Evidence for early and persistent impairment of salivary gland excretion after irradiation of head and neck tumours

Ing Han Liem[1], Renato A. Valdés Olmos[1], Alfons J.M. Balm[2], Ronald B. Keus[3], Harm van Tinteren[4], Robert P. Takes[1], Sara H. Muller[1], Allison M. Bruce[3], Cornelis A. Hoefnagel[1], Frans J. Hilgers[2]

[1] Department of Nuclear Medicine, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[2] Department of Otolaryngology/Head and Neck Surgery, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[3] Department of Radiotherapy, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[4] Department of Biometrics, The Netherlands Cancer Institute, Amsterdam, The Netherlands

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Abstract. Salivary gland scintigraphy with technetium-99m pertechnetate was used to follow changes in the excretion and uptake function of the major salivary glands until 1 year after irradiation. Twenty-five patients who received radiotherapy for head and neck tumours were included in the study. Seventy-nine salivary glands (39 parotid and 40 submandibular) were evaluated in relation to the average received radiation dose. Salivary gland scintigraphy was performed before and 1, 6 and 12 months after radiotherapy. For each gland the excretion response to carbachol, evaluated by calculation of the salivary excretion fraction (SEF), the cumulative gland uptake (CGU) and the absolute excreted activity (AEA) at various intervals after radiotherapy were compared with the baseline values. The excretion response decreased in 20 of 25 patients at 1 month after radiotherapy. One month after radiotherapy both SEF and AEA decreased significantly in relation to the radiation dose. These decreases in excretion parameters persisted during the follow-up period. Parotid excretion was affected significantly more than submandibular excretion. CGU values did not change significantly until 6 months after radiotherapy, but at 12 months a significant decrease related to radiation dose was observed. Xerostomia was assessed during radiotherapy and on the days of the scintigraphic tests. The incidence of xerostomia did not correspond to the effects observed in the scintigraphic studies. It is concluded that radiotherapy induces early and persistent impairment of salivary gland excretion, related to the radiation dose. This impairment is stronger in parotid glands than in submandibular glands.

Correspondence to: R.A. Valdés Olmos, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

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Introduction

Salivary gland dysfunction due to external beam irradiation can lead to serious complaints such as dryness of the mouth, difficulties in speech and swallowing or loss of taste [1, 2]. Radiation influences not only the quantity but also the quality of the saliva with reduction of pH and increase in viscosity [3], resulting in increased incidence of dental caries and mucositis [4].

Salivary gland scintigraphy is used to assess the salivary gland function quantitatively, as this technique correlates to major salivary gland flow rates [5]. In a previous transversally designed study in our institute, salivary gland function was determined using technetium-99m pertechnetate in patients who had undergone radiotherapy in the past. A high incidence of impairment of the excretion of the major salivary glands was observed [6].

In the present study, salivary gland function was determined by means of salivary gland scintigraphy before radiotherapy and at several intervals after radiotherapy. Scintigraphy was performed with ^{99m}Tc-pertechnetate, which, like radioiodine, is trapped and secreted in the ductal epithelium and excreted in the saliva [7]. A stronger influence of radiation on parotid than on submandibular glands has been described [1]; however, other authors have found no clear difference between the effect on parotid and submandibular/sublingual glands [8].

The main aim of the present study was to establish at what period after completion of radiotherapy salivary gland dysfunction occurs, and whether these changes

