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Parotid Gland Function During and Following Radiotherapy of Malignancies in the Head and Neck

A Consecutive Study of Salivary Flow and Patient Discomfort

Lars Franzén, Ulrika Funegård, Thorild Ericson and Roger Henriksson

Radiotherapy of tumours in the head and neck region usually involves the salivary glands in the treatment volume with ensuing dryness and discomfort. In the present study, a prospective evaluation of the same patients were performed before, during radiotherapy and 6, 12 and 18 months after the end of treatment. Three different groups were outlined, one receiving doses not exceeding 45 Gy, another 47–52 Gy and a third group treated with doses over 64 Gy. All but one of the patients receiving doses less than 52 Gy showed a recovery of secretion beginning after 2 months with a continuous improvement of the salivary flow up to 18 months. Doses exceeding 64 Gy caused irreversibly depressed parotid function in the vast majority of glands. The subjective experience of discomfort with dry mouth was not at all correlated to the initial flow rate. Treatment with unilateral technique and doses below 52 Gy caused just no or slight dryness and 3 out of 4 patients with bilateral involvement of the glands displayed problem with subjective dryness even after 18 months. Doses over 64 Gy with one gland involved had only slight dryness, however, patients with both glands affected showed severe problems with dryness. it has to be emphasised that there were relatively large interindividual differences with respect to salivary flow and discomfort of dryness. It is obvious that these patients need a careful dose planning and a close follow up with co-operation between radiotherapeutists and dentists.
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INTRODUCTION

RADIOTHERAPY OF tumours in the head and neck region usually involves the salivary glands in the irradiated volume. The inherent radiosensitivity, especially of parotid glands, is manifested by very early signs of hampered salivary flow [1–4]. A sharp decrease in the salivary flow rate occurs already in the first week with conventional fractionation, i.e. 2 Gy/day [5–9]. The decrease in flow rate continues throughout the treatment period and when both parotid glands are affected by radiation to full dose (66 Gy) the mouth usually becomes permanently dry [10–12]. Subsequently, this leads to chronic oral disease with subjective distress and loss of taste and a pronounced decrease in quality of life [2–4, 8, 13]. In addition to the direct influence on salivary glands the discomforts in speaking, mastication and swallowing are further aggravated by the effects of irradiation on the oral mucosa with the development of erythema, plaque formation and in severe cases ulceration and bleeding.

The present study is a prospective continuous evaluation, as far as we know one of the first, on the effects of different irradiation schedules on parotid gland function and its correlation to patients distress of dryness of the mouth when treating malignancies in the head and neck region. The results of the effects were continuously followed in the patients. Although, the total radiation dose is most important the radiosensitivity of the parotid gland function and recovery varied considerably between the individuals during and 18 months following the end of irradiation.

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PATIENTS AND METHODS

Patients and irradiation

25 of the patients treated at the department of Oncology, University Hospital, Umeå, Sweden during 1985–1989 for

Table 1. Patients' characteristics

Patients, diagnosis and treatment	Total dose (Gy)
(A) 6 patients, bilateral, irradiation fields	
5 Hodgkins disease	40–43
1 malignant lymphoma	40
2 patients, unilateral, irradiation field	
1 thyroid carcinoma	45
1 malignant lymphoma	44
(B) 3 patients, bilateral, irradiation fields	
1 hypopharynx carcinoma (T3, NO, MO)	50
2 oral carcinoma (T3, NO, MO)	50–52
5 patients, unilateral, irradiation field	
5 oral carcinoma (T2-3, NO, MO)	47–50
(C) 5 patients, bilateral, irradiation fields	
3 nasopharyngeal carcinoma (T3-4, NO-1, MO)	66–68
1 hypopharyngeal carcinoma (T3, N1, MO)	65
1 oral carcinoma (T4, NO, MO)	66
4 patients, unilateral, irradiation field	
4 oral carcinoma (T2-3, NO-1, MO)	66–74

malignancies in which radiotherapy involved the parotid glands were included in the study. Informed consent was obtained from each patient. Sampling of data were made before the start of radiotherapy and every week during the irradiation period and regularly after finishing the treatment period. All patients were checked by the same physician and dentist. The dose plan of each patient and simulation films were studied before entering the study. The dose at 1 cm in the parotid gland was at least 90–95% of the prescribed target dose. Verification with portal films was performed regularly at a simulator.

