

Critical Reviews in Oral Biology & Medicine

<http://cro.sagepub.com>

ORAL SEQUELAE OF HEAD AND NECK RADIOTHERAPY

A. Vissink, J. Jansma, F.K.L. Spijkervet, F.R. Burlage and R.P. Coppes

Crit. Rev. Oral Biol. Med. 2003; 14; 199

DOI: 10.1177/154411130301400305

The online version of this article can be found at:
<http://cro.sagepub.com/cgi/content/abstract/14/3/199>

Published by:



<http://www.sagepublications.com>

On behalf of:

International and American Associations for Dental Research

Additional services and information for *Critical Reviews in Oral Biology & Medicine* can be found at:

Email Alerts: <http://cro.sagepub.com/cgi/alerts>

Subscriptions: <http://cro.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

ORAL SEQUELAE OF HEAD AND NECK RADIOTHERAPY

A. Vissink^{1*}
J. Jansma¹
F.K.L. Spijkervet¹
F.R. Burlage²
R.P. Coppes^{2,3}

¹Department of Oral and Maxillofacial Surgery and ²Department of Radiotherapy, University Hospital, PO Box 30.001, 9700 RB Groningen, the Netherlands; and ³Department 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: In addition to anti-tumor effects, ionizing radiation causes damage in normal tissues located in the radiation portals. Oral complications of radiotherapy in the head and neck region are the result of the deleterious effects of radiation on, *e.g.*, salivary glands, oral mucosa, bone, dentition, masticatory musculature, and temporomandibular joints. The clinical consequences of radiotherapy include mucositis, hyposalivation, taste loss, osteoradionecrosis, radiation caries, and trismus. Mucositis and taste loss are reversible consequences that usually subside early post-irradiation, while hyposalivation is normally irreversible. Furthermore, the risk of developing radiation caries and osteoradionecrosis is a life-long threat. All these consequences form a heavy burden for the patients and have a tremendous impact on their quality of life during and after radiotherapy. In this review, the radiation-induced changes in healthy oral tissues and the resulting clinical consequences are discussed.

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

Introduction

In addition to anti-tumor effects, ionizing irradiation causes damage in normal tissues located in the field of radiation. This becomes particularly evident in the head and neck region, a complex area composed of several dissimilar structures that respond differently to radiation: mucosal linings, skin coverings, subcutaneous connective tissue, salivary gland tissue, teeth, and bone/cartilage. Acute changes produced by radiotherapy are observed in the oral mucosa (erythema, pseudomembrane-covered ulceration), salivary glands (hyposalivation, changed salivary composition), taste buds (decreased acuity), and skin (erythema, desquamation). Late changes can occur in all tissues (Cooper *et al.*, 1995; Taylor and Miller, 1999). Although thorough protocols have been developed to minimize or manage the early and late oral sequelae of radiotherapy of the head and neck region (Jansma *et al.*, 1992; Scully and Epstein, 1996; Schiødt and Hermund, 2002), the consequences of radiation-induced salivary gland injury and the other oral sequelae of head and neck radiotherapy are still difficult to manage.

In this review, the radiation-induced changes in healthy oral tissue and the resulting clinical consequences are discussed. The radiation-related changes in the oral mucosa, salivary glands, taste, dentition, periodontium, bone, muscles, and joints are discussed in the order that they appear. They can be divided into early (mucosa, taste, salivary glands), intermediate (taste, salivary glands), and late (salivary glands, dentition, periodontium, bone, muscles, joints) effects.

Radiotherapy

Radiotherapy plays an important role in the management of head and neck cancer. The majority of new cases of invasive head and neck cancer will need radiotherapy as a primary treatment, as an adjunct to surgery, in combination with chemotherapy, or as palliation (Dobbs *et al.*, 1999). The radiation dose needed for the treatment of cancer is based on location and type of malignancy, and whether or not radiotherapy will be used solely or in combination with other modalities. Most patients with head and neck carcinomas, treated with a curative intent, receive a dose between 50 and 70 Gy. This dose is usually given over a five- to seven-week period, once a day, five days a week, 2 Gy *per* fraction (Dobbs *et al.*, 1999). The total dose for pre-operative radiotherapy or radiotherapy for malignant lymphomas is usually lower.

Fractionated radiation is used because there is a difference in the responses of tumor tissue and normal tissue. In general, normal tissue repairs sublethal DNA damage, especially in the low-dose range, better than tumor tissue. Giving radiation in 2-Gy fractions magnifies the differences in responses between tumor and normal tissues. The sparing effect of fractionated radiation is the largest for late-responding tissues, whereas early-responding tissues respond more like tumor tissue. Next to DNA-repair advantages, fractionated irradiation allows for the repopulation of tissue between fractions (especially during the weekend, when the tumor and normal tissues are not irradiated), thereby reducing early effects. This, however, also applies for rapidly proliferating malignant tissue. Another

advantage is that fractionated irradiation allows for re-oxygenation of radio-resistant hypoxic tumors between fractions, leading to a higher percentage of radiosensitive oxygenated cells (Steel, 2002; Hall, 2000).

The most important dose-limiting factor is the tolerance of the adjacent normal tissues. Depending on stage and location of the primary tumor and affected lymph nodes, the oral cavity, salivary glands, and jaws of most head and neck cancer patients may be located in the radiation portals. Even with the most optimal radiotherapeutic schedule, unwanted radiation-induced changes will occur in these tissues. Tissues with rapid turnover rates show acute reactions to radiotherapy (early effects), while in tissues with slower turnover rates, damage may not become evident for months or years after therapy (late effects) (Steel, 2002; Hall, 2000). Since the overall five-year rate for oral cancer survival is about 80% for the early stages of oral cancer and about 35% for advanced stages, the objective of effective cancer therapy includes preservation of normal tissue function and reducing injury as much as possible. Several strategies to increase the tumor control probability (TCP) without increasing or even reducing the normal tissue complication probability (NTCP) have been developed and tested in clinical practice or are currently the subject of clinical trials. Based on the above-mentioned radiobiological assumptions, alternative fractionation schemes like hyperfractionation and accelerated fractionation, techniques that reduce the irradiated volume (3D conformal radiation therapy and intensity-modulated radiotherapy; Horiot *et al.*, 1994; Eisbruch *et al.*, 1996; Russell, 2000; Wu *et al.*, 2000), and schemes which increase oxygenation of tumor tissues (Kaanders *et al.*, 2002) have been developed.

Accelerated fractionation and hyperfractionation seem to be effective strategies for improving tumor control. Hyperfractionation makes use of the difference between the repair capabilities between tumor and normal tissue by further fractionation of the dose to a 1.15 Gy-fraction, for example. For overall conventional treatment time to be maintained, 2 fractions *per* day are given. With this type of fractionation, the total absorbed tumor dose can be increased while not adding to late toxicity. In contrast, accelerated schedules reduce overall treatment time. Accelerated fractionation is based on the observation that radiation injury causes accelerated proliferation of tumor tissue, and shortening of the treatment time would overcome this problem. The fractions typically are given twice a day. Both approaches have been shown to result in a modest gain in curing head and neck cancer when tested in randomized trials (Garden, 2001). Also, combinations of hyperfractionated and accelerated schedules have been shown to be especially successful for rapidly dividing tumors (Awwad *et al.*, 2002). The disadvantage of these new treatment techniques is the higher rates of acute toxicity, especially mucositis. The addition of chemotherapy may, next to systemic cytotoxicity, introduce an exacerbated local tissue reaction (Bensadoun *et al.*, 2001). To reduce chronic and acute tumor hypoxia, investigators have developed "ARCON", which combines accelerated radiotherapy to counteract tumor repopulation with carbogen breathing and nicotinamide to increase oxygenation. Very high local and regional tumor control rates were observed, with an increase in acute toxicity and late morbidity within acceptable limits, although there is some concern regarding late complications in bone (Kaanders *et al.*, 2002). Further reduction of the irradiated volume of normal tissue by means of new computerized planning techniques seems to be the next step.

Three-dimensional (3D) conformal radiation therapy is a treatment technique designed to shape the spatial distribution of the high radiation dose to the target volume, thereby reducing the dose delivered to the normal tissues. Intensity-modulated radiotherapy (IMRT) is even more conformal than the 3D conformal techniques, since this new technique optimally assigns weights to individual rays of a beam as opposed to a single weight to the beam as a whole. The latter makes it possible to produce dose distribution patterns that are much closer to the desired patterns than previously possible, thus optimally minimizing the dose to normal tissues. Completely different treatment plans are constructed in which a smaller volume of tissue receives a high dose of irradiation and a large volume (mostly the whole organ) receives a low dose. Current investigations in our laboratories address the question of whether there are regional differences in radiosensitivity within a particular tissue. Another issue that warrants study is the effect of a low dose to a large volume *vs.* a high dose to a small volume. Mathematical modeling of the data may lead, in the future, to a prediction of the NTCP with each treatment plan (Schilstra and Meertens, 2001).

Oral Mucosa

Damage to oral mucosa is strongly related to radiation dose, fraction size, volume of irradiated tissue, fractionation scheme, and type of ionizing irradiation (Maciejewski *et al.*, 1991; Scully and Epstein, 1996; Denham *et al.*, 1999; Handschel *et al.*, 1999). Oral side-effects develop early during radiotherapy (Dörr and Kummermehr, 1990; Denham *et al.*, 1999). The acute mucosal response to radiotherapy is a result of mitotic death of epithelial cells, since the cell cycle time of the basal keratinocytes is about four days (Scully and Epstein, 1996).

Mucositis induced by radiotherapy is defined as the reactive inflammation of the oral and oropharyngeal mucous membrane during radiotherapy in the head and neck region. It is characterized by atrophy of squamous epithelial tissue, absence of vascular damage, and an inflammatory infiltrate concentrated at the basement region (Handschel *et al.*, 1999). Radiation mucositis is an inevitable but transient side-effect (Spijkervet *et al.*, 1989; Maciejewski *et al.*, 1991; Scully and Epstein, 1996; Denham *et al.*, 1999). It is an integral part of radiotherapy in terms of morbidity, since during a course of curative radiation about 80% of the patients will develop pseudomembranous mucositis. The early radiation reaction causes local discomfort as well as difficulties in drinking, eating, swallowing, and speech. Therefore, it can give rise to nutritional problems, and in severe cases nasogastric feeding, which is very uncomfortable, may become necessary (Donaldson, 1977; Beumer *et al.*, 1979a,b; Wood *et al.*, 1989; Jansma *et al.*, 1992; Lees, 1999; Mekhail *et al.*, 2001). About 20-30% of the patients will need artificial feeding. Severe mucositis may necessitate an interruption of the course of radiotherapy and thus can serve as a dose-limiting factor (Denham *et al.*, 1999; Sonis *et al.*, 1999). Such interruptions must be prevented, because they may result in prolongation of treatment time and thus a reduction in therapeutic effect (Fowler, 1986). As mentioned before, hyperfractionation, accelerated fractionation, and radiochemotherapy, although especially successful for the treatment of rapidly dividing tumors, result in higher rates of acute toxicity, especially mucositis (Bensadoun *et al.*, 2001; Awwad *et al.*, 2002).