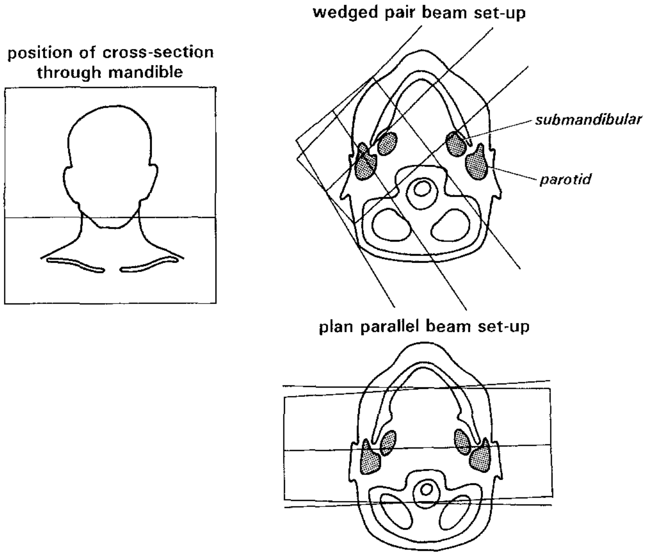

Fig. 1. Schematic diagram showing treatment techniques used for irradiation: on the basis of a cross-section through the mandible (*left above*), the wedged pair field planning (*right above*) and the parallel opposed fields (*right below*) are illustrated

persist or recovery occurs. In addition, functional changes in parotid and submandibular glands were investigated in order to show a difference in radiosensitivity between the two gland types. Finally, evaluation of time-dependent effects on salivary gland function was used to predict an optimal moment for future pharmacological intervention with sialagogues in order to limit salivary gland dysfunction.

Materials and methods

Patients. In total, 25 patients were included in the study, 15 male and 10 female. The mean age was 54.6 years (range 23–79). All patients received radiotherapy for tumours of one of the salivary glands, oropharynx or the nasopharynx, or for non-Hodgkin's lymphoma (NHL) of the tonsil, with a minimal planned radiation dose of 26 Gy, given in 2 Gy per fraction, five fractions per week. Prior to radiotherapy 17 of the patients underwent surgery, during which 11 parotid and 10 submandibular glands were resected. One NHL patient (number 22 in Table 1) received chemotherapy before the radiotherapy. The dose in each salivary gland was calculated by a 3D treatment planning system (3DTPS): the CT scan of the patient is read into the 3DTPS, the salivary glands are contoured and the dose distribution of the treatment plan is calculated. As the salivary gland is now a defined volume, the average dose in that value can be calculated. The average value was 30 Gy

Table 1. Characteristics of patients in the study

Patient	Age (yr)	Sex	Diagnosis	Removed gland(s)	Planned RT dose (Gy)	Max. RT dose per gland (Gy)	RT field	Follow-up studies
1	45	M	SCC oropharynx L	LSM	68	66	W	1
2	49	F	AcCC parotid R	RP	70	NA	W	1
3	44	M	SCC oropharynx L	–	68	72	W	1
4	50	F	Lymph node metastasis neck R	RSM	60	48	W	3
5	66	M	Nasopharyngeal carcinoma L	–	66	59	PO	3
6	52	M	Pl. Ad. parotid L	LP	50	50	W	3
7	54	F	Adenoca parotid L	LP+LSM	60	4	W	3
8	68	M	Adenoca parotid L	LP	60	65	W	3
9	27	F	Pl. Ad. parotid R	RP	50	52	W	2
10	59	M	NHL tonsil L	–	40	47	PO	3
11	23	F	Pl. Ad. parotid L	LP	50	51	W	3
12	53	F	Adenoca parotid R	RP	60	61	W	3
13	61	M	Pl. Ad. parotid L	LP	50	52	W	3
14	59	M	SCC temporal R	RP+RSM	46	22	W	3
15	72	M	AcCC submandibular R	RSM	68	70	PO	1
16	47	M	SCC oropharynx R	RSM+LSM	60	66	W	3
17	48	M	SCC oropharynx L	–	60	69	W	3
18	79	M	SCC oral cavity L	RSM+LSM	64	70	PO	1
19	60	M	SCC oropharynx	–	66	69	PO	3
20	48	M	AcCC parotid L	LP	60	64	W	3
21	65	F	Adenoca parotid L	LP	60	63	W	3
22	76	F	NHL	–	26	35	PO	3
23	47	M	SCC oropharynx L	–	66	72	W	3
24	61	F	AdCC submandibular R	RSM	66	70	W	1
25	51	F	SCC oropharynx	–	70	75	PO	2

