 1998).

A more persistent effect of pilocarpine can be observed when its administration is started before radiotherapy, continued during radiotherapy, and then stopped three months post-radiotherapy (Valdez *et al.*, 1993; Zimmerman *et al.*, 1997). In such a case, the observed sparing effect on salivary gland function lasted for a much longer period of time, but the sparing effect was observed in only those patients in whom at least a part of the salivary glands was not included in the treatment portals. Other studies could not repeat the potential protective effect of pilocarpine on post-radiation xerostomia (Lajtman *et al.*, 2000; Mateos *et al.*, 2001; Sangthawan *et al.*, 2001), but this may be due to the large doses given and volumes irradiated. Valdez *et al.* (1993) and Lajtman *et al.* (2000) posed that the 'protective effect' may be due to stimulation of salivary gland tissue outside the radiation portal. Rat studies, however, showed that pilocarpine has a protective effect on the irradiated tissue as well (Coppes *et al.*, 1997a,b, 2001; Roesink *et al.*, 1999) without influencing tumor response to treatment (Licht *et al.*, 2002). Analysis of all of these data suggests that the administration of pilocarpine, as a prophylactic agent, is effective only when the radiation delivered to the salivary glands is limited in both dose and volume. Thus, a randomized double-blind dose-volume/salivary-gland-function study has to be performed to assess the sub-population of head and neck cancer patients in whom it is worthwhile to use pilocarpine as a protective agent. A clinically significant 'sparing' effect of the administration of pilocarpine can be expected only in those patients in whom a

TABLE 1
Gustatory and Tactile Sialogogues (Vissink *et al.*, 1988a)

Acid-tasting substances:
vitamin C tablets
citric acid crystals
acid (sugar-free) sweets
lemon pastilles
lemon slices
acid or effervescent drinks (lemon juice, citric acid, buttermilk)
cotton-wool gauze soaked in a citric acid and glycerine solution
Miscellaneous substances:
sugar-free chewing gum
sugar-free sweets
dried pieces of reed root (calami rhizome)
vegetables or fruits

TABLE 2
Pharmacological Sialogogues* (Vissink *et al.*, 1988a)

Pilocarpine hydrochloride, pilocarpine nitrate
Anetholetrithione
Carbachol
Cevimeline
Folia Jaborandi and tinctura Jaborandi
Betanechol chloride
Neostigmine, neostigmine bromide, pyridostigmine bromide, destigmine bromide
Trithioparamethoxyphenylpropene
Benzapyrone
Potassium iodide
Nicotinamide and nicotine acid

* The most frequently used sialogogues are discussed in the text.

sufficient volume of salivary gland is treated with a dose on the steep part of the dose-response curve.

Direct radioprotection in a classic way may be achieved by the use of amifostine, a radical scavenger, when systemically administered during radiation treatment. Subjectively, it has been shown that amifostine has a potential to reduce xerostomia during and after radiation treatment (Antonadou *et al.*, 2002; Buntzel *et al.*, 2002). Unfortunately, this drug has also been shown to have the undesirable effect of tumor protection (McChesney *et al.*, 1986). Thus, caution must be exercised, since most clinical studies do not have the power to evaluate the influence of amifostine on the therapeutic index. Also, the trial design of most amifostine studies is at least questionable and the outcomes subject to debate.

Unfortunately, the treatment of hyposalivation still has to be palliative to some extent, because salivary glands are usually located within the treatment portals for head and neck cancer, and because, at present, only part of the irradiation injury to salivary glands can be resolved in the clinic. This treatment consists of good oral hygiene practices, stimulation of residual salivary gland tissue (sialogogues), and symptomatic relief of oral dryness (Vissink *et al.*, 1988a,b).

Sialogogues can be used to treat hyposalivation. Although a significant proportion of the salivary glands may be included in the radiation fields in patients with malignancies in the head and neck, it is rare that all the minor and major glands will be totally compromised by the radiation therapy (Greenspan, 1990). The unaffected or untreated parts of the salivary glands are the target for these sialogogues. Sialogogues can be divided into gustatory, tactile, and pharmacological substances. With regard to gustatory stimuli, acid-tasting substances, in particular, are used as candies to increase salivary secretion (Senahayake *et al.*, 1998). Bitter-tasting substances also stimulate salivary secretion, whereas sweet-tasting substances stimulate salivary flow to a lesser extent and can even exacerbate the sensation of a dry mouth. A combination of tactile and gustatory stimuli is found in chewing gum. In all compositions of gustatory sialogogues, the sugar-free ones are widely recommended. Table 1 presents some frequently used gustatory and tactile sialogogues. With regard to the pharmacological substances, the potential beneficial effects of pilocarpine have already been discussed. Other drugs that have been reported to be of significance in the treatment of hyposalivation include anetholtrithione (Hassenstein *et al.*, 1978; Epstein and Schubert, 1987) and cevimeline (Petrone *et al.*, 2002). Common pharmacological sialogogues are listed in Table 2. Stimulation of the residual capacity by acupuncture has led to some promising results (Blom *et al.*, 1996; Johnstone *et al.*, 2001) and may be of help for certain patients in the future. This procedure, however, needs further study.

When stimulation of residual secretion is insufficient to relieve patients' complaints, one is left with a purely *symptomatic approach.* For such patients, the stored autologous saliva collected before irradiation or the saliva from other patients (saliva bank) might be a worthwhile solution (Sreebny *et al.*, 1995), but many patients regard this treatment as gruesome. Therefore, many rinsing solutions have been developed to moisten the dry, irritated, vulnerable mucosa with the aim of reducing secondary effects. The simplest technique is frequent moistening of the mouth with water, tea, saline, solutions containing sodium (bi)carbonate and sodium chloride, Emser salt, or diluted milk of magnesia (Vissink *et al.*, 1988a,b). Mouthwashes containing irritating substances (sharp tastes, alcohol) must be avoided because of their effect on the thin, dry, atrophic mucosa.

An important disadvantage of all these mouthwashes is the necessity of frequent applications because of poor retention properties (Levine, 1993). For this reason, many clinicians treat xerostomia with more viscous glycerine-containing mouthwashes, which require less frequent application (Klestov *et al.*, 1981; Wiesenfeld *et al.*, 1983). Furthermore, complex saliva substitutes have been developed that contain agents not only to impart viscosity and to keep soft tissues moist but also, *via* inorganic substances, to retard enamel solubility. These substitutes are based on either carboxymethylcellulose (CMC) (Matzker and Schreiber, 1972; Shannon *et al.*, 1977) or mucin ('s-Gravenmade *et al.*, 1974). The addition of fluoride to saliva substitutes increases the potentially enamel-remineralizing properties of the saliva substitute (Shannon *et al.*, 1978; Vissink *et al.*, 1985). Mucin-containing saliva substitutes are usually preferred over CMC-containing substitutes, by patients with both Sjögren's syndrome and radiation-induced xerostomia (Vissink *et al.*, 1983; Visch *et al.*, 1986). In addition, it has been suggested that mucin-based artificial saliva is also more effective in restor-

ing normal oral flora (Weerkamp *et al.*, 1987), an effect that has not been observed with other types of saliva substitutes (Epstein *et al.*, 1999b; Johansson *et al.*, 2000). When compared with the CMC substitutes, mucin-containing substitutes have superior rheological and wetting properties (Vissink *et al.*, 1984, 1986). More recently, a promising substitute which contains xanthan gum as a base has been developed (Van der Reijden *et al.*, 1996; Jellema *et al.*, 2001). It mimics natural saliva better than the CMC-based substitutes (Van der Reijden *et al.*, 1994). In addition to the more 'liquid-like' saliva substitutes, more 'gel-like' saliva substitutes have been developed of which the polyglycerylmethacrylate-based substitute holds promise (Regelink *et al.*, 1998; Epstein *et al.*, 1999b), particularly when used at night and when daily activities are at a low level.

