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The influence of radiation technique on xerostomia in head and neck cancer patients – prospective study

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
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Summary

Background

Irradiation of salivary glands during the treatment of head and neck cancer may lead to an alteration in the amount of saliva produced. Because of this, patients can suffer dryness of the mouth with oral discomfort, taste disturbance and dental decay.

Aim

The aim of this study is to estimate late toxicity dependence on radiotherapy method. The main goal is to investigate the correlations between the radiation doses in salivary glands and their salivary excretion fractions (SEF) measured by dynamic scintigraphy.

Materials/Methods

In 40 patients with pharyngeal and laryngeal cancer irradiated by IMRT or conformal 3D to a total dose of 62.5–72.0Gy, parotid SEFs were measured. Parotid dose-volume histograms were obtained from 3D computer treatment planning. SEF measurements were performed before (baseline), and 6 weeks and 6 months after radiotherapy by 185MBq 99 Tc injected intravenously and next SEF rates were analysed in relation to radiation doses accumulated. The late radiation toxicity of salivary glands was tested according to the CTC v. 3.0 and SOMA-LENT scales. The non-parametric Mann Whitney test was used for the estimation of relationships.

Results

Pre- and post-treatment SEFs were measured in 31 patients treated by IMRT and in 9 patients treated by 3D CRT. Six weeks after radiotherapy SEF was generally lower by 34%, and 6 months after irradiation by 29.3% in IMRT technique. In 3D CRT relatively it was lower: after 6 weeks by average 52% and after 6 months by 35.5%. Late radiation toxicity of salivary glands was observed at a similar level according to CTC and SOMA-LENT scales in both methods of radiotherapy.

Conclusions

The level of SEF in parotid glands measured 6 weeks after radiotherapy clearly reflects the dose-response relationship of irradiated salivary tissue; 6 months later changes of SEF are the result of partial recovery of parotids.

The results of sparing salivary glands can be optimized in the future; that is, a further reduction of xerostomia can be achieved by using improved IMRT techniques and focusing on sparing major and minor salivary glands.

Key words **head and neck cancer • xerostomia • parotids**

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BACKGROUND

Irradiation of salivary glands during the treatment of head and neck cancer may lead to an alteration in the amount of saliva produced. Because of this, patients can suffer dryness of the mouth with oral discomfort, taste disturbance and dental decay [1].

The salivary glands produce over a litre of saliva per day [2]. Ninety percent of salivary secretion is produced by major glands like the parotids, submandibular and sublingual glands; the rest of the saliva is produced by numerous minor salivary glands of the oral cavity [3]. The parotid and submandibular glands are the main contributors to salivary secretion; others produce only 2–5% of total salivary flow [2] or salivary excretion fraction (SEF) [4–6]. Under resting conditions the flow from the submandibular glands is at least as great as that from the parotids, but after stimulation (for instance eating) the parotids are the main contributors [1,7]. Parotids produce mainly serous acini saliva but submandibular and sublingual glands produce both mucous and serous acini saliva. [1–3]. The serous acini are considered to be the most sensitive to ionising radiation [1,8], and the loss of the water part in secretion results in xerostomia during and after irradiation [1], specially when both parotid glands are included in the treatment volume [8]. It should be noted that supportive treatment such as mouth rinses, saliva substitutes, salivary stimulants and often water consumption are generally ineffective and often not tolerated by patients [6].

To determine salivary gland function after radiotherapy, several methods have been employed. The most frequent are scoring systems such as SOMA-LENT [9–11], CTC [12] based on clinical examination or different xerostomic questionnaires [6], visual analogue scales (VASs) and salivary scintigraphy [6,13]. Although xerostomic questionnaires and scoring systems are widely used, their contribution is limited to information about patients' subjective feeling of dryness. Salivary flow had usually been studied by measuring saliva production using sialometry, but it is difficult to determine the function of each gland separately [6]. Salivary scintigraphy after 99Tc administration has been used to assess semi-quantitatively the excretion function of parotids and submandibular glands and correlates well with major salivary gland flow rates [14], thus facilitating post-radiotherapy follow-up.