SCC, Squamous cell carcinoma; AcCC, acinar cell carcinoma; AdCC, adenoid cystic carcinoma; Adenoca, adenocarcinoma; NHL, non-Hodgkin's lymphoma; Pl.Ad., pleomorphic adenoma; L, left; R, right; P, parotid gland; SM, submandibular gland; NA, not available; W, wedged pair fields; PO, parallel opposed fields

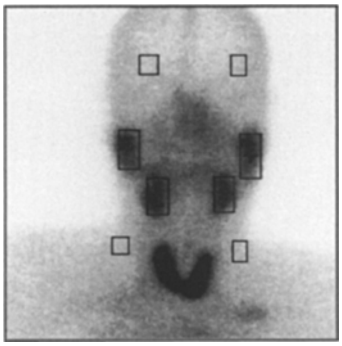

Fig. 2. Anterior image showing ROIs over the major salivary glands as well as in the areas selected for background correction

(range 1–70 Gy). Eighteen patients (72%) were irradiated using wedged pair fields and seven patients (28%) with opposed lateral fields (Fig. 1). Patient data are summarized in Table 1. The maximal radiation dose delivered per salivary gland is also shown in this table: in two patients (number 7 and 14), who had been undergoing homolateral gland resection prior to radiotherapy, the maximal delivered dose to the remaining opposite glands was considerably lower than the planned radiation dose which was principally delivered to the area where the tumour was lying.

Informed consent was obtained from all patients. The protocol was approved by the ethics and scientific committee of the Netherlands Cancer Institute.

Methods. Scintigraphy was performed with dual-head gamma cameras (Vertex/Genesys, ADAC) using low-energy high-resolution collimators, set for the 140-keV photon energy peak of ^{99m}Tc and connected to a Pegasys network system. Follow-up studies were performed under identical circumstances to the baseline study with respect to time of day, position of the head and distance of the camera from the patient. Directly after intravenous administration of 185 MBq ^{99m}Tc-pertechnetate, the acquisition was started on the basis of 1-min frames for 30 min using a 128×128 matrix with a zoom factor of 1.3. After 14 min excretion of all major salivary glands was stimulated by subcutaneous administration of carbachol (0.25 mg in 1.0 ml).

To analyse the salivary gland function a quantification program was developed. After conjugation of the anterior and posterior views, rectangular regions of interest (ROIs) were drawn around each major salivary gland with background correction in the lateral temporal region for the parotids and in the lateral neck for the submandibular glands (Fig. 2). Similar ROIs were used for baseline and subsequent studies. Rectangular ROIs were preferred in order to reduce variability in follow-up studies. The following parameters were calculated:

1. The salivary excretion fraction (SEF) was quantified by determination of the maximal excretion activity per gland as a fraction of the maximal uptake, according to the formula:

$$\mathrm{SEF} = \frac{A_{13-14\,\mathrm{min}} - A_{29-30\,\mathrm{min}}}{A_{13-14\,\mathrm{min}}},$$

where $A_{13-14\ \mathrm{min}}$=activity after 13–14 min and $A_{29-30\ \mathrm{min}}$=activity after 29–30 minutes.