Often patients object to the taste or inconvenience of using artificial saliva (Van der Reijden *et al.*, 1996), and return to the use of water. Klestov *et al.* (1981), Visch *et al.* (1986), and Vissink *et al.* (1987) believe that the most useful indices of the effectiveness of artificial saliva are the degree of night-time discomfort and difficulty in talking. Furthermore, the success of artificial saliva usage is strictly dependent on adequate instructions (Vissink *et al.*, 1988a). In addition, there is also a great variation in the toleration to artificial salivas among patients (Van der Reijden *et al.*, 1996). Because of this variability, it is worthwhile to use different types of saliva substitutes in a particular patient, to select the most effective substitute in that patient (Van der Reijden *et al.*, 1996; Samarawickrama, 2002). A comparison of the effects of saliva substitutes and saliva stimulants (Anderson *et al.*, 1995; Stewart *et al.*, 1998; Rhodus and Bereuter, 2000) indicates that the effect of a treatment also depends on the remaining secretory potential of the salivary glands. Based on the literature, the following recommendations for the treatment of hyposalivation have been proposed (Regelink *et al.*, 1998):

- *Severe hyposalivation:* A saliva substitute with gel-like properties should be used during the night and when daily activities are at a low level. During the day, a saliva substitute with properties resembling the viscoelasticity of natural saliva, such as substitutes which have xanthan gum and mucin (particularly bovine submandibular mucin) as a base, should be applied.
- *Moderate hyposalivation:* If gustatory or pharmacological stimulation of the residual salivary secretion does not provide sufficient amelioration, saliva substitutes with a rather low viscoelasticity, such as substitutes which have carboxymethylcellulose, hydroxypropylmethylcellulose, mucin (porcine gastric mucin), or low concentrations of xanthan gum as a base, are indicated. During the night or other periods of severe oral dryness, the application of a gel is helpful.
- *Slight hyposalivation:* Gustatory or pharmacological stimulation of the residual secretion is the treatment of choice. Little amelioration is to be expected from the use of saliva substitutes.

In summary, other than by meticulous treatment planning and beam arrangement, radiation-induced hyposalivation is difficult to prevent. Radioprotective (pre)treatments, although promising, need further research with respect to dose-volume dependency (pilocarpine) and tumor protection (amifostine). Gene transfer technology may have to be considered, but much basic research has to be done before these techniques can be applied in the clinic. Possibly, the adenoretroviral vector, AdLTR, which infects dividing and non-dividing cells and mediates long-term transgene expression (Zheng *et al.*, 2000) containing, *e.g.*, one or more aquaporin genes, could be effective. The same applies to stem cell transplantation. Since most patients treated for head and neck cancer are elderly, and embryonic stem cells have their ethical problems, such studies may focus on multipotent adult progenitor cells (Jiang *et al.*, 2002). The latter approach is currently under investigation at our institute, and the preliminary results are very promising. Although much research has been performed, a saliva substitute that is effective and can be applied in all patients is not yet available. When such a substitute is developed, it should ideally contain agents that not only lubricate and hydrate the oral tissues, but also other saliva constituents (Nieuw Amerongen and Veerman, 2002; Tenovuo, 2002) that are involved in the maintenance of oral health. Finally, we still do not know how much saliva or how much of a saliva substitute is needed to moisten the oral tissues in xerostomia patients adequately. There are quite a few patients who complain of oral dryness even though they exhibit a moist appearance of the oral mucosa and *vice versa.* This makes the choice of the cut-off point to decide whether a particular curative or symptomatic treatment is effective in xerostomia patients a hard one.

Radiation Caries

Radiation caries is mainly an indirect effect of irradiation-induced changes in salivary gland tissue that result in hyposalivation, altered salivary composition, a shift in oral flora toward cariogenic bacteria (*S. mutans, Lactobacillus* species), and dietary changes. For this reason, prevention of hyposalivation will invariably contribute to the prevention of radiation caries.

In the early days of radiotherapy, extraction of the teeth prior to irradiation was proposed (Del Regato, 1939). Advocates for oral hygiene regimens (Martin and Sugarbaker, 1940) and restorative procedures (Frisch and Sproull, 1962) met with limited success in caries prevention in those days. Since then, comprehensive preventive measures have been recommended for head and neck cancer patients before, during, and after radiotherapy (Daly *et al.*, 1972; Regezi *et al.*, 1976). Some of the recommended measures have included rigorous oral hygiene, daily self-application of topical fluoride, limitation of cariogenic foods, remineralizing mouthrinse solutions, and artificial saliva preparations. Mainly based on clinical experience and empirical evidence, it is now generally accepted that almost complete caries prevention can be achieved in irradiated patients by the daily use of fluoride in conjunction with strict oral hygiene (Dreizen *et al.*, 1977a; Horiot *et al.*, 1983; Jansma *et al.*, 1989, 1992; Joyston-Bechal *et al.*, 1992; Spak *et al.*, 1994; Epstein *et al.*, 1995). Interdental techniques such as flossing, assisted, if necessary, with plaque-disclosing agents, can be beneficial (Horiot *et al.*, 1981; Jansma *et al.*, 1992; Spak *et al.*, 1994; Toljanic *et al.*, 2002). Caries lesions have to be restored before radiotherapy is started. Dietary instructions about non-cariogenic foods should be given. Finally, the patient's ability and willingness to co-operate in the dental therapy and preventive regimen should be assessed, since the level of compliance in this group of patients is often rather poor (Horiot *et al.*, 1981; Jansma *et al.*, 1992; Joyston-Bechal *et al.*, 1992; Spak *et al.*, 1994; Epstein *et al.*, 1996; Toljanic *et al.*, 2002).

Despite the magnitude of the problem of radiation caries, there are few reports of basic research on this topic. The preventive caries program consisting of daily oral hygiene and

daily topical 1.0% NaF gel application by means of custom-made fluoride carriers, developed by Daly and Drane at the M.D. Anderson Cancer Center at Houston, TX (USA) (Daly and Drane, 1976), has been studied most extensively and forms the basis of the majority of the other studies. This regimen dramatically reduced caries incidence and was also successful in arresting existing lesions, regardless of the cariogenicity of the patients' diet (Dreizen *et al.*, 1977a,b). On the basis of a more-than-10-year experience with 935 head and neck cancer patients, Horiot *et al.* (1983) also concluded that this fluoride protocol was a highly reliable method for the prevention of radiation caries, and that the use of a toothpaste with a high fluoride content (3.0% NaF) twice a day was a good alternative, provided its pre-requisites (higher level of compliance) were well-understood by both clinician and patient. Also, fluoride mouthwashes have been used with considerable success (Meyerowitz *et al.*, 1991; Joyston-Bechal *et al.*, 1992), but this requires meticulous oral hygiene. Jansma *et al.* (1989) showed that the daily use of a 0.05% NaF mouthrinse or a weekly application of a neutral 1% NaF gel was ineffective in the presence of inadequate oral hygiene. The latter study showed that a neutral 1% NaF gel must be applied at least every second day. Good results have also been reported in a preventive program incorporating a chlorhexidine/fluoride regimen (Joyston-Bechal *et al.*, 1992; Newbrun, 1996). Thus, although oral hygiene measures are important in the prevention of radiation caries, they are inadequate as a safeguard against radiation caries without self-applied fluoride applications at least every other day.

There is no consensus about the use of acidulated or neutral forms of topical fluorides, or about the use of sodium fluoride or stannous fluoride preparations. Although acidulated forms have the advantage of increased uptake, the low pH may result in significant mucosal irritation, burning pain, erythema, and ulceration, thereby affecting patient compliance with therapy (Beumer *et al.*, 1979a,b). For this reason, many clinicians advocate the use of neutral or slightly acidic forms of NaF gel, since they are well-tolerated by patients (Dreizen *et al.*, 1977a; Horiot *et al.*, 1983; Jansma *et al.*, 1989; Spak *et al.*, 1994; Epstein *et al.*, 1996). Others have prescribed acidulated phosphate fluoride gel (Carl and Schaaf, 1974) or acidulated forms of SnF2 gel (Fleming, 1983) without experiencing the above-mentioned problems. Less than 2% of the patients using an acidulated 0.4% SnF2 gel (pH 3.2) experienced soft-tissue irritation (Fleming, 1983). It appears, therefore, that the form of topical fluoride used may be dictated by the patient's tolerance and acceptance, but it is still our experience that neutral fluoride preparations are better tolerated and result in a higher level of patient compliance than acidulated ones.

Because hyposalivation is irreversible in the majority of head and neck irradiation patients, the application of fluoride must be continued indefinitely, regardless of the chemical formulation and application method; otherwise caries will develop within months (Dreizen *et al.*, 1977a; Horiot *et al.*, 1983; Jansma *et al.*, 1989; Epstein *et al.*, 1996). Although no reliable data exist, it has been stated, on the basis of clinical experience, that, in some cases, fluoride use can be reduced following improvement in salivary gland function and continued good oral hygiene (Beumer and Brady, 1978; Beumer *et al.*, 1979a,b; Spak *et al.*, 1994).