Moderate to severe xerostomia may be prevented in most patients using a conformal-sparing radiotherapy technique [15]. IMRT might reduce the radiation dose to the major salivary glands, so the risk of permanent xerostomia can also be reduced. Alternatively, IMRT might allow target dose escalation at a given level of normal tissue damage.

AIM

We describe here the results of scintigraphy as an objective method to assess postirradiation salivary gland function. Also we have analysed the intensity of SEF reduction in head and neck cancer patients treated with IMRT and conventionally fractionated radiotherapy 3D CRT.

MATERIALS AND METHODS

Forty patients with squamous cell pharyngeal and laryngeal cancer were treated by radiotherapy to a total dose of 62.5–72Gy in the First Radiotherapy Clinic at the Centre of Oncology – Maria Sklodowska-Curie Institute in Gliwice, between March 2004 and November 2006. All patients were irradiated in an accelerated regimen: 7 fractions weekly without weekend break (CAIR), concomitant boost (CB) – 7 fractions from Monday to Friday with boost on Tuesday and Friday, or 5 fractions in 5 days (from Monday to Friday) with fraction dose of 2.5Gy (patients with glottic cancer only). A decision to use IMRT was made in those cases where the use of 3D conformal radiotherapy technique would have resulted in irradiation of all major salivary glands to a cumulative dose greater than 45Gy with a high risk of subsequent post-irradiation xerostomia.

Pretreatment staging of the tumours was done by clinical examination, CT/MRI, endoscopy and biopsies taken from the primary tumour. The tumours were staged according to tumour-node-metastasis (TNM) classification version 1997 [16]. All patients were treated on 6 MV photon linear accelerator beams. The gross tumour volume (GTV) was determined by clinical examination, endoscopy, MRI or CT. GTV was included in the clinical target volume (CTV), where radiotherapy was conducted to 54Gy in an accelerated regimen or to 45Gy in fractionation with 2.5Gy in glottic cancer patients. A 3 mm margin was added to the CTVs to obtain the planning target volume (PTV). This margin was selected based on the set-up accuracy measurements performed with the localisation of the tumour. The dose uniformity criteria inside the PTV were defined according to ICRU 50 [17].

The organs at risk (OAR) were defined on all treatment planning CT slices. Typically, the OARs included the spinal cord, the brain stem, the salivary glands and mandibular bone. The salivary glands treated as OAR included both parotid glands and often both submandibular glands. The decision how to spare parotids depended on the presence of lymph node metastases and the predicted risk of malignant subclinical disease. Sparing of the contralateral submandibular gland was attempted only in cases where the primary tumour did not cross the midline and no contralateral metastases were known to be present.

The salivary excretion fraction (SEF) was assessed before therapy (the baseline values – SEF_0) and 6 weeks and 6 months after completion of radiotherapy, by 185MBq 99 Tc injected intravenously. Pre- and post-treatment SEFs were measured for 62 parotids irradiated respectively in 31 patients by IMRT and for 11 patients treated by 3D CRT. SEF rates were analysed in relation to radiation doses. SEF was measured after inserting diluted lemon juice into the dorsal part of linguae.

Following irradiation the patients were examined by a team of the First Radiotherapy Clinic with two otorhinolaryngologists within clinical examination and endoscopy: 3 months after irradiation and every six months to 30 months after finishing treatment. Late radiation toxicity of salivary glands was scored by CTC criteria v. 3.0 and SOMA-LENT scale (Table 1).

Table 1. Patient, tumour characteristic and dose prescription.

Characteristic	N	(%)
Gender		
Female	11	(27.5)
Male	29	(72.5)
Site		
Oropharynx	9	(22.5)
Hypopharynx	6	(15.0)
Larynx: supraglottic	14	(35.0)
glottic	11	(27.5)
Tumour size		
T2	29	(72.5)
T3	5	(12.5)
T4	6	(15.0)
Nodal status		
N0	23	(57.5)
N1	10	(25.0)
N2	6	(15.0)
Nx	1	(2.5)
Radiotherapy (Gy/fractions/days)		
62.5/ 2.5/ 25	11	(27.5)
68.4/ 1.8/ 38	8	(20.0)
70.2/ 1.8/ 39	6	(15.0)
72.0/ 1.8/ 40	15	(37.5)
Accelerated radiotherapy (scheme regimen)		
CAIR	20	(50.0)
CB	9	(22.5)
Radiotherapy		
IMRT	31	(77.5)
3D	9	(22.5)
Age		
Mean	56.03	
Range	40–70	

Statistical methods

Non-parametric Mann-Whitney test was used for the estimation of relationships between treatment techniques (IMRT vs 3D CRT). The

Table 2. The change of relative saliva before and after irradiation dependence on radiotherapy technique.