Various signs of mucositis may emerge during radiothera-

py (Spijkervet *et al.*, 1989; Scully and Epstein, 1996; Riesenbeck *et al.*, 1998; Denham *et al.*, 1999; Handschel *et al.*, 1999). The first clinical signs of mucositis occur at the end of the first week of a conventional seven-week radiation protocol (daily dose of 2 Gy, five times a week). There is no consensus regarding what is the first sign of mucositis. Some authors describe a white discoloration of the oral mucosa, which is an expression of hyperkeratinization as the first symptom, followed by or in combination with erythema (Spijkervet *et al.*, 1989; Scully and Epstein, 1996). Others consider erythema to be the first reaction (Dreizen *et al.*, 1977b; Riesenbeck *et al.*, 1998; Sonis *et al.*, 1999). Using a mouse model, Dörr and Kummermehr (1990) explain the mucosal changes following radiation as follows. The lack of formation of new basal cells caused by radiotherapy leads to a gradual, linear decrease in cell numbers. If the cellularity of the mucosa drops below 70% of the normal level, the cell production rate from the surviving cells increases dramatically (a possible cause for the whitish aspect of oral mucosa). As radiotherapy continues, a steady state between mucosal cell killing and mucosal cell regeneration may occur and favor an acute reaction in the form of a prominent erythema. Around the third week of radiotherapy, more severe symptoms of mucositis, such as the formation of pseudomembranes and ulceration, may appear (Dreizen *et al.*, 1977b; Spijkervet *et al.*, 1989). Some authors consider pseudomembranes to be ulcers covered by fibrinous exudate (Maciejewski *et al.*, 1991; Riesenbeck *et al.*, 1998). Others suggest that pseudomembranous mucositis is related to yeast stomatitis (Ramirez-Amador *et al.*, 1997) or to colonization of the oral cavity with Gram-negative bacilli (Spijkervet *et al.*, 1990, 1991; Martin and van Saene, 1992). In their mouse model, Dörr and Kummermehr (1990) explained the development of pseudomembranes, when radiotherapy commences, as a cell regeneration process that cannot keep up with cell killing. As a result, partial or complete epithelial denudation develops, which presents as spotted or confluent pseudomembranous mucositis. Healing eventually occurs from the surviving mucosal stem cells. Similar changes have been observed in humans, in whom the mucositis is characterized by loss of epithelial cells, absence of vascular damage, and an inflammatory reaction at the epithelial-connective tissue interface (Handschel *et al.*, 1999). Briefly, mucositis generally persists throughout radiotherapy, is maximum at the end of the irradiation period, and continues for one to three weeks after treatment has ceased (Scully and Epstein, 1996).

The severity of mucositis varies considerably between patients (Denham *et al.*, 1999) and may relate to the fractionation schedule applied. Accelerated fractionation results in a more rapid onset of mucositis (Maciejewski *et al.*, 1991; Denham *et al.*, 1999). Furthermore, the mucosa of the oral cavity does not react in the same manner at all locations. Mucositis is most severe in the soft palate, followed, in order, by the mucosa of the hypopharynx, floor of the mouth, cheek, base of the tongue, lips, and dorsum of the tongue. Patients with compromised oral mucous membranes secondary to alcoholism and/or excessive smoking exhibit the most severe mucosal changes (Beumer *et al.*, 1979a,b; Rugg *et al.*, 1990).

Mucositis is basically a tissue reaction to the trauma of radiation (Maciejewski *et al.*, 1991; Scully and Epstein, 1996; Denham *et al.*, 1999) or chemotherapy (Bensadoun *et al.*, 2001). Other factors that may contribute to the development of mucositis include: the increase in the inflammatory mediator, platelet-activating factor in saliva of irradiated patients

(McManus *et al.*, 1993); leukocyte adhesion to E-selectin or endothelial intercellular adhesion molecule-1 (ICAM-1) which promotes the radiation-induced inflammatory response in squamous epithelium (Handschel *et al.*, 1999); a decrease in the level of salivary epidermal growth factor (Dumbrigue *et al.*, 2000); and an increase in the carriage rate of Gram-negative bacilli in the oropharynx (among others *Enterobacteriaceae*, *Pseudomonaceae*) (Spijkervet *et al.*, 1989; Martin and van Saene, 1992; Scully and Epstein, 1996). This marked increase in oral Gram-negative enterobacteria and pseudomonads has particularly been shown as a possible aggravating factor for development of oral mucositis (Spijkervet *et al.*, 1990, 1991). Less than 10% of healthy individuals exhibit colonization of the oral cavity with these non-indigenous Gram-negative bacilli (Yourassowsky *et al.*, 1987). This is due to the oropharyngeal colonization defense, which is determined by the integrity of the anatomical structures, physiology, motility, secretions, secretory immunoglobulin A, mucosal cell turnover, and the indigenous flora. These factors are impaired by radiotherapy for head and neck cancer and are negatively influenced by more generalized factors, such as advanced age, medical interventions (*e.g.*, surgery), and underlying disease. Selective elimination of Gram-negative bacilli was associated with a reduction of pseudomembranes and ulceration (Spijkervet *et al.*, 1990, 1991). These authors postulated that Gram-negative bacilli or endotoxin released by Gram-negative bacilli could play a major role in the development of the advanced stages of radiation mucositis, while the initial signs are basically related to irradiation only (Spijkervet *et al.*, 1990, 1991).

The most common infection in the oral cavity during or shortly after radiotherapy is candidiasis (Epstein, 1990; Ramirez-Amador *et al.*, 1997). Many patients become colonized intra-orally with *Candida albicans* during radiotherapy (Chen and Webster, 1974). Ramirez-Amador *et al.* (1997) showed that the prevalence of positive *Candida* cultures increased from 43% at baseline to 62% at completion of radiotherapy and to 75% during the follow-up period. Some authors believe that oral mucositis is aggravated by fungal infections (Beumer *et al.*, 1979a,b; Al-Tikriti *et al.*, 1984). However, treatment of yeast and Gram-positive cocci with topical anti-fungals and disinfectants failed to relieve such complications (Chen and Webster, 1974; Martin and van Saene, 1992; Wijers *et al.*, 2001). Thus, many of the oral lesions observed during treatment do not seem to be due to candidiasis or streptococcal infection. Finally, it should be mentioned that herpes simplex virus infection is not a significant contributing factor in irradiation mucositis. This is in contrast to the commonly seen herpes simplex virus re-activation following chemotherapy and radiochemotherapy patients (Redding *et al.*, 1990; Scully and Epstein, 1996).

In summary, although the etiopathogenesis of radiation mucositis still is not fully clear, it most likely can be considered as a four-step inflammation consisting of an inflammatory/vascular phase, an epithelial phase, a bacterial phase, and a healing phase. This sequence of phases has been proposed by Sonis (1998) for chemotherapy-induced stomato-toxicity, but probably also holds true for radiation mucositis. This, however, does not necessarily imply that the treatments for chemotherapy- and radiation-induced mucositis are similar, since many of the treatments to alleviate stomato-toxicity resulting from chemotherapy have been shown to be ineffective for radiation-induced mucositis (Vissink *et al.*, 2003).

Taste

Alteration in taste is an early response to radiation and often precedes mucositis. Radiotherapy to the head and neck affects taste thresholds, food intake, chewing, the hedonics of tasting (Beidler and Smith, 1991; Spielman, 1998), and may result in weight loss (Erkurt *et al.*, 2000). Most patients experience partial or complete loss of taste acuity during radiotherapy (Beumer *et al.*, 1979a, b). Conger (1973) found that taste sensation decreases exponentially with a cumulative dose of about 30 Gy (3 weeks), 2 Gy *per* fraction, after which it becomes virtually absent. The loss in perception of all flavors rarely occurs (Toljanic and Saunders, 1984). Perception of bitter and acid flavors is more susceptible to impairment than perception of salt and sweet flavors (Mossman *et al.*, 1982). The loss of taste is not only a result of the effect of irradiation on the taste buds, but is also related to the reduction in salivary flow rate. A reduced salivary flow decreases transport and solubilization of gustatory stimulants, reduces the ability of saliva to protect the mucosa against bacteria, fungi, and variation in the oral pH, alters the ionic composition of saliva which is important for taste, and affects mastication, nutrition, and the hedonic aspects of tasting (Spielman, 1998).

Direct radiation damage to the taste buds or their innervating nerve fibers has been reported as the main cause of taste loss (Conger, 1973; Dreizen *et al.*, 1977b; Mossman, 1986). Histologically, taste buds showed signs of degeneration and atrophy at 10 Gy (2 Gy *per* day), while at therapeutic levels the architecture of the buds was almost completely destroyed (Conger, 1973).

Loss of taste is usually transient (Tomita and Osaki, 1990). Taste gradually returns to normal or near-normal levels within one year after radiotherapy, although it can take as long as five years. The degree of taste recovery and the recovery time depend on the radiation dose received. Some patients may retain a residual reduction in taste acuity (hypogeusia), or even a permanent impairment in sensation (dysgeusia) (Conger, 1973; Dreizen *et al.*, 1977b; Mossman *et al.*, 1982; Toljanic and Saunders, 1984), but near-normal suprathreshold levels of taste in irradiated patients have been reported as well (Schwartz *et al.*, 1993; Spielman, 1998). These obvious discrepancies between measurable taste loss and subjective awareness of taste loss may be due to adaptation of the patient to the sensory loss (Mossman *et al.*, 1982).

Taste impairment has profound effects on the nutritional status of the patient and is associated with weight loss through reduced appetite and altered patterns of food intake. This is due not only to the loss of taste *per se*, but to the non-equal impairment of the perception of the various flavors as well. The result is that food tastes different, and often unpleasant, after radiation therapy, a fact which, of course, many patients do not appreciate. Also, further studies are needed to evaluate the effect of irradiation on von Ebner's glands and the residual flow from these glands. This may be sufficient to obscure the interpretation of currently available data (Spielman, 1998). If so, radiotherapy treatment plans should attempt to spare these glands if possible.

