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ESTIMATION OF LONG-TERM SALIVARY GLAND DAMAGE INDUCED BY RADIOTHERAPY

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Abstract

A classification is proposed for estimating salivary gland damage induced by radiotherapy to the head and neck. The volume of salivary glands irradiated was evaluated, and their relative proportions of whole saliva output were calculated. Stimulated salivary flow rate was measured in 61 patients treated with radiotherapy for head and neck malignancies. A highly significant negative correlation was found between the classification of salivary gland damage and stimulated salivary flow rate. The volume of the major salivary glands irradiated seems to be the most important factor affecting the postirradiation salivary flow after a curative dose of radiotherapy. If possible, partial sparing of the salivary glands may help to keep the patient's salivary secretion at an acceptable level and promote protection against dental caries. Most patients irradiated to the head and neck, however, need an effective prophylactic programme for the rest of their lives in order to preserve their teeth.

Key words: Radiations, injurious effects; radiotherapy, head and neck cancer, lymphoma, salivary glands, saliva.

Radiotherapy of the head and neck region is known to cause changes in salivary secretion, as a result of radiation damage to the salivary glands (12, 17). A sharp decrease in the salivary flow rate occurs in the beginning of radiotherapy, usually after the first week of treatment with a dose of about 10 Gy (24, 31, 33). The decrease in the flow rate then continues throughout the treatment period, resulting in almost total dryness (23, 33). Depressed salivary flow has been observed to persist as long as five years after radiotherapy (12). FRANK et coll. (12) reported that after a period varying from two to six months, the salivary flow may recover to some degree, depending on the patient's age, the radiation field and the radiation dose.

The volume of salivary glands included in the irradiated volume is an important factor affecting the development of oral dryness. In particular, the included volume of the parotid glands (24) is of central importance, as these have been observed to be the most radiosensitive major salivary glands (17).

The contributions of the different salivary glands to the mixed saliva may vary under different conditions (5, 6, 10, 29, 30). During sleep, submandibular glands play the most important role and accessory glands and sublingual glands play a minor role, with the parotid glands not secreting at all (10). When the patient is awake, submandibular glands still play an important role in the resting state, but after stimulation the contribution of parotid glands is dominant (10).

Since difficulties have been encountered in reporting the results of studies on the state of the salivary glands after head and neck irradiation, a classification for estimating salivary gland damage is proposed in the present paper. It is important to know the probable extent of future radiation damage to the salivary glands when planning radiation treatment of head and neck tumours and a prophylactic programme for preventing damage to the teeth (19, 20).

In the present study salivary gland damage was estimated according to the volume of salivary glands irradiated and their proportional importance in the production of stimulated whole saliva in patients treated for malignancies of the head and neck. Furthermore, the correlation between the proposed classification of salivary gland damage and the stimulated salivary flow rate of these patients was examined five years after radiotherapy.

Material and Methods

The material comprised patients treated for head and neck malignancies between 1974 and 1977 at the Department

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Table

Median values of stimulated salivary flow rate in 61 irradiated patients surviving for five years. The patients were divided into four groups according to the volume of salivary glands irradiated and the proportional radiation damage (PRD) to the salivary output

Patient groups	No. of patients	Upper border of radion field	Median radiation dose (Gy) in the salivary glands	PRD %	Stimulated salivary flow rate ml/min**	
					Range	Median
Group I	13	Below mandible	*	<5	0.6–2.8	1.9
Group II	32	Line from chin to mastoid process	43	40–60	0.1–2.5	0.9
Group III	8	Line from corner of the mouth or wing of the nose to the external acoustic meatus	56	55–75	0.4–1.6	0.7
Group IV	8	Line from the tip of the nose or the floor of the orbita to the external acoustic meatus	62	75–100	0–0.7	0.2
Total	61				0–2.8	

* Only scattered irradiation to the salivary glands.
** Normal value of stimulated salivary flow rate varies from 1.0 to 3.0 ml/min according to Ericsson and Hardwick (9).

of Radiotherapy. Ninety-two of the 224 patients survived for at least five years. Thirty-one patients out of these 92 were excluded from the study for the following reasons: medication known to affect salivary flow, e.g. neuroleptics, antidepressants, anxiolytics, anticholinergics, antihypertensive drugs, diuretics, antihistamines, barbiturates, and teophylline (19 patients), surgery of the parotid gland (4 patients), incomplete data concerning secretion (3 patients), unwillingness to cooperate (4 patients), and gastric tube feeding (1 patient).