Radiotherapy technique	N (parotids)	Mean (%)	Confidence interval –95%	Confidence interval +95%
IMRT				
SEF 6 weeks/ 0 weeks	60	33.96	21.95	45.98
SEF 6 months/ 0 weeks	40	29.32	18.46	40.18
Mean dose (Gy)	62	33.82		
Median dose (Gy)	62	34.0		
Modal dose (Gy)	62	36.31		
Irradiated volume (cm^3)	62	19.03		
3D CRT				
SEF 6 weeks/ 0 weeks	18	51.91	36.13	67.68
SEF 6 months/ 0 weeks	18	35.56	13.93	57.18
Mean dose (Gy)	18	34.61		
Median dose (Gy)	18	33.27		
Modal dose (Gy)	18	35.1		
Irradiated volume (cm^3)	18	24.4		

statistical significance of differences in parameter ΔF ($\Delta F = SEF\ post\ RT - SEF_0/SEF_0$) [4] at less and greater than the dose thresholds was tested using the two-sided Mann-Whitney rank-sum test.

Results

The mean radiation dose to the parotids in analysed material was 33.8Gy.

The mean, median and modal doses to parotid glands, and also their irradiated volume dependence on radiotherapy regimen, are detailed in Table 2.

Scintigraphy results

For the change in the relative saliva excretion rate before and after treatment, the reduction was observed for the two analysed groups' dependence on radiotherapy technique regimen. Six weeks after radiotherapy SEFs were generally lower on average by 34%, 6 months after on average by 29.3% for patients treated by IMRT. There was observed a higher reduction for patients treated by 3D CRT – six weeks after radiotherapy SEFs were lower on average by 52% and 6 months after on average by 35.5% – but this was not statistically significant.

These differences were observed only for absolute values (Table 2).

For the change in the relative excretion rate, ΔF, a reduction was observed for all analysed groups (Figure 1 represents the change of relative excretion rate after 6 weeks and Figure 2 – after 6 months). A comparison of ΔF for doses less than and greater than the defined dose thresholds yielded statistically significant differences for the parotid glands.

The SEF ratio was used to evaluate the percentage of SEF lost after RT (6 weeks and 6 months) with respect to the baseline SEF_0. Nine patients (18 parotids) underwent scintigraphy before 6 weeks and 6 months after radiotherapy in 3D CRT technique. In the IMRT group 30 patients (60 parotids) underwent scintigraphy before 6 weeks and 20 patients (40 parotids) in 6 months after radiotherapy. The reduction in excretion was dependent on the parotid gland dose. There was no significant correlation between the 6-week and 6-month post-RT ratios and the pre-RT excretion fractions and the mean dose in IMRT technique (Figure 3), and also in 3D CRT (Figure 4).

Late radiation toxicity results

The late radiation toxicity of salivary glands was scored according to CTC version 3.0 criteria every 6 months to 30 months of follow-up. The intensity of late radiation reaction for both IMRT and 3D CRT techniques was very similar (Figure 5). According to the SOMA-LENT scale there was also observed very good concordance of the intensity of late reaction in the whole time of observation (Figure 6).

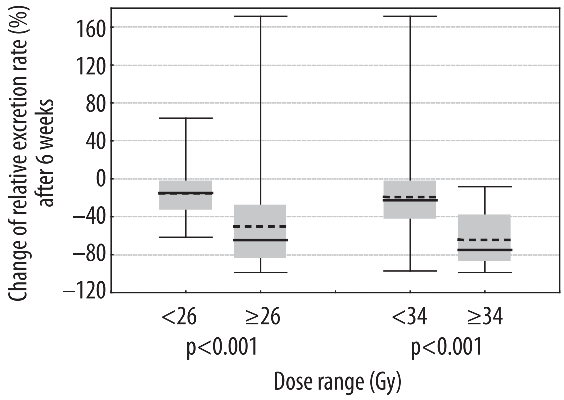

Figure 1. The change of relative excretion rate after 6 weeks.