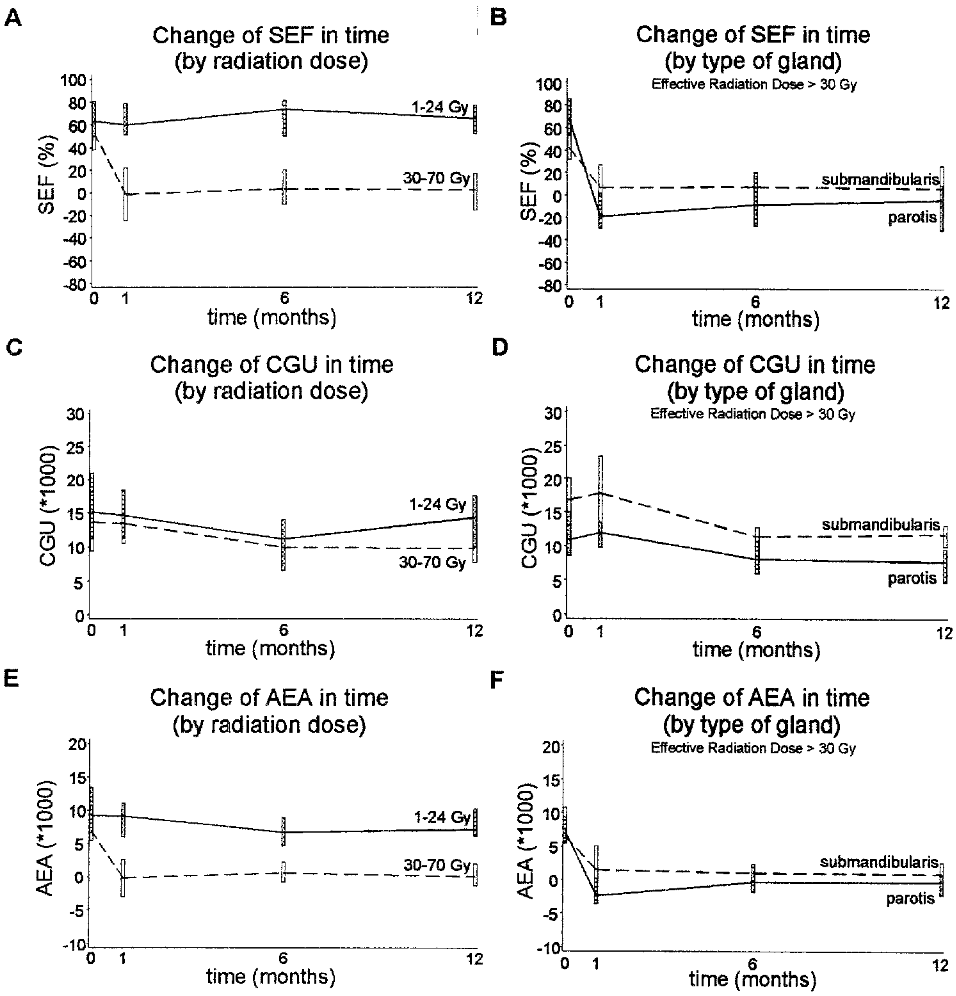

Fig. 3. Time-related changes in salivary excretion fraction (*SEF*), cumulative gland uptake (*CGU*) and absolute excreted activity (*AEA*) in irradiated salivary glands. The *lines* reflect the median values and the variability is shown by the *bars* (25th to the 75th percentile)

After an interval of 13–14 min maximal uptake of activity is observed before excretion stimulation, which starts after 14 min. After 29–30 min the maximal effect of the carbachol excretion stimulation is reached and the activity in the glands at this interval is a measure of the excretion reaction.

2. The cumulative gland uptake (CGU) in each gland was determined by integration of the time-activity curves of the first 12 min, and normalisation for the injected dose of ^{99m}Tc-pertechnetate.

3. The absolute excreted activity (AEA) is the product of CGU and SEF.

Follow-up. The subjective complaints were determined by questionnaires scoring dryness of the mouth, difficulties with speech or swallowing, loss of taste and loss of appetite. At each follow-up period the incidence of xerostomia was determined.

Salivary gland scintigraphy was performed before and 1, 6 and 12 months after radiotherapy. All patients (79 salivary glands) underwent scintigraphy prior to and 1 month after radiotherapy. In 19 patients (61 glands) scintigraphy was performed 6 months and in 17 patients (54 glands) 12 months after radiotherapy. For various reasons (above all recurrent disease), several patients did not continue their participation in the study for the entire period.