Some beneficial effect has been reported with the use of remineralizing solutions and dentifrices, particularly when compared with the caries-preventive effect of conventional fluoride toothpaste in dry mouth patients (Papas *et al.*, 1999). This should be considered as a valuable adjunct to the regular use of fluoride gels. Also, saliva substitutes, especially the ones containing fluoride, have been promoted as potential agents to retard enamel solubility (Shannon *et al.*, 1978; Gelhard *et al.*, 1983; Vissink *et al.*, 1985; Kielbassa *et al.*, 2000). It is questionable, however, whether this is of clinical significance, because of the high caries challenge in and limited use of saliva substitutes by these patients. Furthermore, one must be careful when applying a saliva substitute in a dentate patient, since certain saliva substitutes (*e.g.*, saliva substitutes with a low pH or containing strongly charged polyanion polymers) have been shown to de- rather than remineralize enamel and dentin (Pankhurst *et al.*, 1996; Van der Reijden *et al.*, 1997; Kielbassa *et al.*, 2000; Meyer-Lueckel *et al.*, 2002).

In summary, radiation caries is a lifelong threat to patients who have received radiation treatment for head and neck cancer. Consequently, there is a lifelong need for meticulous oral hygiene and frequent fluoride applications. This preventive regimen, however, is often hampered by poor compliance in this category of patients.

Periodontal Disease

As early as 1965, Silverman and Chierici stated that meticulous care must be taken in evaluating the periodontal status before, during, and after radiation treatment. Mechanical oral hygiene procedures (calculus removal, root planing, soft tissue curettage, tooth surface polishing, and daily plaque removal) must be used to remove the local etiologic factors of inflammatory diseases of the periodontium. The overall effect of the use of mechanical procedures is the reversal or control of inflammation, and there is no controversy that these positive effects on the periodontium are beneficial as pre-treatment interventions (Wright, 1990; Position paper, 1997; Epstein *et al.*, 1998). Optimal oral and periodontal hygiene must be maintained indefinitely, due to the lowered biological potential for healing of the periodontium (alveolar bone, periodontal ligament, cementum) after radiotherapy. The risk for development of periodontal disease and, consequently, osteoradionecrosis is diminished in patients receiving topical fluoride applications and also maintaining good oral hygiene (Yusof and Bakri, 1993; Position paper, 1997; Epstein *et al.*, 1998; Epstein and Stevenson-Moore, 2001; Schiødt and Hermund, 2002).

Osteoradionecrosis

In addition to improved radiotherapy and shielding, the first step toward prevention of osteoradionecrosis is a thorough, early pre-irradiation dental assessment. This pre-treatment oral examination should attempt to identify the main factors that will likely increase the risk for osteoradionecrosis so that steps may be taken to control or eliminate as many factors as are practical before radiotherapy begins (Stevenson-Moore, 1990; Jansma *et al.*, 1992; Constantino *et al.*, 1995; Thorn *et al.*, 2000; Schiødt and Hermund, 2002). The primary goal should be to optimize the condition of the patient's dentition, so that high-risk procedures, such as extraction of teeth, apicoectomies, etc., will not have to be performed in the post-irradiation period (Beumer and Brady, 1978; Beumer *et al.*, 1979a,b; Stevenson-Moore, 1990; Jansma *et al.*, 1992; Curi and Dib, 1997; Tong *et al.*, 1999; Thorn *et al.*, 2000). The value of this oral screening is lim-

ited if it is performed very close to the initiation of radiotherapy so as to preclude dental intervention. For maximum impact of screening, adequate time for treatment and healing must be allowed (Sonis *et al.*, 1990).

Whether or not to extract teeth prior to radiotherapy to eliminate this potential source of infection has been a controversial issue for a long time. The timing of dental extractions in relation to the beginning or completion of radiotherapy has been studied by many investigators, and their findings have varied widely. Pre-irradiation extractions, when performed and timed correctly, do not significantly increase the overall risk of osteoradionecrosis (Starcke and Shannon, 1977; Murray *et al.*, 1980b; Makkonen *et al.*, 1987). It is now generally accepted that all teeth with a questionable prognosis must be extracted before radiotherapy (Table 3) (Stevenson-Moore, 1990; Jansma *et al.*, 1992; Thorn *et al.*, 2000; Schiødt and Hermund, 2002). The less motivated the patient, the more aggressive one should be in extracting teeth prior to radiotherapy (Beumer *et al.*, 1979a,b; Horiot *et al.*, 1981; Jansma *et al.*, 1992; Toljanic *et al.*, 2002). The extractions should be performed as atraumatically (careful tissue handling) as possible and with primary closure (Jansma *et al.*, 1992). Frequently suggested healing intervals ranged from 10 to 14 days (Beumer *et al.*, 1979a,b; Murray *et al.*, 1980b; Jansma *et al.*, 1992; Tong *et al.*, 1999). An interval of 14 days still poses a minor risk for the development of osteoradionecrosis (Marx and Johnson, 1987). The risk was reduced to zero if there was a 21-day or greater interval between extraction and initiation of radiation therapy. However, the time between the diagnosis of the tumor and the start of the radiotherapy should be kept as short as possible if the highest probability of cure is to be attained (see Vissink *et al.*, 2003).

Extraction of teeth or wounding during radiation therapy will create an extremely high risk for osteoradionecrosis and is strongly discouraged, because surgical wounding and radiation wounding result in an additive problem for the patient (Friedman, 1990).

A higher incidence of osteoradionecrosis is observed after cumulative radiation doses to the bone exceed 65 Gy (Murray *et al.*, 1980a; Constantino *et al.*, 1995; Curi and Dib, 1997; Tong *et al.*, 1999; Thorn *et al.*, 2000). Epstein *et al.* (1987a,b) have reported a two-fold increased risk of necrosis if teeth were extracted after radiotherapy compared with pre-irradiation therapy dental extractions. Also, antibiotic coverage is strongly recommended (Maxymiw *et al.*, 1991; Jansma *et al.*, 1992; Tong *et al.*, 1999). There is some evidence that hyperbaric oxygen (HBO) treatment is more beneficial than conventional antibiotic prophylaxis in preventing osteoradionecrosis (5% incidence of osteoradionecrosis *vs.* 30%, respectively; Marx *et al.*, 1985). The real value of HBO in prevention and treatment of osteoradionecrosis still has to be proven in sound randomized controlled clinical trials. HBO therapy stimulates angiogenesis, increases neovascularization, optimizes cellular levels of oxygen for osteoblast and fibroblast proliferation, stimulates collagen formation, and supports ingrowing blood vessels, all of which enhances the healing potential in irradiated compromised tissues (Myers and Marx, 1990). If extensive wounding or extraction in radiation portals is necessary, then HBO treatment should be used both prior to surgery and after wounding occurs (Myers and Marx, 1990). Furthermore, after completion of the course of radiotherapy, there is a five- to six-month window of tissue repair and healing prior to the irradiation-induced onset of progressive fibrosis and loss of vascularity

TABLE 3
Teeth with a Questionable Prognosis and Having to be Removed before the Start of Radiotherapy (Jansma *et al.*, 1992; Schiødt and Hermund, 2002)

- Advanced caries lesions with questionable pulpal status or pulpal involvement
- Extensive periapical lesions
- Moderate to advanced periodontal disease (pocket depth in excess of 5 mm), especially with advanced bone loss and mobility or furcation involvement
- Residual root tips not fully covered by alveolar bone or showing radiolucency
- Impacted or incompletely erupted teeth, particularly third molars, that are not fully covered by alveolar bone or that are in contact with the oral environment
- Teeth close to tumor

(Marx and Johnson, 1987). This healing phase is a much safer time to undertake necessary extractions, and HBO is usually not needed.

There are two goals in the treatment of osteoradionecrosis, *viz*,. elimination of the necrotic bone and improvement in the vascularity of the remaining radiation-damaged tissues (Constantino *et al.*, 1995). The presenting lesion dictates the treatment protocol to be followed, and this requires an effective clinical staging system, particularly for lesions in the mandible (Epstein *et al.*, 1997; Schwartz and Kagan, 2002). The most widely used systems are the system developed by Marx (1983, 1984) and the clinical staging system of Epstein *et al.* (1997). The system of Marx (1983, 1984) focuses chiefly on the use of and response to HBO, and thus on the treatment of osteoradionecrosis; while the clinical staging system proposed by Epstein *et al.* (1997) is more concerned with its pathogenesis. The latter system classifies osteoradionecrosis as resolved, chronic persistent, or active progressive, either with or without pathologic fracture. Recently, Schwartz and Kagan (2002) modified the clinical staging system of Epstein *et al.* (1997) by focusing on the extent and nature of soft-tissue necrosis rather than on the presence or absence of a fracture. They proposed three stages, subdivided into stages with and without soft-tissue necrosis. Careful clinical research will make the treatment of osteoradionecrosis less empirical.