The study group thus consisted of 61 patients (38 males and 23 females). Thirty of these patients had been treated for solid tumours and 31 for malignant lymphomas of the head and neck. The locations of solid tumours were as follows: larynx (20), nasopharynx (2), nose (2), gingiva (2), tongue (1), tonsil (1), cheek (1), and lip (1).

Treatment. A ^{60}Co apparatus (Jupiter Junior V, Generay, Italy or Rocus USSR) or a linear accelerator (6.7 MV photons, Clinac 3, Vickers Limited, UK) was used for treatment. The irradiation was usually administered with opposed lateral and PA-oblique fields. Patients with lymphoma were treated with a mantle field. The weekly dose was 10 Gy delivered in 5 fractions.

Estimation of damage to the salivary glands. First the volume, in percentages, of the different salivary glands included in the radiotherapy fields was calculated, by comparing the extent and borders of the radiation fields with the normal position of the glands (26). Then the corresponding relative proportions of the whole saliva output produced by different salivary glands were calculated and added up. According to Ferguson (10), after mechanical stimulation the parotid glands contribute 58 per cent, submandibular glands 33 per cent, sublingual glands 1.5 per cent and accessory glands 7.5 per cent of all saliva. In the patients with lymphoma, for example, the whole submandibular glands and 20 to 40 per cent of the parotid glands were included in the mantle field. Other salivary glands were usually outside the fields. The corresponding relative proportions of the whole salivary output as mentioned above are 33 per cent for submandibular glands and 12 to 23 per cent for parotid glands: added up they vary from 45 to 56 per cent. In this study these percentages are defined as the proportional radiation damage (PRD).

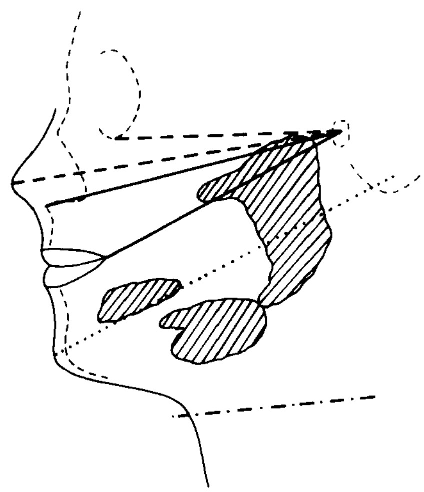

Fig. 1. The upper borders of the radiation fields in patients (n=61) treated for malignancies in different locations of the head and neck. The patients were divided into the following groups according to level of upper border. Group I (n=13); below the mandible (—·—). Group II (n=32); a line from the chin to the mastoid process (· · · ·). Group III (n=8); a line from the corner of the mouth or wing of the nose to the external acoustic meatus (——). Group IV (n=8); a line from the tip of the nose or the floor of the orbita to the external acoustic meatus (- - -).

Patient groups. The patients were divided into four groups according to the volume of the salivary glands irradiated and the proportional radiation damage (PRD) to the salivary output (Table).

Group I consists of 13 male patients (between 54 and 81 years of age, median 62 years), 12 with carcinoma of the vocal chords in stages T1N0 (32) and T2N0 and one patient with a superficial carcinoma of the nose. In all instances the major salivary glands were outside the radiotherapy field and only minor amounts of scattered radiation reached the salivary glands. The radiation dose in the tumour varied from 30 (2 patients) to 65 Gy, the median being 62 Gy and the nominal standard dose (NSD) (7) from 1 100 to 1 760 ret. The PRD in Group I was calculated at <5 %. Four patients had their own teeth, and remaining nine edentulous patients wore complete prostheses.