Statistical analysis. The statistical analysis was performed using the PROC MIXED module of SAS. The average radiation dose was used as a continuous variable. For the short-term effect of the radiotherapy dose, the model contained the value at 1 month as the dependent variable, the effective dose as the exposure variable and the gland type and measurement before radiotherapy as co-variables. Patient was included as a random effect. For the long-term effects, the measurements at 6 and 12 months were used as the dependent variables, while the baseline measurements, the gland types and time served as co-variables. Interactions were taken into account where relevant. For illustrative reasons, the results per gland were arbitrarily divided into two groups according to the radiation doses: in the first group all glands received a dose between 30 and 70 Gy, while in the other all glands received a dose of below 24 Gy (range 1–24 Gy). No glands received a dose between 25 and 29 Gy. The first group contained 21 parotid glands and 23 submandibular glands and the other, 18 and 17, respectively. In both dose groups the median was determined for every parameter at the different times of investigation. To indicate the variability in the values, the 25th and 75th percentiles were calculated. These values are shown in Fig. 3.

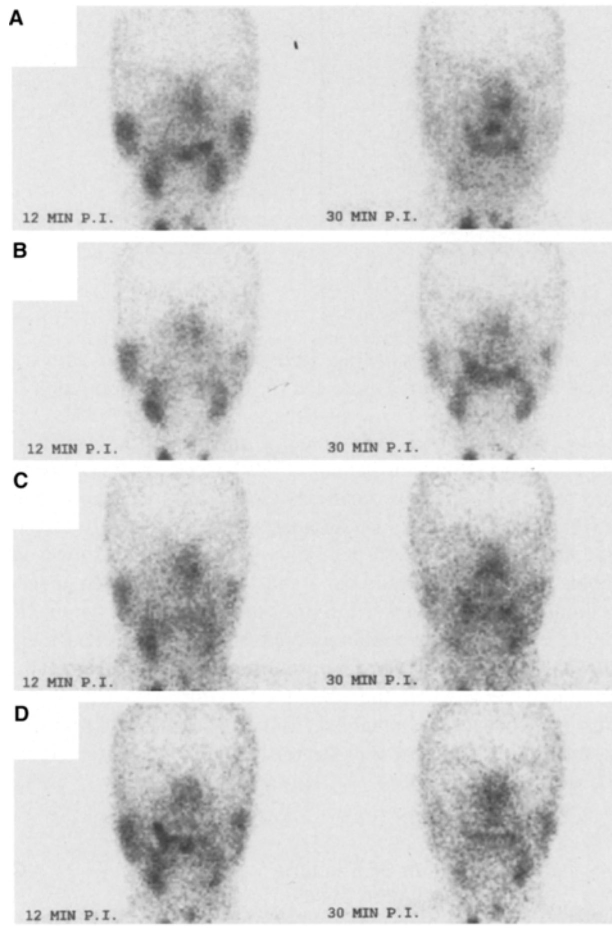

Fig. 4. Sequential salivary gland ^{99m}Tc-pertechnetate scintigrams (**A** before radiotherapy, **B** 1 month after radiotherapy, **C** 6 months after radiotherapy, **D** 12 months after radiotherapy) of a patient with a squamous cell carcinoma of the left tonsil showing decreased excretion response in the salivary glands of the left side, which received higher radiation doses, especially after 6 and 12 months

Results

Changes in excretion patterns were easily identified on visual evaluation (Figs. 4, 5): the most frequent finding after radiotherapy was persistently impaired excretion with gland retention of activity and no decline on time-activity curves after carbachol stimulation.

SEF decreased significantly in relation to the radiation dose (P<0.0001). This level of significance was found in relation to both parotid and submandibular glands, but in parotid glands the effect was significantly stronger than in the submandibular glands (P<0.0001). To illustrate this observation, Fig. 3A shows the effects for glands evaluated in two dose groups: a sharp decrease in SEF was seen as early as 1 month after radiotherapy in the glands that received 30–70 Gy, whereas no change was observed in the glands that received less than 24 Gy. Figure 3B shows the difference between parotid and submandibular glands.