The first step in the treatment of osteoradionecrosis is débridement of all bone that is no longer vascularized. The removal of this dead bone eliminates any nidus for continued infection and inflammation, but does nothing to improve the vascularity of the adjacent tissue bed and the remaining vascularized bone. These tissues remain compromised by the previous radiation and are at continued risk for the development of osteoradionecrosis in the future. Therefore, based on clinical experience and empirical evidence, a protocol has been developed aimed not only to improve the healing of radiation-injured tissue, but also to increase their vascularity permanently. In this so-called Marx protocol, antibiotic therapy, hyperbaric oxygen therapy, and débridement are combined (Marx, 1983; Constantino *et al.*, 1995). This protocol is widely used, but there is some discussion of whether HBO is always necessary, since many clinicians have noted that minor osteoradionecrosis

lesions also can be treated without HBO (Schwartz and Kagan, 2002). According to the Marx protocol, bone exposures of the mandible are initially treated by local débridement and HBO (stage I treatment). Smaller defects frequently close with this management. Defects that do not fully respond are treated by marginal mandibuloectomy of the involved region, followed by additional HBO treatment exposures (stage II). In case of failure of stage II management, initial defects that involve the inferior border of the mandible, defects having an oro-cutaneous fistula, or pathologic fractures are managed by resection of the involved portion of the mandible down to a margin of healthy bone and stabilization of the defect by extra-oral fixation (stage III). Since osteoradionecrosis is a result of hypovascularity and not necessarily an infection, antibiotic therapy is considered adjunctive. The mainstay of treatment is surgical, and in fact HBO is also an adjuvant (Hao *et al.*, 1999).

In summary, osteoradionecrosis is a lifelong threat to patients radiated in the head and neck region. Therefore, these patients need a proper dental check-up before treatment and close monitoring afterward. Since compliance is often a problem in these patients, one should be rather aggressive in extracting teeth prior to radiotherapy.

Trismus

Trismus may be a significant side-effect of radiotherapy, especially in combination with muscular tumor invasion and surgery. The most decisive factor in whether trismus develops or not is probably the inclusion of the medial pterygoid muscles in the treatment portals (Goldstein *et al.*, 1999). Prevention of trismus, rather than its treatment, is the most desirable objective (Goldstein *et al.*, 1999). The maximum mouth opening (inter-arch or inter-incisal distance) should be measured before radiotherapy is started, and the patient and/or clinician should measure this distance frequently thereafter to ensure its maintenance. Patients at risk of trismus should be put on home exercises to maintain maximum opening and jaw mobility as soon as radiotherapy begins (Dreizen *et al.*, 1977b; Engelmeier and King, 1983; Lockhart, 1986). Lockhart (1986) recommended the use of tongue blades or rubber stops in these exercises to increase the size of mandibular opening.

In patients in whom trismus has developed, the exercise program should be intensified and, if necessary, combined with physiotherapy to regain the lost inter-arch distance (Dreizen *et al.*, 1977b). Prosthetic appliances (dynamic bite openers) containing springs and bands designed to re-stretch the muscles have been helpful in some patients (Dreizen *et al.*, 1977b; Engelmeier and King, 1983). Whatever the approach to this problem, patient compliance and perseverance are critical for success, because dramatic results are not achieved immediately (Lockhart, 1986).

Epilogue

As is discussed in this and the preceding review (Vissink *et al.*, 2003), head and neck radiotherapy may result in several unwanted early (mucositis, loss of taste, hyposalivation) and late (hyposalivation, radiation caries, trismus, osteoradionecrosis) side-effects. These sequelae may be dose-limiting and may have a tremendous impact on the patient's quality of life. Prevention or reduction to a minimum of these effects is possible and should be an integral part of head and neck cancer treatment. With the implementation of new radiation schedules such as hyperfractionation, accelerated fractionation, 3D conformal radiotherapy, and intensity-modulated radiotherapy in head and neck radiotherapy, the late-radiation effects can probably be reduced, but the remaining sequelae are still bothersome to the patients. Adequate prevention and treatment are matters of increasing importance because of the increasing numbers of aged, often dentate, patients. A crucial factor in the success of all preventive and treatment regimens is the compliance of the patient. Since compliance is rather poor in many head and neck cancer patients, much effort has to be made in making the patients aware of the dangers of not complying with the preventive protocols.

Acknowledgments

Support for the studies performed at our institutes was obtained from Praeventiefonds (grant 28-1290), the Dutch Cancer Foundation Koningin Wilhelmina Fonds (grants GUKC 83-20, RRTI 84-08, GUKC 86-03, GUKC 88-01, RUG 93.504, RUG 98.1658, RUG 02.2673), and the fellowship program of the Royal Dutch Academy of Arts and Sciences (1987-1992).

References

Adamietz IA, Rahn R, Böttcher HD, Schäfer V, Reimer K, Fleischer W (1998). Prophylaxe der radiochemotherapeutisch bedingten Mukositis. *Strahlenther Onkol* 174:149-155.

Anderson G, Johansson G, Attström R, Edwardsson S, Glantz PO, Larsson K (1995). Comparison of the effect of linseed extract Salinum and a methyl cellulose preparation on the symptoms of dry mouth. *Gerodontology* 12:12-17.

Antonadou D, Pepelassi M, Synodinou M, Puglisi M, Throuvalas N (2002). Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer patients. *Int J Radiat Oncol Biol Phys* 52:739-747.

Atkinson JC, Baum BJ (2001). Salivary enhancement: current status and future therapies. *J Dent Educ* 65:1096-1101.

Baum BJ, O'Connell BC (1999). In vivo gene transfer to salivary glands. *Crit Rev Oral Biol Med* 10:276-283.

Bensadoun RJ, Magne N, Marcy PY, Demard F (2001). Chemotherapy- and radiotherapy-induced mucositis in head and neck cancer patients: new trends in pathophysiology. Prevention and treatment. *Eur Arch Otorhinolaryngol* 258:481-487.

Beumer J, Brady FA (1978). Dental management of the irradiated patient. *Int J Oral Surg* 7:208-220.

Beumer J, Curtis T, Harrison R (1979a). Radiation therapy of the oral cavity: sequelae and management, Part 1. *Head Neck Surg* 1:301-312.

Beumer J, Curtis T, Harrison R (1979b). Radiation therapy of the oral cavity: sequelae and management, Part 2. *Head Neck Surg* 1:392-408.

Blom M, Dawidson I, Fernberg JO, Johnson G, Angmar-Månsson B (1996). Acupuncture treatment of patients with radiation-induced xerostomia. *Oral Oncol Eur J Cancer* 32(B):182-190.

Borowski E, Benhamon E, Pico JL, Laplance A, Margainaud JP, Hayat M (1994). Prevention of oral mucositis in patients treated with high-dose chemotherapy and bone marrow transplantation. A randomised controlled trial comparing two protocols of dental care. *Oral Oncol Eur J Cancer* 30(B):93-97.

Buntzel J, Glazel M, Kuttner K, Weinaug R, Frohlich D (2002). Amifostine in simultaneous radiochemotherapy of advanced head and neck cancer. *Sem Radiat Oncol* 12(Suppl 1):4-13.

Carl W, Schaaf NG (1974). Dental care for the cancer patient. *J Surg Oncol* 6:293-310.