Group II consisted of 32 patients (15 males and 17 females, between 21 and 80 years of age, median 35 years). Thirty-one patients were treated for lymphoma. The upper border of the field was a line going approximately from the chin to the mastoid process (Fig. 1). The radiation dose in the tumour and in the salivary glands varied from 36 to 47 Gy, the median being 41 Gy. NSD ranged from 1 100 to 1 400 ret, median 1 270. Sixteen patients were treated with adjuvant chemotherapy varying from 8 months to 6 years before reexamination. This group also included one patient treated for carcinoma of the cheek, in stage T2N0, with unilateral radiotherapy from two opposite anterior and posterior fields. The radiation dose in the tumour and in the salivary glands in this case was 66 Gy, and the NSD 1 680 ret. The PRD in Group II varied from 40 to 60 per cent. Twenty-four patients had their own teeth. Of eight edentulous patients, seven had complete prostheses and one neither teeth nor prosthesis.

Group III comprised eight patients between 48 and 71 years of age, median 61 years. Seven male patients were treated for carcinoma of the larynx, classified as T1N0, T2N0 or T3N0. The upper border of the field was a line going from the corner of the mouth or the wing of the nose to the external acoustic meatus. Most of the sublingual and submandibular glands, and 55 to 65 per cent of the parotid glands, were included in the field of radiotherapy. The radiation dose varied from 56 to 64 Gy, the median being 62 Gy and the NSD ranged from 1 600 to 1 780 ret, median 1 670. The salivary glands of these patients received about 90 per cent of the total radiation dose. This group also included a female patient who was treated palliatively for inoperable meningeoma of the nose. In this case both parotid glands were included in the radiation fields, but the other major salivary glands were clearly outside the fields. The dose in the parotid glands in this case was 55 Gy, and the NSD 1 500 ret. The PRD in Group III varied from 55 to 75 per cent. Two patients had some of their own teeth with partial prostheses, whereas six edentulous patients had complete prostheses.

Group IV consisted of eight patients (3 males and 5 females, between 39 and 75 years of age, median 58 years) with tumours of the nasopharynx, tongue, lip, larynx, tonsil or gingiva classified as T1N0, T2N0 or T2N1. The upper border of the field was a line going from the tip of the nose or the floor of the orbita to the external acoustic meatus. In all cases the parotid glands were totally and the submandibular glands from 40 to 100 per cent included in the field. The radiation dose in the tumour and in the salivary glands varied from 52 to 65 Gy, median 62 Gy, and the NSD from 1 420 to 1 770 ret, median 1 540. The PRD in Group IV varied from 75 to 100 per cent. Four patients had some of their own teeth and one of them had a partial prosthesis. There were four edentulous patients, of whom two had complete prostheses and two neither teeth nor prosthesis.

Collection of saliva specimens. Stimulated whole saliva was collected and the flow rate determined in 61 patients by one of the authors (TAM) more than five years after radiation therapy, between 1981 and 1982 at the Department of Oral Surgery, Institute of Dentistry.

Saliva specimens were taken, at least one hour after a meal, between 9 a.m. and 3 p.m., using the standardized procedures described by PARVINEN & LARMAS (27). Paraffin stimulated saliva was collected by having patients spit into a graduated glass tube for a five-minute period. For patients who had very sparse saliva secretion, the collection procedure was extended to 10 minutes. The volume obtained was measured with a degree of accuracy of 0.1 ml.

The normal value of paraffin stimulated salivary flow rate in healthy adults varies from 1.0 to 3.0 ml/min (9) and is defined as 2.0 ± 0.8 ml/min for men and 1.7 ± 0.7 ml/min for women (27). According to ERICSSON & HARDWICK (9) a flow rate of 0.7 ml/min is very low. As there are no exact limits for hyposalivation, in this study values $\leq$0.9 ml/min were considered to represent reduced salivary flow rate.

Statistics. The correlation coefficient was calculated with the aid of PEARSON's formula for the product moment correlation coefficient (1).

Results

The median value of the stimulated salivary flow rate decreased in relation to the volume of the salivary glands irradiated (Table). In patients of Group I, all salivary glands outside the radiation field were reached only by minor amounts of scattered radiation. The proportional radiation damage (PRD) was <5 per cent. In 10 patients (77 per cent) the salivary flow rate was more than 1.0 ml/min, which is considered a normal value; it was reduced in three patients (23 per cent) (Fig. 2). The median flow rate in Group I was 1.9 ml/min (range 0.6 to 2.8).