The details of the patients included and the treatment schedules used are shown in Table 1. As can be seen the irradiation delivered varied with the diagnosis according to generally accepted treatment strategies. Three main groups are outlined: one group given less than 46 Gy; another group of patients which were given 47–52 Gy and a third group treated with full dose (65 Gy or more). The first group included 14 parotid glands, the second group contained 11 different glands and the full dose group 14 parotid glands. For some patients (n = 14) both parotid glands were irradiated and in the remaining patients a unilateral technique was used in an attempt to protect the contralateral parotid gland from irradiation (11 patients). Patients with lymphoma were treated with mantle fields.

The irradiation treatment was performed with linear accelerators 4–6 MV, with opposed lateral, posterior–anterior or oblique fields with fixed-SSD or isocentric techniques. The target doses were between 1.45 and 2.37 Gy daily with a dose rate of 2.2 Gy/min, a focus to skin distance 80 cm (4 MV) or 100 cm (6 MV) and delivered with five fractions a week. To avoid doses exceeding 42 Gy to the spinal cord electrons were used with energies from 10–18 MeV (Microton, Scanditronix) (see Fig. 1).

Collection of saliva

Stimulated parotid saliva was collected prior to radiotherapy and weekly during treatment. Moreover, samples were also

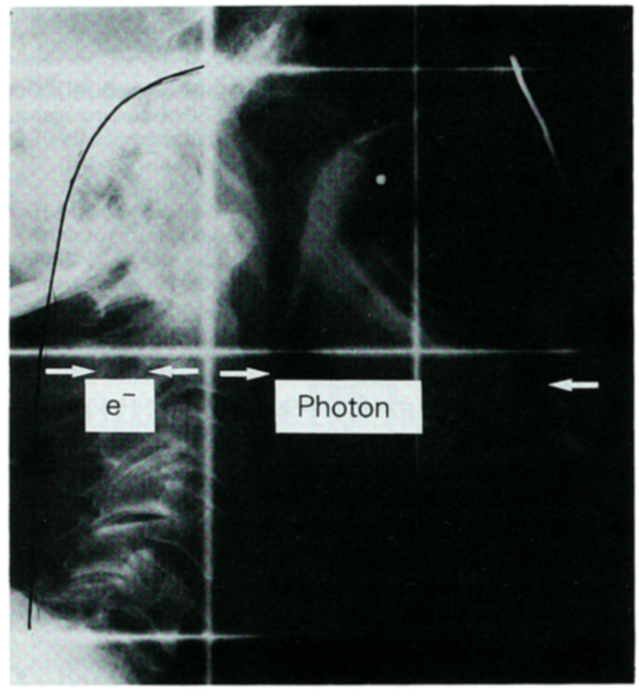

Fig. 1. Radiographic demonstration of a treatment field demonstrating the use of combining electrons (e^-) and photons in order to protect the spinal cord. This patient treated with 65 Gy displayed a recovery of the parotid secretion.

taken 2, 4, 6, 12 and 18 months after the end of radiotherapy. The parotid saliva was collected with Lashley cups which were placed over the orifice of Stenson's duct. Stimulation was carried out with a saliva stimulating tablet (SST, Salix Pharma, Sweden), placed on the tongue. An aliquot of 1 ml saliva was collected between 9 and 12 a.m. and the collection time never exceeded 20 min. Whole saliva stimulated by chewing on paraffin was collected before radiotherapy.

Appearance of dryness

Subjective description of dry mouth conditions were recorded as a part of the patient interview. Distinction was made between lack of dryness (−), a slight dryness (+) which mainly occurred occasionally during the night, and severe dryness (++).

RESULTS

Salivary flow

The average and the individual behaviour of parotid secretion rate from individual glands for the different irradiation doses during and after radiotherapy are shown in Fig. 2a–c. The patients irradiated with 40–45 Gy (target dose per fraction 1.45–2.0 Gy) had a mean parotid salivary secretion rate of 0.54 ml/min (range 0.07–1.45 ml/min) before radiotherapy. The group of the patients subjected to a radiation dose of 47–52 Gy (target dose 2.0–2.37 Gy) displayed a mean salivary rate of 0.33 ml/min (range 0.11–0.9 ml/min). The patients who underwent full dose treatment, 65 Gy or more (target dose 1.95–2.10 Gy) had a mean parotid salivary secretion rate of 0.45 ml/min (range 0.08–1.3 ml/min) before therapy. Initially, a sharp decrease in the salivary secretion rate was encountered in all three groups of patients, already within the first week of treatment, i.e. a delivered dose of 7.25–11.85 Gy.