Consensus statement (1990). Oral complications of cancer thera-

pies. *NCI Monogr* 9:3-8.
Constantino PD, Friedman CD, Steinberg MJ (1995). Irradiated bone and its management. *Otolaryngol Clin North Am* 28:1021-1038.
Cooper JS, Fu K, Marks J, Silverman S (1995). Late effects of radiation therapy in the head and neck region. *Int J Radiat Oncol Biol Phys* 31:1141-1164.
Coppes RP, Zeilstra LJW, Vissink A, Konings AWT (1997a). Sialogogue-related radioprotection of salivary gland function: the degranulation concept revisited. *Radiat Res* 148:240-247.
Coppes RP, Vissink A, Zeilstra LJW, Konings AWT (1997b). Muscarinic receptor stimulation increases tolerance of rat salivary gland function to radiation damage. *Int J Radiat Biol* 72:615-625.
Coppes RP, Zeilstra LJW, Kampinga HH, Konings AWT (2001). Early to late sparing of radiation damage to the parotid gland by adrenergic and muscarinic receptor agonists. *Br J Cancer* 85:1055-1063.
Curi MM, Dib LL (1997). Osteoradionecrosis of the jaws: a retrospective study on the background factors and treatment in 104 cases. *J Oral Maxillofac Surg* 55:540-544.
Curtis TA, Griffith M, Firtell DN (1976). Complete denture prosthodontics for the radiation patient. *J Prosthet Dent* 36:66-76.
Daly TE, Drane JB (1976). Prevention and management of dental problems in irradiated patients. *J Am Soc Prev Dent* 6:21-25.
Daly TE, Drane JB, MacComb WS (1972). Management of problems of the teeth and jaws in patients undergoing irradiation. *Am J Surg* 124:539-542.
Del Regato JA (1939). Dental lesions observed after Roentgen therapy in cancer of the buccal cavity, pharynx and larynx. *Am J Roentgenol* 42:404-410.
Delporte C, O'Connell BC, He X, Lancaster HE, O'Connell AC, Agre P, *et al.* (1997). Increased fluid secretion after adenoviral-mediated transfer of the aquaporin-1 cDNA to irradiated rat salivary glands. *Proc Natl Acad Sci USA* 94:3268-3273.
Denham JW, Peters LJ, Johansen J, Poulsen M, Lamb DS, Hindley A, *et al.* (1999). Do acute mucosal reactions lead to consequential late reactions in patients with head and neck cancer? *Radiother Oncol* 52:157-164.
Dörr W, Noack R, Spekl K, Farrell CL (2001). Modification of oral mucositis by keratinocyte growth factor: single radiation exposure. *Int J Radiat Biol* 77:341-347.
Dreizen SA, Brown LR, Daly TE, Drane JB (1977a). Prevention of xerostomia-related dental caries in irradiated cancer patient. *J Dent Res* 56:99-104.
Dreizen SA, Daly TE, Drane JB, Brown LR (1977b). Oral complications of cancer radiotherapy. *Postgrad Med* 61:85-92.
Eisbruch A, Ten Haken RK, Hyungjin MK, Marsh LH, Ship JA (1999). Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. *Int J Radiat Oncol Biol Phys* 45:577-587.
Eisbruch A, Ship JA, Kim HM, Ten Haken RK (2001). Partial radiation of the parotid gland. *Sem Radiat Oncol* 11:234-239.
El-Sayed S, Epstein JB, Minish E, Burns P, Hay J, Laukkanen E (2002). A pilot study evaluating the safety and microbiologic efficacy of an economically viable antimicrobial lozenge in patients with head and neck cancer receiving radiation therapy. *Head Neck* 24:6-15.
Engelmeier RL, King GE (1983). Complications of head and neck radiation therapy and their management. *J Prosthet Dent* 49:514-522.
Epstein JB (1990). Infection prevention in bone marrow transplantation and radiation patients. *NCI Monogr* 9:73-85.
Epstein JB, Schubert MM (1987). Synergistic effect of sialogogues in management of xerostomia after radiation therapy. *Oral Surg Oral Med Oral Pathol* 64:179-182.
Epstein JB, Stevenson-Moore P (2001). Periodontal disease and periodontal management in patients with cancer. *Oral Oncol* 37:613-619.
Epstein JB, Wong FLW, Stevenson-Moore P (1987a). Osteoradionecrosis: clinical experience and a proposal for classification. *J Oral Maxillofac Surg* 45:104-110.
Epstein JB, Rea G, Wong FLW (1987b). Osteonecrosis: study of the relationship of dental extractions in patients receiving radiotherapy. *Head Neck Surg* 10:48-54.
Epstein JB, Vickars L, Spinelli J, Reece D (1992). Efficacy of chlorhexidine and nystatin rinses in prevention of oral complications in leukemia and bone marrow transplantation. *Oral Surg Oral Med Oral Pathol* 73:682-689.
Epstein JB, Burchell JL, Emerton S, Le ND, Silverman S (1994). A clinical trial of bethanechol in patients with xerostomia after radiation therapy. A pilot study. *Oral Surg Oral Med Oral Pathol* 77:610-614.
Epstein JB, van der Meij EH, Emerton SM, Le ND, Stevenson-Moore P (1995). Compliance with fluoride gel use in irradiated patients. *Spec Care Dentist* 15:218-222.
Epstein JB, van der Meij EH, Lunn R, Stevenson-Moore P (1996). Effects of compliance with fluoride gel application on caries and caries risk inpatients after radiation therapy for head and neck cancer. *Oral Surg Oral Med Oral Pathol Radiol Endod* 82:268-2757.
Epstein JB, van der Meij EH, McKenzie M, Wong F, Lepawsky M, Stevenson-Moore P (1997). Postradiation osteonecrosis of the mandible. A long-term follow-up study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 83:657-662.
Epstein JB, Lunn R, Le ND, Stevenson-Moore P (1998). Periodontal attachment loss in patients after head and neck radiation therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 86:673-677.
Epstein JB, Emerton S, Kolbinson DA, Le ND, Philips N, Stevenson-Moore P, *et al.* (1999a). Quality of life and oral function following radiotherapy for head and neck cancer. *Head Neck* 21:1-11.
Epstein JB, Emerton S, Le ND, Stevenson-Moore P (1999b). A double-blind crossover trial of Oral Balance gel and Biotene toothpaste versus placebo in patients with xerostomia following radiation therapy. *Oral Oncol* 35:132-137.
Erkurt E, Erkisi M, Tunali C (2000). Supportive treatment in weight losing cancer patients due to the additive adverse effects of radiation treatment. *J Exp Clin Cancer Res* 19:431-439.
Farrell CL, Rex KL, Kaufman SA, Dipalma CR, Chen JN, Scully S, *et al.* (1999). Effects of keratinocyte growth factor in the squamous epithelium of the upper aerodigestive tract of normal and irradiated mice. *Int J Radiat Biol* 75:606-620.
Fleming TJ (1983). The use of topical fluoride by patients receiving cancer therapy. *Curr Probl Cancer* 7:37-41.
Foote RL, Loprinzi CL, Frank AR, O'Fallon JR, Gulavita S, Tewfik HH, *et al.* (1994). Randomized trial of a chlorhexidine mouthwash for alleviation of radiation-induced mucositis. *J Clin Oncol* 12:2630-2633.
Franzén L, Henriksson R, Littbrand B, Zackrisson B (1995). Effects of sucralfate on mucositis during and following radiotherapy of malignancies in the head and neck region. *Acta Oncologica* 34:219-223.
Friedman RB (1990). Osteoradionecrosis: causes and prevention. *NCI Monogr* 9:145-149.
Frisch J, Sproull R (1962). Dental treatment after irradiation. *J Prosthet Dent* 12:182-189.
Gelhard TBFM, Fidler V, 's-Gravenmade EJ, Vissink A (1983). Remineralization of softened human enamel in mucin- or