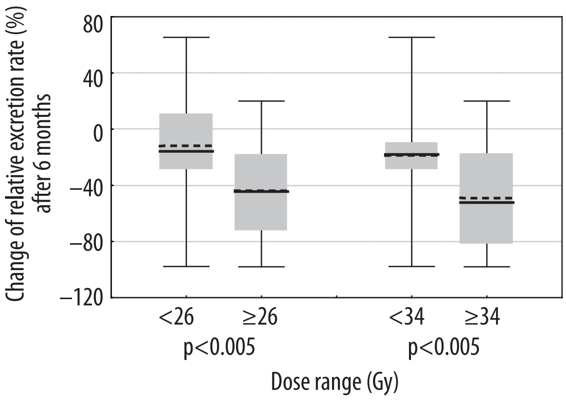

Figure 2. The change of relative excretion rate after 6 months.

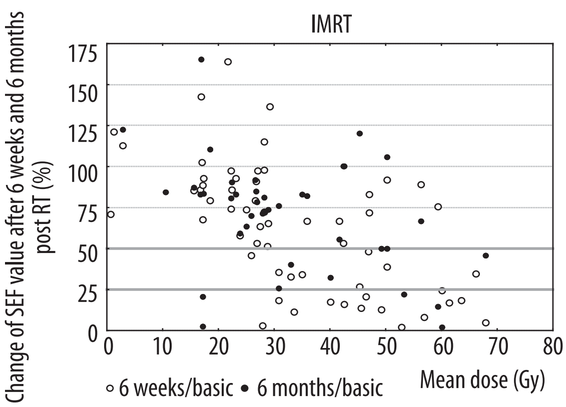

Figure 3. The change of SEF value after 6 weeks and 6 months post RT in the relation to mean dose in IMRT technique.

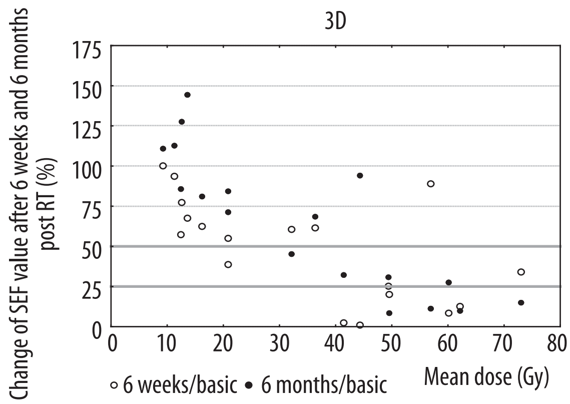

Figure 4. The change of SEF value after 6 weeks and 6 months post RT in the relation to mean dose in 3D technique.

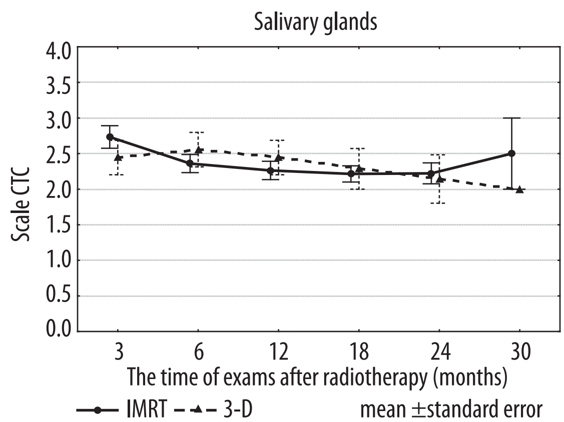

Figure 5. Late radiation reaction of salivary glans according to CTC, v. 3.0.