At the end of the treatment 5 out of 14 irradiated (40–45 Gy)

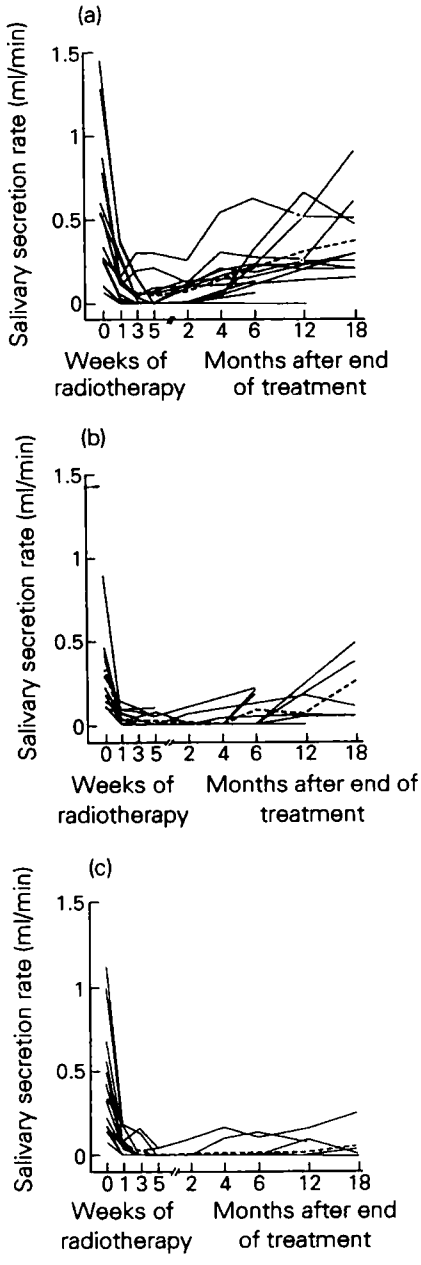

Fig. 2. (a) Parotid salivary secretion rate for the individual patients (–) and the average (--) before, during and after radiotherapy affecting parotid gland with total doses not exceeding 45 Gy. (b) Parotid salivary secretion rate before, during and after radiotherapy with total doses between 47 and 52 Gy. Individual values (–), average (--). (c) Parotid salivary secretion rate before, during and after radiotherapy with total doses between 65 and 74 Gy. Individual values (–), average (--).

parotid glands displayed detectable salivary secretion, however, a significant decrease was obviously encountered. Six months after the end of radiotherapy 12 out of 14 of these parotid glands showed measurable values of secretion. The percentage decrease for each gland was calculated. The mean of these values for all glands was 42% (Table 2). As can be seen the secretory flow was partially restored in some patients already within 2 months following the end of radiotherapy and the secretory capacity was

Table 2. Secretion rate at 6, 12 and 18 months after irradiation as % of initial secretion rate

Total dose (Gy)	Months		
	6	12	18
40–45	42.3 (37.8)	53.5 (35.5)	70.5 (26.6)
47–52	21.0 (21.8)	25.2 (35.1)	62.4 (36.4)
65–74	8.8 (22.3)	8.5 (17.3)	20.7 (36.8)

Mean (S.E.).

then continuously improved in many patients during the follow-up period to 18 months at which time a significant increase ($P < 0.01$) was recorded compared with the 6 months value (Fig. 2a). The secretion rate was fully recovered in some patients (Figs 2a, 3, 4a). Two glands irradiated with 40–45 Gy remained silent throughout the entire experimental period of 18 months.

In the group treated with 47–52 Gy a mean salivary secretion rate was calculated to be 21 and 25% of the initial values 6 and 12 months, respectively following the end of radiotherapy. At 18 months five glands displayed 62% of the initial value (Table 2).