CMC-containing artificial salivas. *J Oral Pathol* 12:336-341.
Goldstein M, Maxymiw WG, Cummings BJ, Wood RE (1999). The effects of antitumour irradiation on mandibular opening and mobility. A prospective study of 58 patients. *Oral Surg Oral Med Oral Pathol Endod* 88:365-373.
Greenspan D (1990). Management of salivary dysfunction. *NCI Monogr* 9:159-161.
Greenspan D, Daniels TE (1987). Effectiveness of pilocarpine in postradiation xerostomia. *Cancer* 59:1123-1125.
Hao SP, Chen HC, Wei FC, Chen CY, Yeh ARM, Su JL (1999). Systematic management of osteoradionecrosis in the head and neck. *Laryngoscope* 109:1324-1328.
Hassenstein E, Muller R, Reinhard HJ (1978). Die Wirkung von SL 25 auf die radiogene Xerostomie bei der Strahlentherapie von Tumoren im Hals- und Gesichtsbereich. *Strahlentherapie* 154:554-558.
Hazuka MB, Martel MK, Marsh L, Lichter AS, Wolf GT (1993). Preservation of parotid function after external beam irradiation in head and neck cancer patients: a feasibility study using 3-dimensional treatment planning. *Int J Radiat Oncol Biol Phys* 27:731-737.
Henson BS, Inglehart MR, Eisbruch A, Ship JA (2001). Preserved salivary output and xerostomia-related quality of life in head and neck cancer patients receiving parotid-sparing radiotherapy. *Oral Oncol* 37:84-93.
Horiot JC, Bone MC, Ibrahim E, Castro JR (1981). Systematic dental management in head and neck irradiation. *Int J Radiat Oncol Biol Phys* 7:1025-1029.
Horiot JC, Schraub S, Bone MC, Bain Y, Ramadier J, Chaplain G, *et al.* (1983). Dental preservation in patients irradiated for head and neck tumours: a 10-year experience with topical fluoride and a randomized trial between two fluoridation methods. *Radiother Oncol* 1:77-82.
Horiot JC, Maingon P, Barillot I (1994). Radiotherapy for head and neck cancers including chemoradiotherapy. *Curr Opin Oncol* 6:274-276.
Horiot JC, Lipinski F, Schraub S, Maulard-Durdux C, Bensadoun RJ, Ardiet JM, *et al.* (2000). Post-radiation severe xerostomia relieved by pilocarpine: a prospective French cooperative study. *Radiat Oncol* 55:233-239.
Jansma J, Vissink A, 's-Gravenmade EJ, Visch LL, Fidler V, Retief DH (1989). In vivo study on the prevention of post-radiation caries. *Caries Res* 23:172-178.
Jansma J, Vissink A, Spijkervet FKL, Panders AK, Vermey A, Roodenburg JLN, *et al.* (1992). Protocol for the prevention and treatment of oral complications of head and neck radiotherapy. *Cancer* 70:2171-2180.
Jellema AP, Langendijk H, Bergenhenegouwen L, van der Reijden WA, Leemans R, Smeele L, *et al.* (2001). The efficacy of Xialine in patients with xerostomia resulting from radiotherapy for head and neck cancer: a pilot-study. *Radiother Oncol* 59:157-160.
Jha N, Seikaly H, McGaw T, Coulter L (2000). Submandibular salivary gland transfer prevents radiation-induced xerostomia. *Int J Radiat Oncol Biol Phys* 46:7-11.
Jiang Y, Jahagirdar BN, Reinhardt RL, Schwartz RE, Keene CD, Ortiz-Gonzalez XR, *et al.* (2002). Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature* 418:41-49.
Joensuu H, Bostrom P, Makkonen T (1993). Pilocarpine and carbacholine in treatment of radiation-induced xerostomia. *Radiother Oncol* 26:33-37.
Johansson G, Andersson G, Attström R, Edwardsson S (2000). Oral mucous membrane flora in patients using saliva substitutes. *Gerodontology* 17:87-90.
Johnson JT, Ferretti GA, Nethery WJ, Valdez IH, Fox PC, Ng D, *et al.* (1993). Oral pilocarpine for postirradiation xerostomia in patients with head and neck cancer. *N Engl J Med* 329:390-395.
Johnstone PA, Peng YP, May BC, Inouye WS, Neimtzow RC (2001). Acupuncture for pilocarpine-resistant xerostomia following radiotherapy for head and neck malignancies. *Int J Radiat Oncol Biol Phys* 50:353-357.
Jones RE, Takeuchi T, Eisbruch A, D'Hondt E, Hazuka M, Ship JA (1996). Ipsilateral parotid sparing study in head and neck cancer patients who receive radiation therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 81:642-648.
Joyston-Bechal S, Hayes K, Davenport ES, Hardie JM (1992). Caries incidence, mutans streptococci and lactobacilli in irradiated patients during a 12-month preventive programme using chlorhexidine and fluoride. *Caries Res* 26:384-390.
Karthaus M, Rosenthal C, Ganser A (1999). Prophylaxis and treatment of chemo- and radiotherapy-induced oral mucositis. Are there new strategies? *Bone Marrow Transplant* 24:1095-1108.
Kielbassa AM, Shohadai SP, Schulte-Mönting J (2000). Effect of saliva substitutes on mineral content of demineralized and sound dental enamel. *Support Care Cancer* 9:40-47.
Klestov AC, Webb J, Latt D, Schiller G, McNamara K, Young DY, *et al.* (1981). Treatment of xerostomia: a double blind trial in 108 patients with Sjögren's syndrome. *Oral Surg* 51:594-599.
Lajtman Z, Krajina Z, Krpan D, Vincelj J, Borcic V, Popovic-Kovacic J (2000). Pilocarpine in the prevention of postirradiation xerostomia. *Acta Med Croatica* 54:65-67.
Lees J (1999). Incidence of weight loss in head and neck cancer patients on commencing radiotherapy treatment at a regional cancer cenre. *Eur J Cancer Care* 8:133-136.
Leslie MD, Dishe S (1991). Parotid gland function following accelerated and conventionally fractionated radiotherapy. *Radiother Oncol* 22:133-139.
Leslie MD, Dishe S (1994). The early changes in salivary gland function during and after radiotherapy given for head and neck cancer. *Radiother Oncol* 30:26-32.
LeVeque FG, Montgomery F, Potter D, Zimmer M, Rieke JW, Steiger BW, *et al.* (1993). A multi-centre randomized, double-blind, placebo-controlled, dose-titration study of oral pilocarpine for treatment of radiation-induced xerostomia in head and neck cancer patients. *J Clin Oncol* 11:1124-1131.
Levine MJ (1993). Development of artificial salivas. *Crit Rev Oral Biol Med* 4:279-286.
Licht R, Kampinga HH, Coppes RP (2002). Salivary gland sparing prophylactic pilocarpine treatment has no effect on tumor regrowth after irradiation. *Radiat Res* 157:596-598.
Lievens Y, Haustermans K, van den Weyngaert D, van den Bogaert W, Scalliet P, Hutsebaut L, *et al.* (1998). Does sucralfate reduce the acute side-effects in head and neck cancer treated with radiotherapy? A double-blind randomized trial. *Radiother Oncol* 47:149-153.
Lockhart PB (1986). Oral complications of radiation therapy. In: Head and neck management of the cancer patient. Peterson DE, Elias EG, Sonis ST, editors. Boston: Martinus Nijhoff, pp. 275-297.
Maciejewski B, Zajusz A, Pilecki B, Swiatnicka J, Skaldowski K, Dörr W, *et al.* (1991). Acute mucositis in the stimulated oral mucosa of patients during radiotherapy for head and neck cancer. *Radiother Oncol* 22:7-11.
Makkonen TA, Kiminki A, Makkonen TK, Nordman E (1987). Dental extractions in relation to radiation therapy of 224 patients. *Int J Oral Maxillofac Surg* 16:56-64.
Makkonen TA, Boström P, Vilja P, Joensuu H (1994). Sucralfate mouth washing in the prevention of radiation-induced mucositis. A placebo-controlled double-blind randomized study. *Int J Radiat Oncol Biol Phys* 30:177-182.
Makkonen TA, Minn H, Jekunen A, Vilja P, Tuominen J, Joensuu H