Salivary Glands

Based on the slow turnover rates of their cells, the salivary glands are expected to be relatively radio-resistant. Yet the changes in quantity and composition of saliva that occur shortly after radiotherapy indicate that the gland tissue is an acutely responding tissue (Vissink *et al.*, 1992; Taylor and Miller,

1999; O'Connell, 2000; Burlage *et al.*, 2001; Nagler, 2002). It is not clear whether the direct effects of radiation on the secretory and ductal cells cause radiation damage of salivary gland tissue, or if it is secondary to injury of the fine vascular structures, increased capillary permeability, interstitial edema, and inflammatory infiltration. In a human *post mortem* study, it has been assessed that, in the lower dose range (< 30 Gy), damage is reversible to a certain level, but after cumulative doses (> 75 Gy), extensive degeneration of acini is observed, along with inflammation and fibrosis in the interstitium (Dreyer *et al.*, 1989). As treatment continues, there is progressive degeneration of the acinar epithelium and development of interstitial fibrosis. Serous acinar cells appear to be more readily affected by irradiation than mucous acinar cells and ductal cells (Kashima *et al.*, 1965; Seifert and Geier, 1971; Dreyer *et al.*, 1989). From non-human primate experiments, it was concluded that the acute functional impairment was caused directly by serous acinar apoptotic cell death rather than being the result of inflammatory processes and circulatory compromise due to vascular injury (Stephens *et al.*, 1989). Also, the later loss of function is not thought to be due to chronic inflammation or fibrosis of the glandular tissue (O'Connell *et al.*, 1999). The most likely course of radiation-related events that occur in rat parotid salivary gland tissue has been recently described by Coppes *et al.* (2001). They observed four phases in the radiation-induced loss of salivary gland function. The first phase (0-10 days) was characterized by a rapid decline in flow rate without changes in amylase secretion or acinar cell number. The second phase (10-60 days) consisted of a decrease in amylase secretion and was paralleled by acinar cell loss. Flow rate, amylase secretion, and acinar cell numbers did not change in the third phase (60-120 days). The fourth phase (120-240 days) was characterized by a further deterioration of gland function but an increase in acinar cell number, albeit with poor tissue morphology. Comparable changes have been observed in rat submandibular tissue (Zeilstra *et al.*, 2000; Coppes *et al.*, 2002).

The early response in gland function has been studied thoroughly in rats (Vissink *et al.*, 1990; Franzén *et al.*, 1991; Nagler *et al.*, 1993; Coppes *et al.*, 1997a,b, 2000, 2001; Zeilstra *et al.*, 2000). Within three days after irradiation with a single dose of 15 Gy of x-rays, a decrease in salivary flow of nearly 50% can be observed (Vissink *et al.*, 1990; Peter *et al.*, 1995; Coppes *et al.*, 1997a,b, 2001; Zeilstra *et al.*, 2000). Lack of obvious quantitative morphological alterations (Franzén *et al.*, 1991; Henricksson *et al.*, 1994; Zeilstra *et al.*, 2000; Coppes *et al.*, 2001), a rather quick recovery of the morphological changes if they occur (Vissink *et al.*, 1991), and a lack of increase in apoptotic cells early after radiotherapy (Paardekooper *et al.*, 1998) point to the presence of altered cell membranes (Sodicoff *et al.*, 1974; El Mofty and Kahn, 1981; Vissink *et al.*, 1992) and/or a disturbed intracellular signaling (Vissink *et al.*, 1991; Coppes *et al.*, 1997b) as the cause of the early effect of radiation on the parotid gland. This was confirmed in an *in vitro* study showing that muscarinic receptor-induced calcium mobilization and protein kinase C activation were affected (Coppes and Kampinga, 2001). The late effects of radiation on the parotid and submandibular glands have been studied less extensively, and have been reported as a dose-dependent further decline in function (Nagler *et al.*, 1998; Coppes *et al.*, 2001) and loss of acinar cells (Henricksson *et al.*, 1994; O'Connell *et al.*, 1999). Unfortunately, in the latter studies the whole or half of the head including the glands was irradiated. Therefore, indirect effects due to dam-

age to other organs confound the interpretation with regard to salivary gland function (Nagler, 2001; Konings *et al.*, 2002).

Also, in humans, depending on the localization of the radiation portals, a rapid decrease of the salivary flow rate is observed during the first week of radiotherapy, after which there is a gradual decrease to less than 10% of the initial flow rate (Fig. 1) (Dreizen *et al.*, 1976; Shannon *et al.* 1978b; Liu *et al.*, 1990; Franzén *et al.*, 1991; Valdez *et al.*, 1993; Jones *et al.*, 1996; Burlage *et al.*, 2001). Although in the older literature the submandibular gland was thought to be less radiosensitive than the parotid gland, both glands have been shown to be as sensitive to radiotherapy, at least with respect to their function (Liu *et al.*, 1990; Valdez *et al.*, 1993; Burlage *et al.*, 2001). In rats, it has been shown that the submandibular gland may be even more sensitive to the late effects of radiation, due to its inability to restore the damage (Coppes *et al.*, 2002), but it remains to be established if it is true for humans. It has been suggested that the final degree of radiation-induced hyposalivation depends on individual patient characteristics, such as pre-irradiation salivary gland activity, age, and sex (Eneroth *et al.*, 1972a,b; Mira *et al.*, 1981). It has been stated that salivary glands with high flow rates before the initiation of radiotherapy show less reduction in salivary flow rate (Eneroth *et al.*, 1972a,b; Mira *et al.*, 1981, 1982), but this observation could not be confirmed in recent dose-volume studies (Eisbruch *et al.*, 1999, 2001; Roesink *et al.*, 2001). Clinically, of more importance is the observation that the irradiated volume of salivary gland tissue correlates directly with the severity of oral complications (Cheng *et al.*, 1981; Mira *et al.*, 1981; Tsujii, 1985; Liu *et al.*, 1990; Hazuka *et al.*, 1993; Jones *et al.*, 1996; Nishioka *et al.*, 1997; Eisbruch *et al.*, 1999, 2001; Wu *et al.*, 2000; Roesink *et al.*, 2001). The implementation of alternative fractionation schedules, like hyperfractionation and accelerated fractionation, to reduce the side-effects of radiotherapy on normal tissues has also been proposed (Leslie and Dishe, 1991, 1994), but its effect on salivary gland function and morphology is negligible (Price *et al.*, 1995; Coppes *et al.*, 2002), which is advantageous for tumor control.

The early (Burlage *et al.*, 2001) and late (Liu *et al.*, 1990; Valdez *et al.*, 1993) human data on the radiation-induced severe drop in flow rate of both the parotid and submandibular gland somewhat contradict the functional data derived from scintigraphic studies (Valdés Olmos *et al.*, 1994; Liem *et al.*, 1996). These authors showed a failure of the major salivary glands to excrete saliva early post-irradiation, and a decreased uptake of ^{99m}Tc-pertechnetate together with a loss of secretory function in the post-irradiation stage. This effect was stronger in parotid than in submandibular glands, although the incidence of xerostomia did not correlate with the effects observed in the scintigraphic studies (Liem *et al.*, 1996), once again pointing to the obvious discrepancy between the actual salivary flow and the scintigraphic (Liem *et al.*, 1996) and morphological changes (Vissink *et al.*, 1991) induced by irradiation. Therefore, we strongly suggest that, from a clinical point of view, the combination of objective (measurement of salivary flow rate) and subjective (questionnaires) parameters still provides the best assessment with regard to the pattern of patients' complaints and the effects of various therapies on these complaints.

Recent prospective studies of salivary flow following non-homogeneous irradiation of the parotid glands with fractionated radiotherapy have utilized dose-volume histograms and various models to assess these relationships. These studies found that the mean dose to the gland is correlated with the

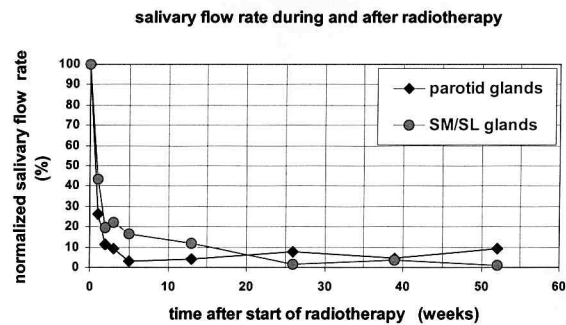


Figure 1. Flow rate of parotid and submandibular-sublingual (SM/SL) saliva as a function of time after start of radiotherapy (conventional fractionation schedule, 2Gy per day, 5 days per week, total dose 60-70 Gy). The parotid, submandibular, and sublingual glands are located in the treatment portal. Initial flow rates were set to 100% (modified after Burlage *et al.*, 2001).

reduction of the salivary output. This is consistent with the suggested parallel architecture of the functional subunits (each functional subunit, *e.g.*, an acinus, functions independently of other subunits, in contrast to serially organized organs, *e.g.*, the spinal cord) of the salivary glands (Eisbruch *et al.*, 2001; Schilstra and Meertens, 2001). The range of the mean doses, which have been found in these studies to cause significant salivary flow reduction, is from 26 to 39 Gy (Kaneko *et al.*, 1998; Eisbruch *et al.*, 2001; Roesink *et al.*, 2001). These calculations, however, have been made with the assumption that the dose on the gland can be averaged disregarding the possibility of regional differences in sensitivity.

Aside from the quantity of saliva, radiotherapy also results in a change of salivary composition. Saliva turns into a very viscous, white, yellow, or brown fluid (Ben-Aryeh *et al.*, 1975; Dreizen *et al.*, 1976). The obvious qualitative salivary changes are a reduced pH and buffering capacity, altered salivary electrolyte levels, and changed non-immune and immune antibacterial systems. The average pH decreases from about 7.0 to 5.0 (Ben-Aryeh *et al.*, 1975; Dreizen *et al.*, 1976). The reduced buffering capacity is primarily due to a reduction of bicarbonate concentration in parotid saliva (Dreizen *et al.*, 1976; Marks *et al.*, 1981). An increase in the concentrations of sodium, chloride, calcium, and magnesium has been reported, while the concentration of potassium is only slightly affected (Ben-Aryeh *et al.*, 1975; Dreizen *et al.*, 1976; Anderson *et al.*, 1981; Valdez *et al.*, 1993). The concentrations of immunoproteins (*e.g.*, sIgA), lysozyme, and lactoferrin are increased (Brown *et al.*, 1976, 1978; Makkonen *et al.*, 1986; Valdez *et al.*, 1993; Almstahl *et al.*, 2001). The decrease in salivary flow rate, however, is greater than the increase in immunoprotein and lysozyme levels, and this results in a significant immunoprotein deficit. Since oral clearance and immunologic mechanisms are potent means of host protection, their compromise is intrinsically related to changes in the oral flora of irradiated patients (Brown *et al.*, 1975). One of the major radiation-induced changes in the oral flora is a pronounced increase in acidogenic, cariogenic microorganisms, at the expense of non-cariogenic microorganisms. The most clinically significant changes are the increase of *Streptococcus mutans*, *Lactobacillus* species, and *Candida* species (Llory *et al.*, 1972; Brown *et al.*, 1978; Keene *et al.*, 1981; Ramirez-

TABLE
Consequences of Radiation-induced Hyposalivation

| | |
|----------------------------------|-----------------------------|
| Dryness of the mouth | Burning sensation |
| Thirst | Taste disturbances |
| Difficulties in oral functioning | Alterations of soft tissues |
| Difficulties in wearing dentures | Shift in oral microflora |
| Nocturnal oral discomfort | Radiation caries |
| Mucus accumulation | Periodontal disease |

Amador *et al.*, 1997; Epstein *et al.*, 1998a). Comparable changes in oral flora have been observed in patients with hyposalivation from other causes, indicating that a low salivary secretion rate mainly promotes a flora associated with the development of dental caries (Almståhl and Wikström, 1999). The major changes in the oral flora as a result of hyposalivation after radiotherapy are observed in the period from the onset of radiotherapy to three months after completion. From the sixth month after radiotherapy, the composition of the oral microflora remains constant or partially returns to baseline composition (Brown *et al.*, 1978).