The vast majority of glands affected by radiation doses exceeding 65 Gy displayed a total disappearance of salivary flow (Figs 2c and 3). It is also clearly evident that there is a great interindividual variation. In the full dose treated parotid glands only 3 out of 14 had measurable secretion at the follow-up at 6, 12 and 18 months (Fig. 3). These three glands showed a lower secretory flow than comparable glands following irradiation with the lower doses.

As can be seen in Fig. 4a–c there was no obvious correlation between parotid gland function 6, 12 or 18 months following irradiation and the target dose in any of the three radiation doses (glands). However, as already stated a relationship was seen between the total dose delivered and gland function, individual values (Fig. 3), and mean values (Table 2). Nevertheless, it has to be emphasised that there is an interindividual variation in restoration of secretion.

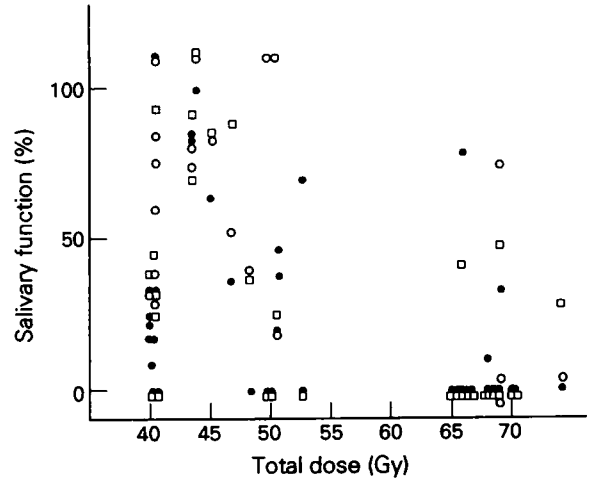

Fig. 3. Parotid salivary gland function, 6, 12 and 18 months after end of radiotherapy expressed as per cent of initial secretion rate versus total dose for the individual patients. ● = 6 months, □ = 12 months, ○ = 18 months.

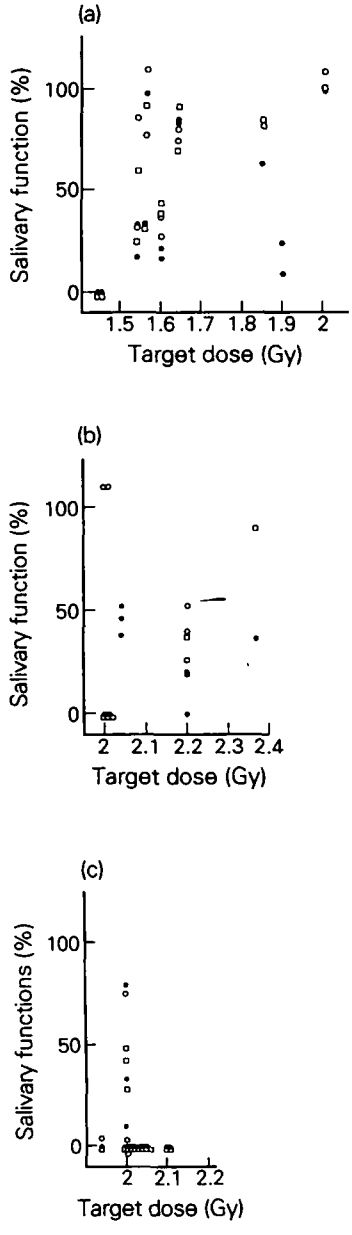

Fig. 4. Parotid salivary gland function, 6 (●), 12 (□) and 18 (○) months after end of radiotherapy for the individual patients expressed as % of initial secretion rate versus target doses. (a) Total dose ≤ 45 Gy, (b) total dose 47–52 Gy, and (c) total dose ≥ 65 Gy.