(2000). Granulocyte macrophage-colony stimulating factor (GM-CSF) and sucralfate in preventin of radiation-induced mucositis. A prospective randomized study. *Int J Radiat Oncol Biol Phys* 46:525-534.
Martin HE, Sugarbaker EL (1940). Cancer of the floor of the mouth. *Surgery Gynec Obstet* 71:347-359.
Martin MV (1993). Irradiation mucositis: a reappraisal. *Oral Oncol Eur J Cancer* 29B:1-2.
Martin MV, van Saene HKF (1992). The role of microorganisms in cancer therapy. *Oral Maxillofac Surg Infect* 2:81-84.
Marx RE (1983). A new concept in the treatment of osteoradionecrosis. *J Oral Maxillofac Surg* 41:351-357.
Marx RE (1984). Osteonecrosis of the jaws: a review and update. *Hyperbaric Oxygen Rev* 5:78-127.
Marx RE, Johnson RP (1987). Studies in the radiobiology of osteoradionecrosis and their clinical significance. *Oral Surg Oral Med Oral Pathol* 64:379-390.
Marx RE, Johnson RP, Kline SN (1985). Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin. *J Am Dent Assoc* 111:49-54.
Mascarin M, Franchin G, Minatel E, Gobitti C, Talamini R, de Maria D, *et al.* (1999). The effect of granulocyte colony-stimulating factor on oral mucositis in head and neck cancer patients treated with hyperfractionated radiotherapy. *Oral Oncol* 35:203-208.
Mateos JJ, Setoain X, Ferre J, Rovisora A, Navalpotro B, Martin F, *et al.* (2001). Salivary scintigraphy for assessing the protective effect of pilocarpine in head and neck irradiated tumours. *Nucl Med Commun* 22:651-656.
Matsuo R (2000). Role of saliva in the maintenance of taste sensitivity. *Crit Rev Oral Biol Med* 11:216-229.
Matzker J, Schreiber J (1972). Synthetischer Speichel zur Therapie der Hyposalien insbesondere bei der radiogenen Sialadenitis. *Z Laryngol Rinol Otol* 51:422-428.
Maxymiw WG, Wood RE, Liu FF (1991). Postradiation dental extractions without hyperbaric oxygen. *Oral Surg Oral Med Oral Pathol* 72:270-274.
McChesney SL, Gillette EL, Dewhirst MW, Withrow SJ (1986). Influence of WR 2721 on radiation response of canine soft tissue sarcomas. *Int J Radiat Oncol Biol Phys* 12:1957-1963.
Meredith R, Salter M, Kim R, Spencer S, Weppelmann B, Rodu B, *et al.* (1997). Sucralfate for radiation mucositis. Results of a double-blind randomized trial. *Int J Radiat Oncol Biol Phys* 37:275-279.
Meyer-Lueckel H, Schulte-Mönting J, Kielbassa AM (2002). The effect of commercially available saliva substitutes on predemineralized bovine dentin in vitro. *Oral Diseases* 8:192-198.
Meyerowitz C, Featherstone JD, Billings RJ, Eisenberg AD, Fu J, Shariati M, *et al.* (1991). Use of an intra-oral model to evaluate 0.05% sodium fluoride mouthrinse in radiation-induced hyposalivation. *J Dent Res* 70:894-898.
Miaskowski C (1990). Management of mucositis during therapy. *NCI Monogr* 9:95-98.
Momm F, Muller M, Tsekos A, Guttenberger R (2001). Xerostomie nach Strahlentherapie. Effektivere Behandlung durch ein mucinhaltiges Spray? *HNO* 49:831-836.
Mossman KL (1986). Gustatory tissue injury in man: radiation dose response relationship and mechanism of taste loss. *Br J Cancer* 53:9-11.
Murray CG, Herson J, Daly TE, Zimmerman S (1980a). Radiation necrosis of the mandible: a 10-year study. Part I. Factors influencing the onset of necrosis. *Int J Radiat Oncol Biol Phys* 6:543-548.
Murray CG, Herson J, Daly TE, Zimmerman S (1980b). Radiation necrosis of the mandible: a 10-year study. Part II. Dental factors, onset, duration and management of necrosis. *Int J Radiat Oncol Biol Phys* 6:549-553.
Myers RAM, Marx RE (1990). Use of hyperbaric oxygen in postradiation head and neck surgery. *NCI Monogr* 9:151-157.
Newbrun E (1996). Current treatment modalities or oral problems of patients with Sjögren's syndrome. Caries prevention. *Adv Dent Res* 10:29-34.
Nicolatou O, Sotiropoulou-Lontou A, Skarlatos J, Kyprianou K, Kolitsi G, Dardoufas K (1998). A pilot study of the effect of granulocyte-macrophage colony-stimulating factor on oral mucositis in head and neck cancer patients during x-irradiation therapy. A preliminary report. *Int J Radiat Oncol Biol Phys* 42:551-556.
Niedermeier W, Matthaeus C, Meyer C, Staar S, Müller RP, Schulze HJ (1998). Radiation-induced hyposalivation and its treatment with oral pilocarpine. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 86:541-549.
Nieuw Amerongen AV, Veerman ECI (2002). Saliva—the defender of the oral cavity. *Oral Diseases* 8:12-22.
Nishioka T, Shirato H, Arimoto T, Kaneko M, Kitahara T, Oomori K, *et al.* (1997). Reduction of radiation-induced xerostomia in nasopharyngeal carcinoma using CT simulation with laser patient marking and three-field irradiation technique. *Int J Radiat Oncol Biol Phys* 38:705-712.
Okuno SH, Foote RL, Loprinzi CL, Gulavita S, Sloan JA, Earle J, *et al.* (1997). A randomized trial of a nonadsorbable antibiotic lozenge given to alleviate radiation-induced mucositis. *Cancer* 79:2193-2199.
Pankhurst CL, Smith EC, Rogers JO, Dunne SM, Jackson SH, Proctor G (1996). Diagnosis and management of the dry mouth. Part 1. *Dent Update* 23:56-62.
Papas A, Russell D, Singh M, Stack K, Kent R, Triol C, *et al.* (1999). Double blind clinical trial of a remineralizing dentifrice in the prevention of caries in a radiation therapy population. *Gerodontology* 16:2-10.
Petrone D, Condemi JJ, Fife R, Gluck O, Cohen S, Dalgin P (2002). A double-blind, randomized, placebo-controlled study of cevimeline in Sjögren's syndrome patients with xerostomia and keratoconjunctivitis sicca. *Arthritis Rheum* 46:748-754.
Plevovà P (1999). Prevention and treatment of chemotherapy- and radiotherapy-induced oral mucositis. A review. *Oral Oncol* 35:453-470.
Position Paper (1997). Periodontal considerations in the management of the cancer patient. *J Periodontol* 68:791-801.
Regelink G, Vissink A, Reintsema H, Nauta JM (1998). Efficacy of a synthetic polymer based saliva substitute in reducing oral complaints of patients suffering from irradiation-induced xerostomia. *Quintessence Int* 29:383-388.
Regezi JA, Courtney RM, Kerr DA (1976). Dental management of patients irradiated for oral cancer. *Cancer* 8:994-1000.
Rhodus NL, Bereuter J (2000). Clinical evaluation of a commercially available oral moisturizer in relieving signs and symptoms of xerostomia in postirradiation head and neck cancer patients and patients with Sjögren's syndrome. *J Otolaryngol* 29:28-34.
Rice DH, Gill G (1979). The effect of irradiation upon the bacterial flora in patients with head and neck cancer. *Laryngoscope* 89:1839-1841.
Rieke JW, Hafermann MD, Johnson JT, LeVeque FG, Iwamoto R, Steiger BW, *et al.* (1995). Oral pilocarpine for radiation-induced xerostomia: integrated efficacy and safety results from two prospective randomized clinical trials. *Int J Radiat Oncol Biol Phys* 31:661-669.
Ripamonti C, Zecca E, Brunelli C, Fulfaro F, Villa S, Balzarini A, *et al.* (1998). A randomized, controlled clinical trial to evaluate the effects of zinc sulfate on cancer patients with taste alterations caused by head and neck irradiation. *Cancer* 82:1938-1945.
Roesink JM, Konings AW, Terhaard CH, Battermann JJ, Kampinga

HH, Coppes RP (1999). Preservation of the rat parotid gland function after radiation by prophylactic pilocarpine treatment: radiation dose dependency and compensatory mechanisms. *Int J Radiat Oncol Biol Phys* 45:483-489.

Roesink JM, Moerland MA, Battermann JJ, Hordijk GJ, Terhaard CH (2001). Quantitative dose-volume response analysis of changes in parotid gland function after radiotherapy in the head-and-neck region. *Int J Radiat Oncol Biol Phys* 51:938-946.

Russell NS (2000). Individual variation in normal tissue reactions to radiotherapy: correlations with radiobiological parameters (thesis). Amsterdam: Free University of Amsterdam.

's-Gravenmade EJ, Roukema DA, Panders AK (1974). The effects of mucin-containing artificial saliva on severe xerostomia. *Int J Oral Surg* 3:435-439.

Samarawickrama DYD (2002). Saliva substitutes: how effective and safe are they? *Oral Diseases* 8:177-179.

Sangthawan D, Watthanaarpornchai S, Phungrassami T (2001). Randomized double blind, placebo-controlled study of pilocarpine administered during head and neck irradiation to reduce xerostomia. *J Med Assoc Thai* 84:195-203.

Schiødt M, Hermund NU (2002). Management of oral disease prior to radiation therapy. *Support Care Cancer* 10:40-43.

Schwartz HC, Kagan AR (2002). Osteoradionecrosis of the mandible. Scientific basis for clinical staging. *Am J Clin Oncol (CCT)* 25:168-171.

Scully C, Epstein JB (1996). Oral health care for the cancer patient. *Oral Oncol Eur J Cancer* 32B:281-292.

Senahayake F, Piggott K, Hamilton-Miller JMT (1998). A pilot study of Salix SST (saliva stimulating lozenges) in post-irradiation xerostomia. *Curr Med Res Opin* 14:155-159.

Shannon IL, McCrary BR, Starcke EN (1977). A saliva substitute for use by xerostomic patients undergoing radiotherapy to the head and neck. *Oral Surg* 44:656-661.

Shannon IL, Trodahl JN, Starcke EN (1978). Remineralization of enamel by a saliva substitute designed for use by irradiated patients. *Cancer* 41:1746-1750.

Silverman S, Chierici G (1965). Radiation therapy of oral carcinoma. I. Effects on oral tissues and management of the periodontium. *J Periodontol* 36:478-484.

Sonis ST, Woods PD, White A (1990). Pretreatment oral assessment. *NCI Monogr* 9:29-32.

Sonis ST, Eilers JP, Epstein JB, LeVeque FG, Liggett WH, Mulagha MT, *et al.* (1999). Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. *Cancer* 85:2103-2113.

Spak CJ, Johnson G, Ekstrand J (1994). Caries incidence, salivary flow rate and efficacy of fluoride gel treatment in irradiated patients. *Caries Res* 28:388-393.

Spielman AI (1998). Chemosensory function and dysfunction. *Crit Rev Oral Biol Med* 9:267-291.

Spijkervet FKL, van Saene HKF, Panders AK, Vermey A, Mehta DM (1989a). Scoring irradiation mucositis in head and neck cancer patients. *J Oral Pathol Med* 18:167-171.