In the patients of Group II, the median radiation dose in the salivary glands was 43 Gy. In 31 patients with lymphoma, 60 to 80 per cent of parotid glands were outside the radiation field. In one patient with a tumour in the cheek

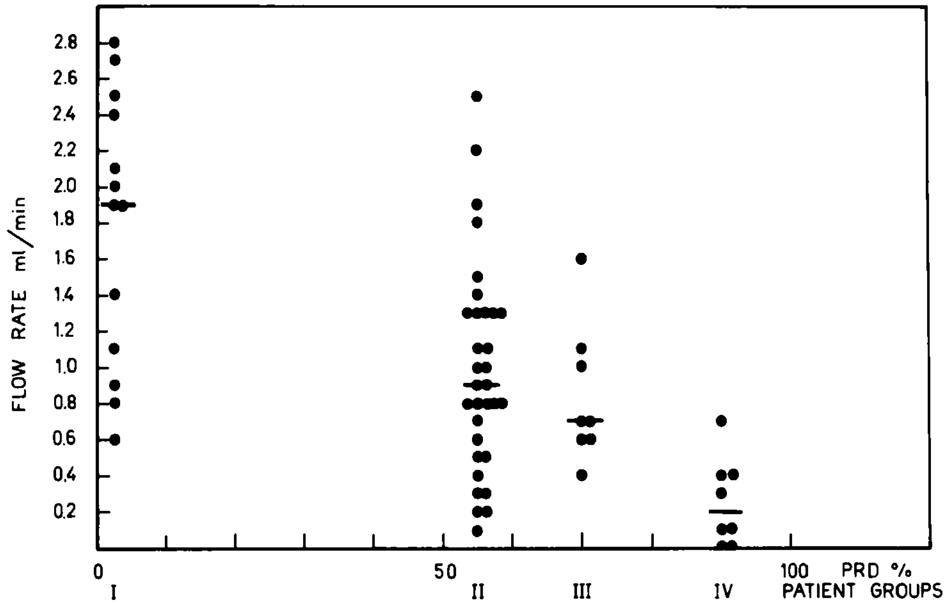

Fig. 2. Individual flow rates of stimulated whole saliva in the irradiated patients (n=61) in relation to the mean proportional radiation damage (PRD, per cent). The patients were divided into study groups according to the upper border of the radiotherapy field as described in Fig. 1. The horizontal lines indicate the median values.

no major salivary glands on the opposite side were irradiated. PRD in Group II varied from 40 to 60 per cent. The salivary flow rate in this group was 1.0 ml/min or more in 15 patients (47 per cent) and clearly reduced in 17 patients (53 per cent). The median flow rate in Group II was 0.9 ml/min (range 0.1 to 2.5).

In the eight patients of Group III, with a median radiation dose of 56 Gy in the salivary glands, about one third to half of the upper part of parotid glands was outside the radiation field. PRD varied from 55 to 75 per cent. The salivary flow rate was 1.0 ml/min or more in 3 patients (38 per cent) and clearly reduced in 5 patients (62 per cent). The median flow rate in Group III was 0.7 ml/min (range 0.4 to 1.6).

In all eight patients of Group IV, the salivary flow rate was greatly reduced. The median radiation dose was 62 Gy to the salivary glands, which were totally included in the radiation fields. PRD varied from 75 to 100 per cent. The median flow rate was 0.2 ml/min (range 0 to 0.7).

The negative linear correlation between the study groups and the stimulated salivary flow rate was highly significant ($r=-0.580$, $N=61$, $p<0.001$) (Fig. 2). No linear correlation was found between the salivary flow rate and the total dose of irradiation within the study Groups I to III, but there was a significant correlation in Group IV ($r=-0.839$, $N=8$, $p<0.01$).