Saliva is an important host defense component of the oral cavity (Nieuw Amerongen and Veerman, 2002). Thus, the quantitative and qualitative salivary changes predispose the irradiated patient to a variety of problems that develop either directly or as an indirect result of the diminished salivary output. The Table provides a list of the consequences of radiation-induced hyposalivation. Oral function (speech, chewing, and swallowing) is hampered because of, *e.g.*, insufficient wetting and lubrication of the mucosal surfaces. Moreover, swallowing and chewing are impeded because of insufficient moistening of food by saliva (Hamlet *et al.*, 1997). The increased viscosity and reduced flow of saliva cause intolerance to prosthetic appliances. Saliva is an effective lubricant at the denture-mucosal interface. With lesser amounts of saliva present, retention of the denture is poor and more friction is produced during function, which may easily traumatize the vulnerable irradiated oral mucosa. Many patients suffer from nocturnal oral discomfort. They are often awakened at night by a serious dryness of the mouth or have to get up frequently because of polyuria due to polydipsia throughout the day. The oral mucosa can have a dry, atrophic, pale, or hyperemic appearance. The mucosa of the tongue can exhibit similar features or appear fissured. The lips may be dry, cracked, or fissured. These changes in the oral mucosa are, in general, typical for xerostomia of any origin. The shift in oral microflora toward cariogenic bacteria, the reduced salivary flow (oral clearance), and the altered saliva composition (buffer capacity, pH, immunoproteins, oral clearance) may result in rapidly progressing radiation caries, along with a greater incidence of periodontal infections. The caries susceptibility is further increased by altered eating habits. Due to the radiation-mediated changes such as mucositis, atrophy of oral mucous membranes, hyposalivation, and taste loss, the diet of irradiated patients shifts to softer, sticky, carbohydrate-rich foods, with an increase in the frequency of intake—all of which promote caries. The average daily energy intake is about 300 kcal lower in irradiated patients with dry mouth symptoms (Bäckström *et al.*, 1995).

In summary, the salivary glands show, in contrast to the

other tissues, both early *and* late responses to radiation. This probably makes radiation damage to salivary gland tissue the most frequently occurring inconvenient side-effect of head and neck radiation. Unfortunately, although extensively studied, the target of ionizing radiation within salivary gland tissue is still unknown, and thus the treatment strategy is still based mainly on prevention of radiation damage to the salivary gland tissue by careful planning of the radiation portals (Vissink *et al.*, 2003). Most likely, there are different targets for the early and late damage to salivary gland tissue, and prevention and treatment must be directed accordingly.

Dentition

During and following a full course of radiotherapy, many patients experience an increased dental sensitivity to temperature changes and to sweet- and sour-tasting foods which possibly is related to the loss of the protective layer of saliva (Toljanic and Saunders, 1984). The most threatening complication for the dentition, however, is radiation-related caries. Radiation caries is a highly destructive form of dental caries which has a rapid onset and progression (Del Regato, 1939; Frank *et al.*, 1965; Karmiol and Walsh, 1975; Jansma *et al.*, 1993). Dental caries may become evident as early as three months following the initiation of radiotherapy. In severe cases, a previously healthy dentition can be completely lost within a year (Dreizen *et al.*, 1977b).

Clinically, three types of caries lesions can be observed (Del Regato, 1939; Frank *et al.*, 1965; Karmiol and Walsh, 1975). All three types of lesions can be observed within the same mouth. In view of the rapid progression, it is surprising that there is rarely any acute pain associated with radiation caries, even in its most severe manifestations. The histological features of the initial radiation caries lesions are similar to those observed in normal incipient dental caries lesions (Jongebloed *et al.*, 1988; Jansma *et al.*, 1993), but erosive types of lesions can be observed as well (Jansma *et al.*, 1993).

The first type is a frequently observed lesion that starts on the labial surface at the cervical area of the incisors and canines. Initially, the lesion extends superficially around the entire cervical area of the tooth, and then progresses inward, often resulting in complete amputation of the crown. In the region of the molars, complete amputation of the tooth occurs less frequently; however, the caries tends to spread over all surfaces of the molar with changes in translucency and color leading to increased friability and breakdown of the tooth. Occasionally, only a rapid wearing away of the incisal and occlusal surfaces of the teeth is seen either with or without cervical lesions.

The second type of lesion is a generalized superficial defect that first affects the buccal and later the lingual or palatal surfaces of the tooth crowns. The proximal surfaces are less affected. This lesion often begins as a diffuse, punctate defect and then progresses to generalized, irregular erosion of the tooth surfaces. In this type of lesion, decay localized at the incisal or occlusal edges is often observed. The result is a destruction of the coronal enamel and dentin, especially on the buccal and palatal surfaces.

The third type is less frequently observed. It consists of a heavy brown-black discoloration of the entire tooth crown, accompanied by wearing away of the incisal and occlusal surfaces.

Besides the rapid onset and progression, radiation caries is most commonly found on tooth surfaces (buccal, labial, lingual, palatal, incisal, occlusal) that are normally relatively immune to

dental caries. The areas just below the contact points seem to be the last areas to be affected by radiation caries. Furthermore, the mandibular anterior teeth, which normally are the teeth most resistant to caries, are equally if not more affected by radiation caries (Karmioli and Walsh, 1975). The characteristic attack on normally caries-immune, self-cleansing areas may be caused by changes in salivary flow and consistency that give rise to accumulation of a highly acidogenic dental plaque on these surfaces, and the result is a rapid decalcification of enamel.

It has always been a matter of debate whether radiation caries is due to a direct or indirect effect of irradiation on teeth, or to both. Several investigators have reported that the development of radiation caries was not dependent on the presence of teeth in the field of irradiation, but that the determining factor was whether the main salivary glands were within the radiation field (Del Regato, 1939; Frank *et al.*, 1965; Karmioli and Walsh, 1975; Brown *et al.*, 1976; Dreizen *et al.*, 1976). Notwithstanding the study by Grötz *et al.* (1997), which showed that irradiation also resulted in dentinal changes in vital teeth, the current opinion still is that radiation caries is mainly due to salivary gland damage resulting in hyposalivation (Jansma *et al.*, 1989; Joyston-Bechal *et al.*, 1992; Spak *et al.*, 1994; Al-Nawas *et al.*, 2000; Kielbassa *et al.*, 2001). Thus, collectively, hyposalivation-related alterations in microbial, chemical, immunologic, and dietary parameters of cariogenicity contribute to an enormous increase in the caries challenge in irradiated patients (Dreizen *et al.*, 1977a,b). This enormous caries challenge becomes even more obvious since both loss of enamel (type II lesion) and severe destruction at the dentin-enamel junction (type I lesion) can be observed within a few weeks of exposure of enamel slabs in the oral cavities of patients with radiation-induced hyposalivation (Jansma *et al.*, 1988b). The changes observed were similar to the changes occurring in natural hyposalivation-related dental caries (Jansma *et al.*, 1993). So both the coronal enamel and the cervical area, where cementum or dentin is directly exposed to the oral environment, are areas at risk in dry-mouth patients. Clinically, the most striking and most difficult to treat phenomenon is the type I, wrapping around, caries lesion at the base of the crown which often results in an amputation of the crown. The mechanism behind and treatment of this type of lesion need further study.

Whether a direct effect of irradiation on teeth, other than the already-mentioned dentinal changes in vital teeth, also contributes to the development of radiation caries has not been fully elucidated, and reports are contradictory. Some investigators have reported that irradiated teeth decalcify more readily than non-irradiated teeth (Castanera *et al.*, 1963), while others noted no differences in decalcification rates *in vitro* (Wiemann *et al.*, 1972; Walker, 1975; Shannon *et al.*, 1978a) or even reported decreased enamel and dentin solubility after therapeutic radiation (Joyston-Bechal, 1985; Jansma *et al.*, 1988a; Kielbassa *et al.*, 1999, 2002). Also, it has been shown that ionizing irradiation of dental enamel, at a therapeutic level, has no influence on its permeability and thus on the organic component of enamel (Jansma *et al.*, 1990). In addition, there are some indications that the mechanical properties of enamel and, to a lesser extent, dentin deteriorate after exposure to radiation (Al-Nawas *et al.*, 2000), but again, this effect is of minor significance, and indeed xerostomia-related changes constitute the major contributory factor in the development of radiation caries.

High levels of radiation exposure can markedly affect tooth development. The extent of the effect is dependent on the

radiation dose and the stage of tooth development (Gorlin and Mishkin, 1963). In general, there is agreement that odontogenic cells in the pre-formative and differentiation phases are more radiosensitive than cells in the secretory or mature stage. If exposure to irradiation occurs before calcification, the tooth bud may be destroyed. Radiation at a later stage of development may arrest further growth and result in irregularities in enamel and dentin together with shortened roots (Scheibe *et al.*, 1980; Dahllöf *et al.*, 1994b; Kaste *et al.*, 1994). According to Scheibe *et al.* (1980), tooth eruption is mostly delayed but not hindered, but this phenomenon still needs further study.

In summary, the effects of radiation on the dentition are predominantly thought to be indirect, mainly caused by the reduced salivary flow rate and its related consequences. Prevention therefore has to be directed to the treatment of xerostomia-related complaints, meticulous oral hygiene, change of diet, control of cariogenic flora, and prevention of caries with frequent fluoride applications (Vissink *et al.*, 2003).

Periodontium

Decreased vascularity and acellularity of the periodontal membrane with rupturing, thickening, and disorientation of Sharpey's fibers and widening of the periodontal space have been reported after irradiation (Silverman and Chierici, 1965; Anneroth *et al.*, 1985). Others, however, found normal alignment of periodontal fibers (Scheibe *et al.*, 1980). The cementum appears completely acellular, and its capacity for repair and regeneration is severely compromised (Silverman and Chierici, 1965). Early changes include radiographic widening of the periodontal ligament spaces and destruction of bony trabeculae (Fujita *et al.*, 1986).

The changes in cementum and periodontal ligament may predispose individuals to infection (Schüle and Betzhold, 1969). The risk of periodontal infection is also increased due to radiation-induced hyposalivation, the concomitant increased plaque accumulation and shift in oral microflora (Markitziu *et al.*, 1992; Position paper, 1997; Leung *et al.*, 1998). However, the major components of the subgingival flora of shallow pockets in head- and neck-irradiated individuals are similar to those of gingivitis sites in the normal population, although they may contain bacterial or fungal species that are uncommon in normal subjects (Leung *et al.*, 1998). That the prevalence of (advanced) periodontal disorders is somewhat lower in irradiated patients than expected is probably related to the development of dental caries: If radiation caries develops, its progression is often so fast that the affected teeth are lost before (advanced) periodontal pathosis can occur.

The direct and indirect effects of high-dose radiotherapy on the periodontium result in an increased risk of periodontal attachment loss and tooth loss, and even in an increased risk for the development of osteoradionecrosis (Yusof and Bakri, 1993; Epstein *et al.*, 1998b). This underscores the need for proper pre- and post-irradiation treatment planning (Jansma *et al.*, 1992; Position paper, 1997; Epstein *et al.*, 1998b; Epstein and Stevenson-Moore, 2001; Schiødt and Hermund, 2002).