Spijkervet FKL, van Saene HKF, Panders AK, Vermey A, Metha DM, Fidler V (1989b). Effect of chlorhexidine rinsing on the oropharyngeal ecology in patients with head and neck cancer who have irradiation mucositis. *Oral Surg Oral Med Oral Pathol* 67:154-161.

Spijkervet FKL, van Saene HKF, van Saene JJM, Panders AK, Vermey A, Mehta DM (1990). Mucositis prevention by selective elimination of oral flora in irradiated head and neck cancer patients. *J Oral Pathol Med* 19:486-489.

Spijkervet FKL, van Saene HKF, van Saene JJM, Panders AK, Vermey A, Mehta DM, *et al.* (1991). Effect of selective elimination of the oral flora on mucositis in irradiated head and neck cancer patients. *J Surg Oncol* 46:167-173.

Sreebny LM, Zhu WX, Schwartz SS, Meek AG (1995). The preparation of an autologous saliva for use with patients undergoing therapeutic radiation for head and neck cancer. *J Oral Maxillof Surg* 53:131-139.

Starcke EN, Shannon IL (1977). How critical is the interval between extractions and irradiation in patients with head and neck malignancy. *Oral Surg Oral Med Oral Pathol* 43:333-337.

Stevenson-Moore P (1990). Essential aspects of a pretreatment oral examination. *NCI Monogr* 9:33-36.

Stewart CM, Jones AC, Bates RE, Sandow P, Pink F, Stillwell J (1998). Comparison between saliva stimulants and a saliva substitute in patients with xerostomia and hyposalivation. *Spec Care Dentist* 18:142-148.

Sutherland SE, Browman GP (2001). Prophylaxis of oral mucositis in irradiated head and neck cancer patients: a proposed classification scheme of interventions and meta-analysis of randomized controlled trials. *Int J Radiat Oncol Biol Phys* 49:917-930.

Symonds RP, McIlroy P, Khorrami J, Paul J, Pyper E, Alcock SR, *et al.* (1996). The reduction of radiation mucositis by selective decontamination antibiotic pastilles: a placebo-controlled double-blind trial. *Br J Cancer* 74:312-317.

Tenovuo J (2002). Clinical applications of antimicrobial host proteins lactoperoxidase, lysozyme and lactoferrin in xerostomia: efficacy and safety. *Oral Diseases* 8:23-29.

Thorn JJ, Sand Hansen H, Specht L, Bastholt L (2000). Osteoradionecrosis of the jaws: clinical characteristics and relation to the field of irradiation. *J Oral Maxillofac Surg* 58:1088-1093.

Toljanic JA, Heshmati RH, Bedard JF (2002). Dental follow-up compliance in a population of irradiated head and neck cancer patients. *Oral Surg Oral Med Oral Pathol Endod* 93:35-38.

Tomita Y, Osaki T (1990). Gustatory impairment and salivary gland pathophysiology in relation to oral cancer treatment. *Int J Oral Maxillofac Surg* 19:299-304.

Tong AC, Leung AC, Cheng JC, Sham J (1999). Incidence of complicated healing and osteoradionecrosis following tooth extraction in patients receiving radiotherapy for treatment of nasopharyngeal carcinoma. *Aust Dent J* 44:187-194.

Valdez IH, Wolff A, Atkinson JC, Macynski AA, Fox PC (1993). Use of pilocarpine during head and neck radiation therapy to reduce xerostomia and salivary dysfunction. *Cancer* 71:1848-1851.

Van der Reijden WA, Veerman ECI, Nieuw Amerongen AV (1994). Rheological properties of commercially available polysaccharides with potential use in saliva substitutes. *Biorheology* 31:631-642.

Van der Reijden WA, Van der Kwaak H, Vissink A, Veerman ECI, Van Nieuw Amerongen A (1996). Treatment of xerostomia with polymer-based saliva substitutes in patients with Sjögren's syndrome. *Arthritis Rheum* 39:57-69.

Van der Reijden WA, Buijs MJ, Damen JJ, Veerman ECI, Ten Cate JM, Nieuw Amerongen AV (1997). Influence of polymers for use in saliva substitutes on de- and remineralization of enamel in vitro. *Caries Res* 31:216-223.

Visch LL, 's-Gravenmade EJ, Schaub RMH, Van Putten WLJ, Vissink A (1986). A double-blind crossover trial of CMC- and mucin-containing saliva substitutes. *Int J Oral Maxillofac Surg* 15:395-400.

Vissink A, 's-Gravenmade EJ, Panders AK, Vermey A, Petersen JK, Visch LL, *et al.* (1983). A clinical comparison between commercially available mucin- and CMC-containing saliva substitutes. *Int J Oral Surg* 12:232-238.

Vissink A, Waterman HA, 's-Gravenmade EJ, Panders AK. Vermey A (1984). Rheological properties of saliva substitutes containing

mucin, carboxymethylcellulose or polyethylenoxide. *J Oral Pathol* 13:22-28.
Vissink A, 's-Gravenmade EJ, Gelhard TBFM, Panders AK, Franken MH (1985). Rehardening properties of mucin- or CMC-containing saliva substitutes on softened human enamel. Effects of sorbitol, xylitol and increasing viscosity. *Caries Res* 19:212-218.
Vissink A, de Jong HP, Busscher HJ, Arends J, 's-Gravenmade EJ (1986). Wetting properties of human saliva substitutes. *J Dent Res* 65:1121-1124.
Vissink A, Schaub RMH, van Rijn LJ, 's-Gravenmade EJ, Panders AK, Vermey A (1987). The efficacy of mucin-containing artificial saliva in alleviating symptoms of xerostomia. *Gerodontology* 6:95-101.
Vissink A, Panders AK, 's-Gravenmade EJ, Vermey A (1988a). The causes and consequences of hyposalivation. *Ear Nose Throat J* 67:166-176.
Vissink A, 's Gravenmade EJ, Panders AK, Vermey A (1988b). Treatment of hyposalivation. *Ear Nose Throat J* 67:179 185.
Vissink A, Jansma J, Spijkervet FKL, Burlage FR, Coppes RP (2003). Oral sequelae of head and neck radiotherapy. *Crit Rev Oral Biol Med* 14:199-212.
Vitolo JM, Baum BJ (2002). The use of gene transfer for the protection and repair of salivary glands. *Oral Diseases* 8:183-191.
Wagner W, Alfrink M, Haus U, Matt J (1999). Treatment of irradiation-induced mucositis with growth factors (rhGM-CSF) in patients with head and neck cancer. *Anticancer Res* 19:799-804.
Weerkamp AH, Wagner K, Vissink A, 's-Gravenmade EJ (1987). Effect of the application of a mucin-based saliva substitute on the oral microflora of xerostomic patients. *J Oral Pathol* 16:474-478.
Wiesenfeld D, Stewart AM, Mason DK (1983). A critical assessment of oral lubricants in patients with xerostomia. *Br Dent J* 155:155-157.
Wijers OB, Levendag PC, Harms ER, Gan-Teng AM, Schmitz PI, Hendriks WD, *et al.* (2001). Mucositis reduction by selective elimination of oral flora in irradiated cancers of the head and neck: a placebo-controlled double-blind randomized study. *Int J Radiat Oncol Biol Phys* 50:343-352.
Worthington HV, Clarkson JE, Eden OB (2002). Interventions for treating oral mucositis for patients with cancer receiving treatment (Cochrane Review). In: The Cochrane Library; Issue 1. Oxford: Update Software.
Wright WE (1990). Pretreatment oral health care interventions for radiation patients. *NCI Monogr* 9:57-59.
Wu Q, Manning M, Schmidt-Ullrich R, Mohan R (2000). The potential for sparing of parotids and escalation of biologically effective dose with intensity-modulated radiation treatments of head and neck cancers: a treatment design study. *Int J Radiat Oncol Biol Phys* 46:195-205.
Yusof ZW, Bakri MM (1993). Severe progressive periodontal destruction due to radiation tissue injury. *J Periodontol* 64:1253-1258.
Zheng C, Baum BJ, Iadarola MJ, O'Connell BC (2000). Genomic integration and gene expression by a modified adenoviral vector. *Nat Biotech* 18:176-180.
Zimmerman RP, Mark RJ, Tran LM, Juillard GF (1997). Concomitant pilocarpine during head and neck irradiation is associated with decreased posttreatment xerostomia. *Int J Radiat Oncol Biol Phys* 37:571-575.
Zimmermann JS, Niehoff P, Wilhelm R, Schneider R, Kovàcs G, Kimmig B (1998). Prophylaxe und Therapie akuter Strahlenfolgen an Haut und Sleimhaut. Teil II: Empfehlungen der Literatur. *Strahlenther Onkol* 174:187-192.