For both parotid and submandibular glands that received more than 30 Gy, the decrease in SEF persisted during the follow-up at 6 and 12 months after radiotherapy (Fig. 3A). In patients in whom the excretion failed and accumulation of activity continued after stimulation with carbachol, calculation of the SEF resulted in a negative value.

The CGU showed no significant changes in relation to radiation dose at 1 month after radiotherapy. In the follow-up this situation remained unchanged at 6 months, but 12 months after radiotherapy the relation between radiation dose and CGU decrease was significant (P<0.0001). Figure 3C illustrates this effect with salivary glands divided into two dose groups. The effect of radiotherapy dose on the uptake function did not differ significantly between parotid and submandibular glands (Fig. 3D).

The AEA decreased significantly in relation to the ra-

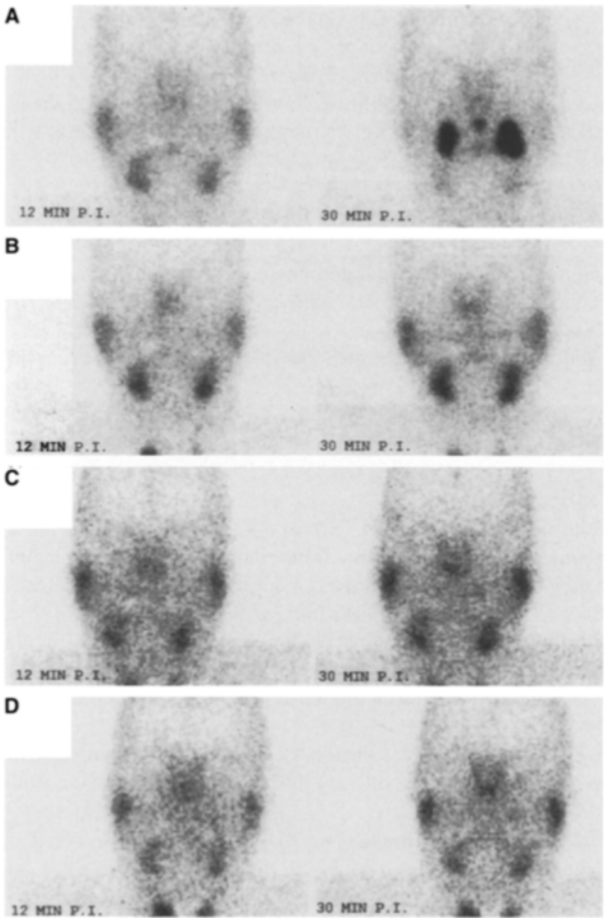

Fig. 5. Sequential salivary gland ^{99m}Tc-pertechnetate scintigrams (**A** before radiotherapy, **B** 1 month after radiotherapy, **C** 6 months after radiotherapy, **D** 12 months after radiotherapy) of a patient with non-Hodgkin's lymphoma, treated with radiotherapy on Waldeyer's ring, showing decreased excretion response in all salivary glands which had been irradiated with doses of more than 40 Gy

diation dose (P<0.0001) at 1 month after irradiation. In accordance with the SEF, this effect was observed in both parotid and submandibular glands (P<0.0001), but the difference between the two groups was less significant than with respect to SEF (P<0.04). At 6 and 12 months after radiotherapy the correlation between radiation dose and AEA decrease was still significant, but no significant difference was seen between parotid and submandibular glands (Fig. 3E, F).

One month after radiotherapy, 14 of 21 patients (67%) complained of xerostomia. After 6 months it was present in 6 of 15 patients (40%) and after 12 months in 4 of 10 patients (40%). The incidence of xerostomia did not show a correlation with the salivary gland dysfunction as assessed by scintigraphy.

Discussion

The most relevant finding of the present study is that the excretory function is affected in relation to the radiation dose as early as 1 month after irradiation, with persistent impairment until 1 year at higher dose levels. In the radiation dose range studied, the excretion function of the parotid glands appears to be affected more strongly than that of the submandibular glands. In contrast to the excretion, the uptake function of the glands remains unaffected until 6 months after radiotherapy, but at 12 months the gland uptake tends to be decreased in relation to increasing radiation dose.