Bone

The gross changes in the bone matrix after irradiation develop relatively slowly. The initial changes in bone result from injury to the remodeling system (osteocytes, osteoblasts, and osteoclasts). Osteoblasts tend to be more radiosensitive than osteoclasts; thus a relative increase in the lytic activity may occur.

Whether the altered bone remodeling activity is the result of direct irradiation injury to the cells of the remodeling system or the indirect result of irradiation-induced vascular injury, or a combination of both phenomena, is still a matter of debate. Radiation injury to the fine vasculature of bone and its surrounding tissues first leads to hyperemia, followed by endarteritis, thrombosis, and a progressive occlusion and obliteration of small vessels. Within bone, this results in a further reduction of the number of cells and progressive fibrosis. With time, the marrow exhibits marked acellularity and hypo- or avascularity, with significant fibrosis and fatty degeneration. Some lacunae may become devoid of osteocytes. The endosteum atrophies, with significant loss of active osteoblasts and osteoclasts. The periosteum demonstrates significant fibrosis, with a similar loss of remodeling elements (Silverman and Chierici, 1965; Dreizen *et al.*, 1977b; Beumer *et al.*, 1979a,b; Marx and Johnson, 1987; Constantino *et al.*, 1995). Marx and Johnson (1987) found hypovascularity and fibrosis to be the common end-stage of irradiation-induced tissue injury. Taken together, these observations lead to the obvious conclusion that irradiated bone is likely to respond poorly to trauma and infection.

The most severe potential complication of bone irradiation is osteoradionecrosis. The incidence of osteoradionecrosis of the mandible varies from 2.6% to 22%; the range is most commonly from 5% to 15% in recent reports (Constantino *et al.*, 1995; Epstein *et al.*, 1997; Thorn *et al.*, 2000). The incidence of osteoradionecrosis of the maxilla is much lower (Curi and Dib, 1997; Tong *et al.*, 1999; Thorn *et al.*, 2000).

The definition of osteoradionecrosis is "bone death secondary to radiotherapy" (Marx and Johnson, 1987; Constantino *et al.*, 1995). Some authors have advocated using the more general term "osteonecrosis", since necrosis of bone and soft tissue can also occur in other conditions, including cancer patients receiving chemotherapy and in diabetics (Epstein *et al.*, 1987a,b). The latter authors have stressed that in radiotherapy, the exposure of soft and hard tissues—with subsequent hypoxia, hypovascularity, and hypocellularity—markedly increases the risk of necrosis. For those cases, they proposed the term "post-radiation osteonecrosis", but in this paper the more commonly used term "osteoradionecrosis" is used. The diagnosis of osteoradionecrosis is based mainly on patient history and clinical signs such as severe pain, non-healing (exposed) bone within the treatment area after completion of radiotherapy, and repeated infections. This process may progress to fistula or sequester formation and eventual spontaneous fracture (Marx, 1983a,b; Epstein *et al.*, 1987a,b, 1997; Constantino *et al.*, 1995; Thorn *et al.*, 2000). The presenting lesion (*e.g.*, superficial involvement *vs.* localized or diffuse involvement of the mandible) dictates the treatment protocol to be followed and stresses the need for an effective clinical staging system (Epstein *et al.*, 1997; Schwartz and Kagan, 2002; Vissink *et al.*, 2003).

In the early literature, the pathogenesis of osteoradionecrosis of the jaws was regarded as the inevitable triad sequelae of radiation, trauma, and infection (Watson and Scarborough, 1938; Meyer, 1958, 1970). In this concept, trauma serves as a portal of entry for oral bacteria into the underlying bone. Osteoradionecrosis is thus considered to be an infectious process, which progresses rapidly and spreads throughout the bone that cannot wall off the infection because of compromised vascularity and minimal regenerative capabilities. The source of trauma may be anything, including denture irritation, sharp

or hard food particles, and sharp bony ridges. Tooth removal is said to be the most common cause of trauma (Meyer, 1970). Later, Marx (1983a,b) suggested that the underlying problem in osteoradionecrosis is a compromised wound-healing rather than an infection. Furthermore, osteoradionecrosis is as much a disease process of the covering soft tissues as that of the underlying bone (Epstein *et al.*, 1987a,b, 1997; Constantino *et al.*, 1995; Curi and Dib, 1997; Thorn *et al.*, 2000). According to Marx (1983a,b), the sequence in the development of osteoradionecrosis is:

- (a) radiation;
- (b) hypoxic-hypovascular-hypocellular tissue: the ability of bone to replace normal collagen loss or normal cellular loss is severely compromised or non-existent;
- (c) tissue breakdown: unrelated to micro-organisms but related to the degree of radiation damage and the rate of normal or induced cellular death (Collagen lysis and cell death exceed synthesis and cellular replication.); and
- (d) chronic non-healing wounds: energy, oxygen, and metabolic demands exceed the supply.

Conceptually, spontaneous and trauma-induced osteoradionecrosis are different entities. Spontaneous osteoradionecrosis, which has been reported to occur in almost 35% of all cases of osteoradionecrosis, is related to increased age, high radiation dose (> 65 Gy), field of radiation (volume of the mandible included in the field and proximity of maximal dosing to bone), hyperfractionation, use of implant sources too close to the bone, and combined interstitial and external beam irradiation (Murray *et al.*, 1980a; Marx, 1983a,b; Marx and Johnson, 1987; Kluth *et al.*, 1988; Constantino *et al.*, 1995; Glanzmann and Grätz, 1995; Curi and Dib, 1997; Tong *et al.*, 1999; Thorn *et al.*, 2000). It represents a greater outright cellular kill of normal tissue elements, and an inability of soft and hard tissue to sustain cell turnover and collagen synthesis. This type of necrosis usually occurs within the first 2 years after radiotherapy (Marx, 1983a,b; Marx and Johnson, 1987; Thorn *et al.*, 2000), but it can occur at any time following irradiation (Epstein *et al.*, 1997; Thorn *et al.*, 2000). However, late cases mostly occur as a result of trauma (Thorn *et al.*, 2000).

Trauma-induced osteoradionecrosis represents a mixture of cell death and cell injury. As the years pass after irradiation, the tissue becomes more fibrotic and more hypovascular. If the tissue is traumatized by surgical procedures (*e.g.*, extractions) or by persistent infection, it is suddenly required to meet the demands of wound healing. The reduced healing capacity may result in osteoradionecrosis—a risk which increases with time (Marx and Johnson, 1987; Constantino *et al.*, 1995; Curi and Dib, 1997; Thorn *et al.*, 2000). Several pre- and post-irradiation factors may increase the risk of osteoradionecrosis. Pre-irradiation extraction followed by inadequate healing time is known to predispose to osteoradionecrosis (Marx and Johnson, 1987; Constantino *et al.*, 1995; Tong *et al.*, 1999). In edentulous patients, the osteoradionecrosis risk is increased after radiotherapy if there is a trauma in the radiation field, such as tooth removal or other surgical procedures (periodontal procedures, biopsies), poor oral hygiene and inadequate home care, and ongoing periodontal or periapical infection (Murray *et al.*, 1980b; Marx and Johnson, 1987; Epstein *et al.*, 1997; Tong *et al.*, 1999). In edentulous patients, trauma induced by prosthetic appliances is regarded as a predisposing factor (Dreizen *et al.*, 1977b), especially when related to certain mastication and parafunctional habits (Marunick and Leveque, 1989). However, the use of

implants can minimize the trauma induced by prosthetic appliances. To date, no cases of osteoradionecrosis related to dental implants have been reported. In both the irradiated mandible and the maxilla, the placement of implants seems to be a reliable procedure, at least in the short term (Esser and Wagner, 1997; Niimi *et al.*, 1998).

In summary, osteoradionecrosis is a very unfortunate complication of head and neck radiotherapy that may result in loss of a significant volume of bone, mostly mandibular. Prevention of this condition has to be achieved by all means, since its treatment is difficult and time-consuming and causes much discomfort to the patient (Vissink *et al.*, 2003).

Muscles and Joints

Trismus, or limited jaw opening, may develop due to tumor invasion of the masticatory muscles and/or the temporomandibular joint (TMJ), or be the result of radiotherapy if masticatory muscles and/or the TMJ is included in the field of radiation, or a combination of both (Steelman and Sokol, 1986; Ichimura and Tanaka, 1993; Dahllöf *et al.*, 1994a; Goldstein *et al.*, 1999). The limited jaw opening interferes with oral hygiene, speech, nutritional intake, examination of the oropharynx, and dental treatment, and can be particularly discomfiting to the patient.

Trismus occurs with unpredictable frequency and severity. Generally, trismus develops three to six months after radiation treatment is completed and frequently becomes a lifelong problem (Ichimura and Tanaka, 1993). Trismus is attributed to muscle fibrosis and scarring in response to radiation injury as well as to fibrosis of the ligaments around the TMJ and scarring of the pterygo-mandibular raphes (Steelman and Sokol, 1986; Dahllöf *et al.*, 1994a). Besides tumor growth and surgical procedures, the severity of trismus is dependent on the configuration of the radiation field (unilateral or bilateral), the radiation source, and the radiation dose (Wollin *et al.*, 1976; Goldstein *et al.*, 1999). It has been reported that trismus develops after high radiation doses to the TMJ only (Ichimura and Tanaka, 1993), while other authors reported that trismus may already develop after low doses and increases with increasing doses (Dahllöf *et al.*, 1994a; Goldstein *et al.*, 1999). The most decisive factor which determines whether trismus will develop is probably the inclusion of the pterygoid muscles in the treatment portals (Goldstein *et al.*, 1999). This may explain the differences observed among the various studies reported in the literature.