Table 3. Patients subjective experience of dry mouth

Initial flow rate (ml/min)	Irradiation period (weeks) 0	1	3	5	After treatment (months) 2	4	6	12	18
(a) Doses 40–45 Gy									
Unilateral treatment									
0.6	o	o	+	o	o	o	o	o	o
1.3	o	o	o	o	o	+	+	+	o
Bilateral treatment									
0.3	o	+	++	++	++	+	+	+	o
0.6*	o	+	++	++	++	++	++	++	
1.3	o	o	+	o	++	+	o	o	o
1.6*	o		+	+	+	o	o		
1.6	o	+	+	++	o	o	o	o	o
2.6	o		++		++	++	++	++	++
(b) Doses 47–52 Gy									
Unilateral treatment									
1.0	+	+	++	++	+				o
1.1	o	o	+	+	+	o	o	o	o
2.1	o	o	+	o	o	o	o	o	o
3.0	o	o	+	+	+	o			o
†	o	++	++	++	++	++	++	+	+
Bilateral treatment									
2.3	o	o	+	+	++	++	++	+	+
2.3	o	+	++	++	++	++	++	++	+
2.3	o	o	+	+					o
(c) Doses 65–74 Gy									
Unilateral treatment									
2.2	o	o	++	++	+	+	o	o	o
3.1	o	o	+	++	+	+	+	+	+
4.2	o	o	+	+	o	o	o	o	
4.3	o	+	++	++	+	+	+	+	o
Bilateral treatment									
0.7	o	+	++	++	++	++	++	++	
0.9*	o	o	o	+	+	++	++	++	
1.7*	o	+	++	++	+				
1.9*	o	o	+	++	+				
‡	o	+	++	++	++	++	++		

* Patient died, † not determined due to motoric incapacity, ‡ not determined due to tube feeding.
o = No dryness, + = slight dryness, ++ = severe dryness.

Subjective dry mouth

Unilateral radiation with doses less than 46 Gy did not cause any major subjective distress with regard to mouth dryness during and following radiotherapy (Table 3). In the patients subjected to bilateral irradiation all patients suffered from severe mouth dryness during the time of irradiation. 2 out of 6 patients treated with bilateral irradiation displayed persistent dryness after the end of irradiation (Table 3).

Irradiation doses between 47 and 52 Gy caused discomfort with mouth dryness in all patients irrespective of whether a unilateral or bilateral technique was used (Table 3b). The problem was more pronounced in the bilateral group with persistent dry mouth in 2/3 of the patients.

In the group of patients subjected to more than 64 Gy all patients experienced mouth dryness during some periods during or following the radiotherapy (Table 3c). All patients treated with bilateral technique suffered from severe problems with dryness. No relationship could be seen with regard to initial secretion rate of whole saliva and the discomfort with dryness of the mouth.

DISCUSSION

Most earlier studies are retrospective and cross-sectional. In the present study, with prospective and continuous evaluation of patients irradiated for malignancies in the head and neck region, a dose-dependent decrease in parotid flow rate was demonstrated. No correlation was seen between distress from mouth dryness and initial secretory rate for whole saliva stimulated by chewing. There was a wide range within all irradiation

schedules of experienced discomfort and level of restoration of the secretory rate. In all doses there were some glands which never obtained a recovered function. The fraction of silent glands increased with higher doses. The changes encountered at the end of radiotherapy with 40–45 Gy was continuously improved during the follow-up period to 18 months. Radiation doses exceeding 64 Gy caused irreversibly depressed parotid function in the vast majority of irradiated glands. Moreover, the patients subjected to bilateral treatment fields suffer from higher frequency of discomfort when compared with those subjected to unilateral treatment. When using the unilateral treatment technique the contralateral salivary glands and the oral mucosa were protected and less affected.

The results are in accordance with earlier studies, of which most are retrospective. The decrease in salivary secretion seems to be dose related [3, 11, 14]. A pronounced decrease occurs in the beginning of radiotherapy [6, 15], usually during the first week of treatment, as seen in the present study. When evaluating separately, the individual parotid glands affected by radiation we observed a relationship with the dose delivered. At higher doses, i.e. $\geq$ 65 Gy, most glands were without secretory capacity up to 12 months following the end of radiotherapy. In doses below 52 Gy almost all glands regained some function up to 18 months after irradiation. Nevertheless, it must be stressed that there is a great interindividual variation in the long term effects of irradiation (see Fig. 3). Moreover, our results did not point out any obvious correlation between the used target dose (1.5–2.35 Gy) and the impaired parotid gland function. Signs of recovery in the secretory rate was seen already within 2 months in the lower doses ($\leq$ 45 Gy) (Fig. 2a). In a small number of patients a recovery was observed also in the higher doses at more late stages. Earlier results indicate a salivary gland function as late as 5 years after irradiation [12]. It must, however, be emphasised that no base line data were obtained in this study. The recovery seen in the clinical situation may have an explanation from the suggestion in animal studies that acinar cells have a potential regenerative capacity [16].