This deleterious effect of radiotherapy has already been extensively reported in the literature, with complete loss of function observed with irradiation doses over 60 Gy [8, 9]. Doses below 50 Gy were found to have less influence on salivary gland function, with gradual recovery even 4 years after completion of radiotherapy [10]. Parotid gland function was affected more severely than submandibular gland function in some studies [1, 3], but no difference was found in another [8].

To analyse gland excretion in more detail, two parameters, SEF and AEA, were studied. SEF, which is a relative expression of the excretion response, was calculated from the decrease in activity in the particular gland after stimulation. If response to stimulation failed completely and further accumulation of activity occurred in the gland, the calculation of SEF even resulted in negative values. Although a negative SEF has not been proven to be specific for certain disorders of the salivary gland, it could be indicative of extracellular damage (e.g. neurotransmitter deficiency) [11] or an obstruction of the salivary duct. SEF was also used by Bohuslavizki et al. [12], who standardized uptake and excretion values in 116 patients [13]. This parameter appears especially to be influenced during the first month after irradiation, and particularly in parotid glands.

Since SEF may remain unchanged in spite of a reduction in gland uptake, a second excretion parameter, AEA, was evaluated: AEA is a more absolute parameter that is intended to evaluate the saliva production per gland, since it corresponds to the excreted part of the activity that has accumulated in the gland. Kohn et al. demonstrated a significant correlation between scintigraphy and salivary flow rates using a scale in which several factors such as uptake and excretion response were included [5]. One month after radiotherapy AEA is mainly influenced by the changes in SEF, because SEF decreases strongly and CGU is not significantly affected.

The early changes in SEF and the later onset of CGU decrease appear to confirm our earlier observations [6[that initial damage is characterized by failure of the gland excretion whereas late irradiation effects are associated with damage to the gland parenchyma and decreased trapping ability. All excretory function tests were more seriously affected in parotid glands than in submandibular glands. This difference in radiosensitivity can be explained by the higher concentration of serous acinar cells in the parotid glands, which are selectively radiosensitive, as has been shown in animal studies [14].

Salivary gland dysfunction frequently leads to complaints which seriously affect the quality of life. Xerostomia and related symptoms – difficulties in speech and swallowing, loss of taste and increased tooth decay – can be a burden to patients undergoing radiotherapy in the head and neck region [4]. Interestingly, the incidence of xerostomia did not parallel the function test results and showed a tendency to decrease, whereas the salivary gland function showed no significant recovery. This could be explained by adaptation to the salivary gland dysfunction. Another explanation may rest on the role of saliva mucins, which are known to provide effective lubrication in the oral cavity. This aspect has been emphasized by LeVeque et al. [15] to explain why small increases in salivary volume are able to result in improvements in the symptoms of xerostomia in patients receiving pilocarpine after irradiation. Mucins are contributed by the submandibular glands, which were less affected by irradiation than parotid glands in the present study, and sublingual glands, as well as by minor salivary glands which have a wide distribution throughout the oral cavity; although these minor glands only produce approximately 10% of the total salivary output, they account for 70% of the total mucin in saliva [16].

Promising results of treatment of radiation-induced xerostomia with sialagogues have already been reported [17, 19], even when pharmacological intervention started 4 months after radiotherapy. A randomized placebo-controlled trial of a limited number of nine patients who received pilocarpine, commencing 1 day before irradiation and continuing for 3 months, showed promising results. The incidence of xerostomia in the pilocarpine-treated group was lower, with less impaired gland function [19].

In conclusion, post-irradiation salivary gland dysfunction, affecting the parotid glands more strongly than the submandibular glands, is based on an excretory function disorder which is present 1 month after radiotherapy. This stresses the need for early pharmacological intervention in an attempt to reduce the incidence and severity of salivary gland dysfunction after radiotherapy.

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