Nutritional Status

Several studies have shown that up to 60% of head and neck cancer patients were nutritionally compromised at initial diagnosis (Donaldson and Lenon, 1979; Bassett and Dobie, 1983; Wood *et al.*, 1989; Bäckström *et al.*, 1995; Lees, 1999; Van Bokhorst-van der Schueren *et al.*, 2001). A pre-operative weight loss of 10% of body weight has been reported as a predictive risk factor for major post-operative complications (Van Bokhorst-van der Schueren *et al.*, 1997). During radiotherapy, oral intake of food may be impeded due to mucositis, loss of taste acuity, hyposalivation, and changes in viscosity of saliva. Fig. 2 outlines the time frame involved in the development of each particular problem. Pain during chewing and swallowing due to mucositis or yeast stomatitis which predisposes the patient to lose appetite, nausea, and malaise may further decrease the nutritional status and result in significant weight loss (Beumer *et al.*, 1979a,b; Bassett and Dobie, 1983; Logemann

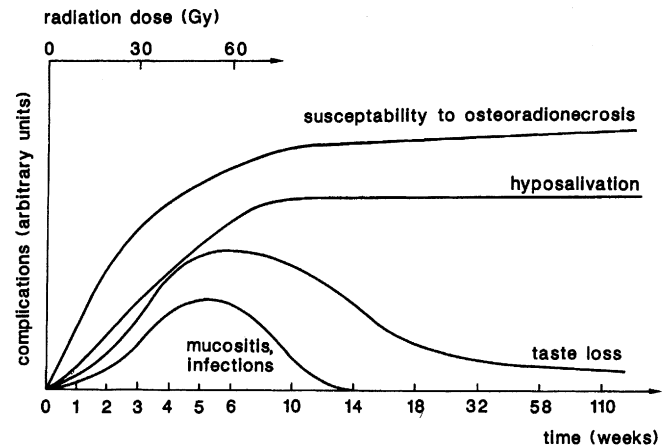


Figure 2. Schematic diagram illustrating time of onset and duration of radiation-induced oral sequelae (modified after Maxymiw and Wood, 1989).

et al., 2001). The more frequent use of intensive chemoradiotherapy in head and neck cancer exacerbates this problem, since swallowing dysfunction is prevalent after such therapy (Eisbruch *et al.*, 2002). Donaldson and Lenon (1979) reported that their patients lost about 3.7 kg during the course of radiation therapy, while Beumer *et al.* (1979a,b) reported weight losses of 7-11 kg not to be uncommon. In general, it can be stated that a 10% loss of body weight is not uncommon following head and neck radiotherapy (Lees, 1999). In severe cases of weight loss, enteral nutrition either by, *e.g.*, a nasogastric tube or a percutaneous endoscopic gastrostomy (PEG) may become necessary (Magne *et al.*, 2001; Mekhail *et al.*, 2001). Patients often prefer a PEG rather than a nasogastric tube, but it has been reported that a PEG is often required for longer periods of time and is associated with more persistent dysphagia and an increased need for pharyngo-esophageal dilatation (Mekhail *et al.*, 2001). These observations need further study. Weight loss leads to weakness, inactivity, discouragement, anorexia, and susceptibility to infection. It has been postulated that patients with a good nutritional and emotional status have improved tumor response to both radiotherapy and chemotherapy (Copeland *et al.*, 1979), but this hypothesis still needs to be validated (Van Bokhorst-van der Schueren *et al.*, 2001). In addition, the early and late morbidity of radiation treatment is less in patients who are in good health (Van Bokhorst-van der Schueren *et al.*, 1997). It is therefore of the utmost importance that a good nutritional and positive emotional status be maintained in the head and neck receiving radiotherapy.

Epilogue

The early and late sequelae of head and neck radiotherapy have a large impact on the quality of life (Vissink *et al.*, 1987; Epstein *et al.*, 1999; Ohrn *et al.*, 2001). Although the pathogenesis of many of the oral sequelae of head and neck radiotherapy is not fully understood, the radiation-induced side-effects often can be reduced with appropriate prevention and/or treatment. Notwithstanding the reduction of these side-effects that currently can be achieved, many patients will continue to experience these side-effects to some extent. In addition, appropriate prevention and treatment of both early and late radiation mor-

bility also become increasingly important, because more and more patients with head and neck cancer will be cured. In a separate review, the prevention and treatment considerations are discussed (Vissink *et al.*, 2003).

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

- Al-Nawas B, Grötz KA, Rose E, Duschner H, Kann P, Wagner W (2000). Using ultrasound transmission velocity to analyse the mechanical properties of teeth after in vitro, in situ, and in vivo irradiation. *Clin Oral Invest* 4:168-172.
- Al-Tikriti U, Martin MV, Bramley A (1984). A pilot study of the clinical effects of irradiation on the oral tissues. *Br J Oral Maxillofac Surg* 22:77-86.
- Almståhl A, Wikström M (1999). Oral microflora in subjects with reduced salivary secretion. *J Dent Res* 78:1410-1416.
- Almståhl A, Wikström M, Groenink J (2001). Lactoferrin, amylase and mucin MUC5B and their relation to the oral microflora in hyposalivation of different origins. *Oral Microbiol Immunol* 16:345-352.
- Anderson MW, Izutsu KT, Rice JC (1981). Parotid gland pathophysiology after mixed gamma and neutron irradiation of cancer patients. *Oral Surg* 52:495-500.
- Anneroth G, Holm LE, Karlsson G (1985). The effect of radiation on teeth. A clinical, histological and microradiographic study. *Int J Oral Surg* 14:269-274.
- Awwad HK, Lotayef M, Shouman T, Begg AC, Wilson G, Bentzen SM, *et al.* (2002). Accelerated hyperfractionation (AHF) compared to conventional fractionation (CF) in the postoperative radiotherapy of locally advanced head and neck cancer: influence of proliferation. *Br J Cancer* 86:517-523.
- Bäckström I, Funegård U, Andersson I, Franzén L, Johansson I (1995). Dietary intake in head and neck irradiated patients with permanent dry mouth symptoms. *Oral Oncol Eur J Cancer* 31(B):253-257.
- Bassett MR, Dobie RA (1983). Patterns of nutritional deficiency in head and neck cancer. *Otolaryngol Head Neck Surg* 91:119-125.
- Beidler LM, Smith JC (1991). Effects of radiation therapy and drugs on cell turnover and taste. In: Smell and taste in health and disease. Getchell TV, Doty RL, Bartoshuk LM, Snow JB Jr, editors. New York: Raven Press, pp. 753-763.
- Ben-Aryeh H, Gutman D, Szargel R, Laufer D (1975). Effects of irradiation on saliva in cancer patients. *Int J Oral Surg* 14:205-210.
- 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, 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.
- Brown LR, Dreizen S, Handler S, Johnston DA (1975). The effect of radiation-induced xerostomia on human oral microflora. *J Dent Res* 54:740-750.
- Brown LR, Dreizen S, Rider LJ, Johnston DA (1976). The effect of radiation-induced xerostomia on saliva and serum lysozyme and immunoglobulin levels. *Oral Surg Oral Med Oral Pathol* 1:83-92.
- Brown LR, Dreizen S, Daly TE, Drane JB, Handler S, Riggan LJ, *et al.* (1978). Interrelations of oral microorganisms, immunoglobulins, and dental caries following radiotherapy. *J Dent Res* 57:882-893.
- Burlage FR, Coppes RP, Meertens H, Stokman MA, Vissink A (2001). Parotid and submandibular/sublingual flow during high dose radiotherapy. *Radiother Oncol* 61:271-274.
- Castanera TJ, Jones DC, Kimeldorf DJ (1963). Gross dental lesions in the rat induced by x-ray and neutrons. *Radiat Res* 20:577-580.
- Chen TY, Webster JH (1974). Oral Monilia study on patients with head and neck cancer during radiotherapy. *Cancer* 34:246-249.
- Cheng VST, Downs J, Herbert D, Aramany M (1981). The function of the parotid gland following radiation therapy for head and neck cancer. *Int J Radiat Oncol Biol Phys* 7:253-258.
- Conger AD (1973). Loss and recovery of taste acuity in patients irradiated to the oral cavity. *Radiat Res* 53:338-347.
- 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.
- Copeland EM, Daly JM, Ota DM, Dudrick SJ (1979). Nutrition, cancer, and intravenous hyperalimentation. *Cancer* 43:2108-2116.
- Coppes RP, Kampinga HH (2001). Early radiation-induced loss of rat salivary gland function is not due to apoptotic or necrotic cell death but to impaired intracellular signalling. *ERRS Newsletter* 9:2-3.
- 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, Roffel AF, Zeilstra LJW, Vissink A, Konings AWT (2000). Early radiation effects on muscarinic receptor-induced secretory responsiveness of the parotid gland in the freely moving rat. *Radiat Res* 53:339-346.
- 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.
- Coppes RP, Vissink A, Konings AWT (2002). Comparison of radiosensitivity of rat parotid and submandibular glands after different radiation schedules. *Radiother Oncol* 63:321-328.
- 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.
- Dahllöf G, Krekmanova L, Kopp S, Borgström B, Forsberg CM, Ringden O (1994a). Craniomandibular dysfunction in children treated with total-body irradiation and bone marrow transplantation. *Acta Odontol Scand* 52:99-105.
- Dahllöf G, Rozell B, Forsberg CM, Borgström B (1994b). Histologic changes in dental morphology induced by high dose chemotherapy and total body irradiation. *Oral Surg Oral Med Oral Pathol* 77:56-60.
- 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.
- Denham JW, Peters LJ, Johansen J, Poulsen M, Lamb DS, Hindley A, *et al.* (1999). Do acute mucosal reactions lead to consequen-