Discussion

According to the present and previous studies (2, 24), the volume of major salivary glands irradiated is the most important factor affecting the postirradiation salivary flow after a curative dose of radiotherapy. In Group IV in the present study, where the parotid glands were totally and the other major salivary glands partially or totally included in the radiation field and radiation dose varied from 52 to 65 Gy, median 62 Gy, the flow rate was markedly reduced in all patients, examined more than five years after therapy. A wide variation was found in the flow rates in Groups I to III, with partly spared salivary glands (Table). In patients who had received only scattered irradiation to the salivary glands (Group I), decreased values ($\leq$0.9 ml/min) of salivary flow were detected in only 3 out of 13 patients.

Cheng et coll. (2) found that when 100 per cent of the parotid glands' volume was irradiated, the parotid glands did not produce saliva at all, but when even a small portion (10 to 20 per cent) of the parotid gland was outside the radiation fields the glands could be stimulated to produce saliva. This fact should be kept in mind when radiation treatment is planned.

The whole saliva which bathes the teeth and mucosa contains secretions from many salivary glands (10). Attention should also be paid to the importance of other glands besides the parotid. Sparing parts or all of submandibular glands, for example, may help to keep the patient's salivary secretion at an acceptable level. The importance of oral mucosal glands in the production of antimicrobial factors has been shown in previous studies (3, 16). Saving these minor oral glands may play an important role in protection against new colonization by microorganisms (14, 18, 21, 22) or against dental caries (3, 16).

Stimulated whole saliva measurements were used in the present study because 1) the method is simple, 2) variation during the day is slight (11), 3) the volume of saliva collected in a resonable time is greater than when resting saliva is used and greater volume improves the reliability of the measurement, and 4) a good correlation has been reported between resting and paraffin stimulated flow (15).

According to many previous studies the decrease in salivary secretion is dose-related (21, 22, 24, 33). The most pronounced decrease, however, occurs at the beginning of radiotherapy, usually during the first week of treatment (21, 33). In some patients with a low initial salivary flow rate even two doses of irradiation (2.25 Gy) may produce a greatly reduced salivary flow (23). Wescott et coll. (33) showed that the decrease in the salivary flow rate produced by irradiation follows an exponential decay type curve, and the decreasing rate constant is percentually related to the radiation doses.

The dose of irradiation which results in xerostomia is considered to be 70 Gy (28), 60 to 65 Gy (24, 25) or as low as 40 Gy (8, 33). If all the salivary glands are irradiated with a total dose of about 40 Gy most patients develop a very low salivary secretion (21, 24), and after a total dose of about 60 Gy no recovery in salivary flow rate has been observed during the follow-up period varying from half a year (21) to one year (19). However, in certain patients treated with a rather low dose of about 40 Gy who have also had partly spared salivary glands, a minor increase in salivary flow rate has been measured during the first postirradiation year (19).

Although the decrease in salivary secretion is clearly dose-related, many of our patients (53%) treated with a rather low dose (i.e. lymphoma patients) had a very low salivary flow rate, whereas in others in this group (47%) the salivary secretion remained at an acceptable level (≥0.9 ml/min). However, even in those patients the salivary secretion was usually reduced compared with the initial level (19).

According to the present and previous results (21), the irradiated volume of salivary glands seems to play a more important role than the radiation dose in patients treated for head and neck malignancies.

In spite of individual treatment programmes and more effective radiotherapy with modern accelerators, radiation-induced damage to the salivary glands cannot be avoided during curative treatment of malignant primary tumours and lymph nodes in the head and neck. The irreversible changes in the salivary glands predispose to develop dental caries and impair the ability to eat, talk and use prostheses. There is also a risk of late osteoradionecrosis. Saving part of the parotid or submandibular glands from radiation may help the patient markedly. However, even these patients must be considered caries-risk patients, because the salivary flow rate is often reduced.

In the present investigation, a classification for the evaluation of radiation-induced salivary gland damage is proposed. Nowadays, in patients scheduled for radiotherapy to the head and neck, all teeth with a good prognosis should be preserved (13, 20). When the borders of the radiotherapy fields are known, it is possible beforehand to estimate the expected proportional radiation damage (PRD) to the salivary output, and plan a more effective prophylactic fluoride programme (4, 19) for patients expected to develop reduced salivary flow.

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