It is reasonable to assume that parts of the glands left unirradiated may continue to function [10]. We have been careful in only including patients in which parotid gland were totally comprised in the irradiation volume. However, a small portion of parotid gland may have been occasionally protected from irradiation. This may be the cause to the persistent parotid function even at higher doses, but differences in radiosensitivity between individuals can not be excluded. Obviously, the interpretation will have an impact on the assessment of the critical total dose in avoiding irreversible damage to salivary glands. The critical target dose causing dry mouth have been suggested; in some studies to be 70 Gy [17], 60–65 Gy [14, 18] or as low as 40 Gy [7, 19]. In one study [15] it was reported that a very low salivary secretion was obtained after a total dose of 40 Gy. After a total dose about 60 Gy no recovery in salivary flow rate has been observed during the follow up period varying from 6 to 12 months [15].

Reports of discomfort with dryness of the mouth during and following the irradiation were just as frequent among patients with high initial secretion rate as among the patients with low initial salivary flow when stimulated by chewing. Thus, no strict correlation seems to exist between the baseline salivary secretion rate and the irradiation associated mouth dryness. All patients experience dryness with variation in duration and severity during and following irradiation. The inconsistency between saliva flow and the dryness reported by the patients can be due to preserved function of the minor salivary glands. The secretion from the minor salivary glands in the mucosal membrane is primarily responsible for the lubrication of the oral mucosa. From this point of view protection of the major salivary glands from irradiation should have a limited impact upon the problem with dry mouth. However, such protection is motivated by the importance of the secretion from the major salivary gland in maintaining oral health. More studies are of interest in evaluating the response of the minor salivary glands to therapeutic irradiation.

The sensitivity of salivary cells to irradiation is a unique radiobiological phenomenon [20]. Other well differentiated glandular cells are reported to be more or less radioresistant [17]. The mechanism by which irradiation exerts its effect on salivary cells is not clearly outlined. It is generally accepted that in the case of radiosensitivity, proliferating, immature cells, DNA damage is responsible for ensuring mitotic delay and replication linked cell death [21–23]. However, DNA damage can not solely cause glandular cell deaths [24, 25] and irradiated salivary cells have been suggested to die in interphase. Cell membranes have also been proposed as an important target for injury leading to interphase cell death [26–30]. Recently, it has been shown that the membrane coupled potassium fluxes were affected by fractionated irradiation, whereas the enzyme secretion and morphology were unaffected in rat parotid glands [29]. Radiation-induced disturbances in ionic and water homeostatis in intact cells, in contrast to lysosomal enzyme changes, are early events and are elicited by relatively small doses of X-rays. Excessive leakiness of cells to K^+ and influx of Na^+ and water has been observed shortly following irradiation of a variety of cells including yeast [31] bacteria [32] human red blood cells [33] and rat muscle cells [34]. Moreover, destabilisation of ionic homeostasis have also been observed following other types of injury and have been extensively documented in the case of toxic and anoxic cell death in the liver and heart muscle. On the basis of these observations it has been postulated that lethal damage probably results from a sequence of events common to all or most non-dividing cells. Specifically, it has been suggested that membrane injury and a consequent uncontrolled accumulation of Ca^{2+} is the common pathway leading to cell death [35–37].

In conclusion, this prospective study of parotid gland function in patients subjected to irradiation of head and neck cancer demonstrated a great interindividual variation in the recovery with regard to salivary flow rate. Irradiation doses about 40–50 Gy caused generally reversible changes with sometimes almost a restored function of salivary secretion within 6–18 months following the end of radiotherapy. Doses exceeding 65 Gy induces principally irreversible alterations. It must, however, be emphasised from the present results that it is of great importance to follow all patients continuously during and after radiotherapy due to great interindividual variations in salivary flow rate as well as in the radiosensitivity in order to minimise the secondary negative effects from dryness [6, 38]. Therefore, it is of value to estimate the feature of radiation damage when planning for radiation treatment of head and neck cancer, and especially in the prophylactic approach in preventing infections and damage to the teeth [39, 40]. Thus, by using an isocentric and/or unilateral irradiation technique the salivary gland function can be maintained to the benefit of quality of life.

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