- tial late reactions in patients with head and neck cancer? *Radiother Oncol* 52:157-164.
- Dobbs J, Barrett A, Ash D (1999). Practical radiotherapy planning. London: Arnold.
- Donaldson SS (1977). Nutritional consequences of radiotherapy. *Cancer Res* 37:2407-2413.
- Donaldson SS, Lenon RA (1979). Alterations of nutritional status: impact of chemotherapy and radiation therapy. *Cancer* 43:2036:2052.
- Dörr W, Kummermehr J (1990). Accelerated repopulation in mouse tongue epithelium during fractionated irradiation or following single doses. *Radiother Oncol* 17:249-257.
- Dreizen SA, Brown LR, Handler S, Levi BM (1976). Radiation induced xerostomia in cancer patients. *Cancer* 38:273-278.
- 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.
- Dreyer JO, Sakuma Y, Seifert G (1989). Die Strahlen-Sialadenitis. Stadieneinteilung und Immunhistologie, *Pathologe* 10:165-170.
- Dumbrigue HB, Sandow PL, Nguyen KHT, Humphreys-Beher MG (2000). Salivary epidermal growth factor levels decrease in patients receiving radiation therapy to the head and neck. *Oral Surg Oral Med Oral Pathol Radiol Endod* 89:710-716.
- Eisbruch A, Ship JA, Martel MK, Ten Haken RK, Marsch LH, Wolf GT, et al. (1996). Parotid gland sparing in patients undergoing bilateral head and neck irradiation: techniques and early results. *Int J Radiat Oncol Biol Phys* 36:469-480.
- 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, Hyungjin MK, Ten Haken RK (2001). Partial radiation of the parotid gland. *Semin Radiat Oncol* 11:234-239.
- Eisbruch A, Lyden T, Bradford CR, Dawson LA, Haxer MJ, Miller AE, et al. (2002). Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 53:23-28.
- El Mofty SK, Kahn AJ (1981). Early membrane injury in lethally irradiated salivary gland cells. *Int J Radiat Biol* 9:55-62.
- Eneroth CM, Henrikson CO, Jakobsson PA (1972a). Pre-irradiation qualities of a parotid gland in predicting the grade of functional disturbance by radiotherapy. *Acta Otolaryngol* 7:436-444.
- Eneroth CM, Henrikson CO, Jakobsson PA (1972b). Effect of fractionated radiotherapy on salivary gland function. *Cancer* 30:1147-1153.
- Epstein JB (1990). Infection prevention in bone marrow transplantation and radiation patients. *NCI Monogr* 9:73-85.
- Epstein JB, Stevenson-Moore P (2001). Periodontal disease and periodontal management in patients with cancer. *Oral Oncol* 37:613-619.
- Epstein JB, Wong FLW, Spinelli J, 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, van der Meij E, McKenzie M, Wong FLW, Lepawsky M, Stevenson-Moore P (1997). Postirradiation necrosis of the mandible. A long-term follow-up study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 83:657-662.
- Epstein JB, Chin EA, Jacobson JJ, Rishiraj B, Le N (1998a). The relationships among fluoride, cariogenic oral flora, and salivary flow rate during radiation therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 86:286-292.
- Epstein JB, Lunn R, Le N, Stevenson-Moore P (1998b). 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, Phillips N, Stevenson-Moore P, et al. (1999). Quality of life and oral function following radiotherapy for head and neck cancer. *Head Neck* 21:1-11.
- Erkurt E, Erkisi M, Tunali C (2000). Supportive treatment in weight-losing cancer patients due to the additive adverse effects of radiation treatment and/or chemotherapy. *J Exp Clin Cancer Res* 19:431-439.
- Esser E, Wagner W (1997). Dental implants following radical oral cancer surgery and adjuvant radiotherapy. *Int J Oral Maxillofac Implants* 12:552-557.
- Fowler JF (1986). Potential for increasing the differential response between tumors and normal tissue: can proliferation rate be used? *Int J Radiat Oncol Biol Phys* 12:641-646.
- Frank RM, Herdly J, Philippe E (1965). Acquired dental defects and salivary gland lesions after irradiation for carcinoma. *J Am Dent Assoc* 70:868-883.
- Franzén L, Funegård U, Sundström S, Gustafsson H, Danielsson A, Henriksson R (1991). Fractionated irradiation and early changes in salivary glands. Different effects on potassium efflux, exocytotic amylase release and gland morphology. *Lab Invest* 64:279-283.
- Fujita M, Tanimoto K, Wada T (1986). Early radiographic changes in radiation bone injury. *Oral Surg Oral Med Oral Pathol* 61:641-644.
- Garden AS (2001). Altered fractionation for head and neck cancer. *Oncology (Huntingt)* 15:1326-1332.
- Glanzmann C, Grätz KW (1995). Radionecrosis of the mandible: a retrospective analysis of the incidence and risk factors. *Radiother Oncol* 84:94-100.
- 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.
- Gorlin RJ, Mishkin LH (1963). Severe irradiation during odontogenesis. *Oral Surg* 16:35-38.
- Grötz KA, Duschner H, Kutzner J, Thelen M, Wagner W (1997). Neue Erkenntnisse zur Aetiologie der sogenannten Strahlenkarie. *Strahlenther Onkol* 173:668-676.
- Hall EJ (2000). Radiobiology for the radiobiologist. Philadelphia: Lippincott, Williams and Wilkins.
- Hamlet S, Faull J, Klein B, Aref A, Fontanesi J, Stachler R, et al. (1997). Mastication and swallowing in patients with postirradiation xerostomia. *Int J Radiat Oncol Biol Phys* 37:789-796.
- Handschel J, Prott FJ, Sunderkötter C, Metze D, Meyer U, Joos U (1999). Irradiation induces increase of adhesion molecules and accumulation of β 2-integrin-expressing cell in humans. *Int J Radiat Oncol Biol Phys* 45:475-481.
- 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.
- Henricksson R, Fröjd O, Gustafsson H, Johansson S, Yi-Qing C, Franzén L, et al. (1994). Increase in mast cells and hyaluronic acid correlates to radiation-induced damage and loss of serous acinar cells in salivary glands. The parotid and submandibular glands differ in radiation sensitivity. *Br J Cancer* 69:320-326.
- Horiot JC, Maingon P, Barillot I (1994). Radiotherapy for head and neck cancers including chemoradiotherapy. *Curr Opin Oncol* 6:274-276.
- Ichimura K, Tanaka T (1993). Trismus in patients with malignant

- tumours in the head and neck. *J Craniomandib Prac* 107:1017-1020.
- Jansma J, Buskes JAKM, Vissink A, Metha DM, 's-Gravenmade EJ (1988a). The effect of x-ray irradiation on the demineralization of bovine dental enamel. A constant composition study. *Caries Res* 22:199-203.
- Jansma J, Vissink A, 's-Gravenmade EJ, De Josselin de Jong E, Jongebloed WL, Retief DH (1988b). A model to investigate xerostomia-related dental caries. *Caries Res* 22:357-361.
- 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, Borggreven JMPM, Driessens FCM, 's-Gravenmade EJ (1990). Effect of x-ray irradiation on the permeability of bovine dental enamel. *Caries Res* 24:164-168.
- 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.
- Jansma J, Vissink A, Jongebloed WL, Retief DH, 's-Gravenmade EJ (1993). Natural and induced radiation caries. A SEM study. *Am J Dent* 6:130-136.
- 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.
- Jongebloed WL, 's-Gravenmade EJ, Retief DH (1988). Radiation caries. A review and SEM study. *Am J Dent* 1:139-146.
- Joyston-Bechal S (1985). The effect of x-radiation on the susceptibility of enamel to an artificial caries-like attack *in vitro*. *J Dent* 13:41-44.
- 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.
- Kaanders JH, Pop LA, Marres HA, Bruaset I, van den Hoogen FJ, Merkx MA, *et al.* (2002). ARCON: experience in 215 patients with advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 52:769-778.
- Kaneko M, Shirato H, Nishioka T, Ohmori K, Takinami S, Arimoto T, *et al.* (1998). Scintigraphic evaluation of long-term salivary function after bilateral whole parotid gland irradiation in radiotherapy for head and neck tumour. *Oral Oncol* 34:140-146.
- Karmiol M, Walsh RF (1975). Dental caries after radiotherapy of the oral regions. *J Am Dent Assoc* 91:838-845.
- Kashima HK, Kirkham WR, Andrews JR (1965). Postirradiation sialadenitis: a study of the clinical features, histopathological changes, and serum enzyme variations following irradiation of human salivary glands. *Am J Roentgenol Rad Ther Nucl Med* 94:271-291.
- Kaste SC, Hopkins KP, Jenkins JJ (1994). Abnormal odontogenesis in children treated with radiation and chemotherapy. Imaging finding. *Am J Roentgenol* 162:1407-1411.
- Keene HJ, Daly T, Brown LR, Dreizen S, Drane JB, Horton IM, *et al.* (1981). Dental caries and *Streptococcus mutans* prevalence in cancer patients with irradiation-induced xerostomia: 1-13 years after radiotherapy. *Caries Res* 15:416-427.
- Kielbassa AM, Schulte-Mönting J, Hellwig E (1999). Correlation between microhardness transversal microradiography and *in situ*-induced demineralization in irradiated human dental enamel. *Arch Oral Biol* 44:243-251.
- Kielbassa AM, Shohadai SP, Schulte-Mönting J (2001). Effect of saliva substitutes on mineral content of demineralized and sound dental enamel. *Support Care Cancer* 9:40-47.
- Kielbassa AM, Munz I, Bruggmoser G, Schulte-Mönting J (2002). Effect of demineralization and remineralization on microhardness of irradiated dentin. *J Clin Dent* 13:104-110.
- Kluth EV, Rani Jain P, Stuchell RN, Frich JC (1988). A study of factors contributing to the development of osteoradionecrosis of the jaws. *J Prosthet Dent* 59:194-201.
- Konings AWT, Vissink A, Coppes RP (2002). Comments on extended-term effects of head and neck irradiation in a rodent (Eur J Cancer 37:1938-1945, 2001). *Eur J Cancer* 38:851-852.
- Lees J (1999). Incidence of weight loss in head and neck cancer patients on commencing radiotherapy treatment at a regional cancer centre. *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.
- Leung WK, Jin LJ, Samaranyake LP, Chiu GKC (1998). Subgingival microbiota of shallow periodontal pockets in individuals after head and neck irradiation. *Oral Microbiol Immunol* 13:1-10.
- Liem IH, Valdés Olmos RA, Balm AJM, Keus RB, van Tinteren H, Takes RP, *et al.* (1996). Evidence for early and persistent impairment of salivary gland excretion after irradiation of head and neck tumours. *Eur J Nucl Med* 23:1485-1490.
- Liu RP, Fleming TJ, Toth BB, Keene HJ (1990). Salivary flow rates in patients with head and neck cancer 0.5 to 25 years after radiotherapy. *Oral Surg Oral Med Oral Pathol* 70:724-729.
- Llory H, Dammron A, Gioanni N, Frank RM (1972). Some population changes in oral anaerobic micro-organisms. *Streptococcus mutans* and yeasts following irradiation of the salivary glands. *Caries Res* 6:298-311.
- Logemann JA, Smith CH, Pauloski BR, Rademaker AW, Lazarus CL, Colangelo LA, *et al.* (2001). Effects of xerostomia on perception and performance of swallow function. *Head Neck* 23:317-321.
- 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.
- Magne N, Marcy PY, Foa C, Falewee MN, Schneider M, Demard F, *et al.* (2001). Comparison between nasogastric tube feeding and percutaneous fluoroscopic gastrostomy in advanced and neck cancer patients. *Eur Arch Otorhinolaryngol* 258:89-92.
- Makkonen TA, Tenovu J, Vilja P, Heimdahl A (1986). Changes in the protein composition of whole saliva during radiotherapy in patients with oral or pharyngeal cancer. *Oral Surg Oral Med Oral Pathol* 62:270-275.
- Markitziu A, Zafiroopoulos G, Tsalikis L, Cohen L (1992). Gingival health and salivary function in head and neck-irradiated patients. *Oral Surg Oral Med Oral Pathol* 73:427-433.
- Marks JE, Davis CC, Gottsman VL, Purdy JE, Lee F (1981). The effects of radiation on parotid salivary function. *Int J Radiat Oncol Biol Phys* 7:1013-1019.
- Martin MV, van Saene HKF (1992). The role of microorganisms in cancer therapy. *Oral Maxillofac Surg Infect* 2:81-84.
- Marunick MT, Leveque F (1989). Osteoradionecrosis related to mastication and parafunction. *Oral Surg Oral Med Oral Pathol* 68:582-585.
- Marx RE (1983a). Osteoradionecrosis. A new concept of its pathophysiology. *J Oral Maxillofac Surg* 41:283-288.
- Marx RE (1983b). A new concept in the treatment of osteoradionecrosis. *J Oral Maxillofac Surg* 41:351-357.
- Marx RE, Johnson RP (1987). Studies in the radiobiology of osteoradionecrosis and their clinical significance. *Oral Surg Oral Med Oral Pathol* 64:379-390.
- Maxymiw WG, Wood RE (1989). The role of dentistry in head and neck radiation therapy. *J Canad Dent Assoc* 55:193-198.

- McManus LM, Ostrom KK, Lear C, Luce EB, Gander DL, Pinckard N, *et al.* (1993). Radiation-induced increased platelet-activating factor activity in mixed saliva. *Lab Invest* 68:118-124.
- Mekhail TM, Adelstein DJ, Rybicki LA, Larto MA, Saxton JP, Lavertu P (2001). Enteral nutrition during the treatment of head and neck carcinoma. Is a percutaneous endoscopic gastrostomy tube preferable to a nasogastric tube? *Cancer* 91:1785-1790.
- Meyer I (1958). Osteoradionecrosis of the jaws. In: *Pract Dent Monographs*. Chicago: Year Book, 51 pp.
- Meyer I (1970). Infectious diseases of the jaws. *J Oral Surg* 28:17-22.
- Mira JG, Wescott WB, Starcke EN, Shannon IL (1981). Some factors influencing salivary function when treating with radiotherapy. *Int J Radiol Oncol Phys* 71:535-541.
- Mira JG, Fullerton GD, Wescott WB (1982). Correlation between initial salivary flow rate and radiation dose in production of xerostomia. *Acta Radiol Oncol* 21:151-154.
- Mossman KL (1986). Gustatory tissue injury in man: radiation dose response relationship and mechanism of taste loss. *Br J Cancer* 53:9-11.
- Mossman KL, Shatzman AR, Chencharick JD (1982). Long-term effects of radiotherapy on taste and salivary function in man. *Int J Radiat Oncol Biol Phys* 8:991-997.
- 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, Daly TE, Zimmerman S (1980b). The relationship between dental disease and radiation necrosis of the mandible. *Oral Surg Oral Med Oral Pathol* 49:99-104.
- Nagler RM (1998). Long-term salivary effects of single-dose head and neck irradiation in the rat. *Arch Oral Biol* 43:297-303.
- Nagler RM (2002). The enigmatic mechanism of irradiation-induced damage to the major salivary glands. *Oral Dis* 8:141-146.
- Nagler RM, Baum BJ, Fox PC (1993). Acute effects of x-irradiation on the function of rat salivary gland. *Radiat Res* 136:42-47.
- Nagler RM, Baum BJ, Miller G, Fox PC (2001). Extended-term effects of head and neck irradiation in a rodent. *Eur J Cancer* 37:1938-1945.
- Nieuw Amerongen AV, Veerman ECI (2002). Saliva—the defender of the oral cavity. *Oral Dis* 8:12-22.
- Niimi A, Ueda M, Keller EE, Worthington P (1998). Experience with osseointegrated implants placed in irradiated tissues in Japan and the United States. *Int J Oral Maxillofac Implants* 13:407-411.
- 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.
- O'Connell AC (2000). Natural history and prevention of radiation injury. *Adv Dent Res* 14:57-61.
- O'Connell AC, Redman RS, Evans RL, Ambudkar IS (1999). Radiation-induced progressive decrease in fluid secretion in rat submandibular glands is related to decreased acinar volume and not impaired calcium signalling. *Radiat Res* 151:150-158.
- Ohrn KE, Wahlin YB, Sjoden PO (2001). Oral status during radiotherapy and chemotherapy: a descriptive study of patient experiences and the occurrence of oral complications. *Support Care Cancer* 9:247-257.
- Paardekooper GMRM, Cammelli S, Zeilstra LJW, Coppes RP, Konings AWT (1998). Radiation induced apoptosis is not the cause of acute impairment of rat salivary gland function. *Int J Radiat Biol* 73:641-648.
- Peter B, van Waarde MAWH, Vissink A, 's-Gravenmade EJ, Konings AWT (1995). The role of secretory granules in radiation-induced dysfunction of rat salivary glands. *Radiat Res* 141:176-182.
- Position Paper (1997). Periodontal considerations in the management of the cancer patient. *J Periodontol* 68:791-801.
- Price RE, Ang KK, Stephens LC, Peters LJ (1995). Effects of continuous hyperfractionated accelerated and conventionally fractionated radiotherapy on the parotid and submandibular salivary glands of rhesus monkeys. *Radiother Oncol* 34:39-46.
- Ramirez-Amador V, Silverman S, Mayer P, Tyler M, Quivey J (1997). Candidal colonization and oral candidiasis in patients undergoing oral and pharyngeal radiation therapy. *Oral Surg Oral Med Oral Pathol Radiol Endod* 84:149-153.
- Redding SW, Luce EB, Boren MW (1990). Oral herpes simplex virus infection in patients receiving head and neck radiation. *Oral Surg Oral Med Oral Pathol* 69:578-580.
- Riesenbeck D, Dörr W, Feyerabend T, Fietkau R, Henne K, Richter E, *et al.* (1998). A photographic documentation of acute radiation-induced side effects of the oral mucosa. *Strahlenther Onkol* 174(Suppl III):40-43.
- 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.
- Rugg T, Saunders MI, Dische S (1990). Smoking and mucosal reactions. *Br J Radiol* 63:544-546.
- Russell NS (2000). Individual variation in normal tissue reactions to radiotherapy: correlations with radiobiological parameters (thesis). Amsterdam: Free University of Amsterdam.
- Scheibe B, Düker J, Wannemacher M (1980). Das Zahnwurzelwachstum nach Bestrahlung. Eine tierexperimentelle Studie. *Dtsch Zahnärztl Z* 35:78-81.
- Schilstra C, Meertens H (2001). Calculation of the uncertainty in complication probability for various dose-response models applied to the parotid gland. *Int J Radiat Oncol Biol Phys* 50:147-158.
- Schiødt M, Hermund NU (2002). Management of oral disease prior to radiation therapy. *Support Cancer Care* 10:40-43.
- Schüle H, Betzold J (1969). Experimentelle Untersuchungen über den Einfluss von Röntgenstrahlen auf das marginale Parodontium. *Dtsch Zahnärztl Z* 24:140-143.
- Schwartz HC, Kagan AR (2002). Osteoradionecrosis of the mandible. Scientific basis for clinical staging. *Am J Clin Oncol (CCT)* 25:168-171.
- Schwartz LK, Weiffenbach JM, Valdez IH, Fox PC (1993). Taste intensity performance in patients irradiated to the head and neck. *Physiol Behav* 53:671-677.
- Scully C, Epstein JB (1996). Oral health care for the cancer patient. *Oral Oncol Eur J Cancer* 32(B):281-292.
- Seifert G, Geier W (1971). Zur Pathologie der Strahlen-Sialadenitis. *Z Laryngol Rhinol* 24:376-388.
- Shannon IL, Wescott WB, Starcke EN, Mira J (1978a). Laboratory study of cobalt-60-irradiated human dental enamel. *J Oral Med* 33:23-27.
- Shannon IL, Trodahl JN, Starcke EN (1978b). Radiosensitivity of the human parotid gland. *Proc Soc Exp Biol Med* 157:50-53.
- 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.
- Sodicoff M, Pratt NE, Sholley MM (1974). Ultrastructural radiation injury of rat parotid gland. A histopathological dose response study. *Radiat Res* 58:196-208.
- Sonis ST (1998). Mucositis as a biological process: a new hypothesis for the development of chemotherapy induced stomatotoxicity. *Oral Oncol* 34:34-43.
- 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 (1989). Scoring irradiation mucositis in head and neck cancer patients. *J Oral Pathol Med* 18:167-171.
- 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.
- Steel GG (2002). Basic clinical radiobiology. London: Arnold.
- Steelman R, Sokol J (1986). Quantification of trismus following irradiation of the temporomandibular joint. *MO Dent J* 66:21-23.
- Stephens LC, Schultheiss TE, Kiang Ang K, Peters LJ (1989). Pathogenesis of radiation injury to the salivary glands and potential methods of protection. *Cancer Bull* 41:106-114.
- Taylor SE, Miller EG (1999). Preemptive pharmacologic intervention in radiation-induced salivary dysfunction. *Proc Soc Exp Biol Med* 221:14-26.
- 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, Saunders VW (1984). Radiation therapy and management of the irradiated patient. *J Prosthet Dent* 52:852-858.
- 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.
- Tsujii H (1985). Quantitative dose-response analysis of salivary function following radiotherapy using sequential RI-sialography. *Int J Radiat Oncol Biol Phys* 11:1603-1612.
- Valdés Olmos RA, Keus RB, Takes RP, Van Tinteren H, Baris G, Hilgers FJ, et al. (1994). Scintigraphic assessment of salivary function and excretion response in radiation-induced injury of the major salivary glands. *Cancer* 73:2886-2893.
- Valdez JH, Atkinson JC, Ship JA, Fox PC (1993). Major salivary gland function in patients with radiation-induced xerostomia: flow rates and sialochemistry. *Int J Radiat Oncol Biol Phys* 25:41-47.
- Van Bokhorst-van der Schueren MAE, Van Leeuwen PAM, Sauerwein HP, Kuik DJ, Snow GB, Quak JJ (1997). Assessment of malnutrition parameters in head and neck cancer and their relation to post-operative complications. *Head Neck* 19:419-425.
- Van Bokhorst-van der Schueren MAE, Quak JJ, Von Blomberg-van der Flier BME, Kuik DJ, Langendoen SI, Snow GB, et al. (2001). Effect of perioperative nutrition, with and without arginine supplementation, on nutritional status, immune function, post-operative morbidity, and survival in severely malnourished head and neck cancer patients. *Am J Clin Nutr* 73:323-332.
- 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, 's-Gravenmade EJ, Ligeon EE, Konings AWT (1990). A functional and chemical study of radiation effects on rat parotid and submandibular/sublingual glands. *Radiat Res* 124:259-265.
- Vissink A, Kalicharan D, 's-Gravenmade EJ, Jongebloed WL, Ligeon EE, Nieuwenhuis P, et al. (1991). Acute irradiation effects on morphology and function of rat submandibular glands. *J Oral Pathol Med* 20:449-456.
- Vissink A, Down JD, Konings AWT (1992). Contrasting dose rate effects of gamma-irradiation on rat salivary gland function. *Int J Radiat Biol* 61:275-282.
- Vissink A, Burlage FR, Spijkervet FKL, Jansma J, Coppes RP (2003). Prevention and treatment of the consequences of head and neck radiotherapy. Oral sequelae of head and neck radiotherapy. *Crit Rev Oral Med* 14:213-225.
- Walker R (1975). Direct effect of radiation on the solubility of human teeth *in vitro*. *J Dent Res* 54:901.
- Watson WJ, Scarborough JE (1938). Osteoradionecrosis in intraoral cancer. *Am J Roentgenol* 40:524-534.
- Wiemann MR, Davis MK, Besic FC (1972). Effects of x-radiation on enamel solubility. *J Dent Res* 51:868.
- 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.
- Wollin M, Gilbert HA, Kagan AR (1976). Unequal weighting of given doses in opposed fields in treatment of cancer of the tonsillar region using 60Co, 4-, 8-, 15-, 24-Mvp photons. *Med Phys* 3:113-116.
- Wood RM, Lauder VL, Mosby EL, Hiatt WR (1989). Nutrition and the head and neck cancer patient. *Oral Surg Oral Med Oral Pathol* 68:391-395.
- 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.
- Yourassowsky E, Van der Linden MP, Pardaens Y, Crokaert F, Glupczynski Y (1987). Selection and counting of aerobic Gram-negative bacilli in saliva by the spiral system. *Eur J Clin Microbiol* 6:634-636.
- Yusof ZW, Bakri MM (1993). Severe progressive periodontal destruction due to radiation tissue injury. *J Periodontol* 64:1253-1258.
- Zeilstra LJ, Vissink A, Konings AWT, Coppes RP (2000). Radiation induced cell loss in rat submandibular gland and its relation to gland function. *Int J Radiat Biol* 76:419-429.