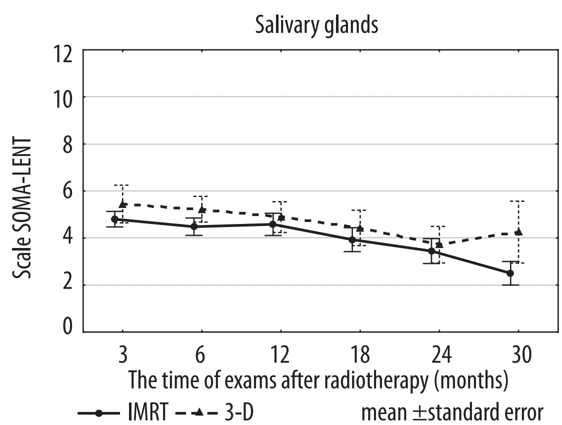

Figure 6. Late radiation reaction of salivary glans according to SOMA-LENT scale.

Discussion

In the treatment of head and neck cancer by radiotherapy the major salivary glands are often included in the irradiated volume. Tumour site, stage and the need for nodal irradiation will determine which salivary glands are included. The risk of dryness can be reduced if during treatment planning volume of salivary tissue irradiated can be minimised [1,18]. If only submandibular and sublingual glands can be spared within the treatment volume and both parotids are outside the radiation volume included, most patients note little or no difference in the quantity and character of saliva [1]. Although the minor salivary glands have only limited contribution to the basal or the stimulated saliva flow rates, preservation of their function is also of importance, because the minor salivary glands produce up to 70% of the total mucin secreted by salivary glands. [19]. Mira et al. [20] suggest that it is necessary to exclude more than 50% of both parotids from the treatment volume to prevent severe dryness. It is also important to avoid oral cavity and oropharyngeal mucosa when possible [21].

There are a number of ways to increase the effectiveness of radiation in cancer of the head and neck. During the past decade altered fractionation and various combinations have been clinically tested [22–27]. Finally, 3D CRT and IMRT are means which allow application of high doses of radiation through minimising toxicity [28–30]. Braaksma et al. [31] described the optimisation of conformal radiotherapy by intensity modulation for laryngeal cancer patients only with a high percentage of T1-T2 glottic irradiated to a total dose of 70Gy, where it was possible to exclude one parotid. The results of Saarilathi et al. have suggested that much of salivary gland function can be maintained with IMRT [21]. They described the treatment technique: in addition to the OARs, a volume of healthy tissue was delineated outside the PTV for dose optimisation. This technique has been found to be efficient in minimizing the risk of hot spots outside the PTV. Eisbruch et al. showed that in addition to the major salivary glands, sparing the non-involved oral cavity should be considered as a planning objective to further reduce xerostomia [32].

In our material with high stages of tumour and nodal metastases all patients were irradiated to both sides of the neck with similar dryness in both techniques (IMRT and 3D CRT) according to CTC and SOMA-LENT scales. Also the oral cavity and oropharyngeal mucosal membrane were not always avoided in our planning. However, scintigraphy, which was used as an objective method to assess toxicity, demonstrated lower reduction of SEFs in IMRT than in 3D CRT.

M.D. Leslie and S. Dische have described parotid gland function following accelerated CHART (54Gy in 36 fractions over 12 consecutive days) and conventionally fractionated radiotherapy. Following CHART, there was less impairment of parotid gland function as compared with that after conventionally radiotherapy to doses of 60–66Gy. This has confirmed their clinical impression that following CHART to squamous cell cancer in the head and neck there was less than expected dryness of the mouth [33]. The better function of the parotid gland following CHART was connected with the much lower total dose of 35–40Gy in comparison to the total dose of 60–66Gy fractionated conventionally [18]. In our study all patients were treated in an accelerated way, but with no reduction of total dose; thus the accumulated dose within the parotids was much higher than in the CHART study.

Scintigraphic methods continue to play a role in the study of functional disorders [34]. They are able to detect minor impairment of glandular function. The parotid glands may be imaged and their function assessed using technetium. The scan can supply additional features by following changes in the excretion function of the parotid glands. In our study parotid gland function was assessed by scintigraphy with technetium before radiotherapy, and early (6 weeks) and later (6 months) after finishing irradiation. Later changes, after 6 months, in SEFs have shown partial recovery in parotids better in IMRT technique than in 3D CRT. These results associating partial recovery of parotids with time after treatment are in correlation with others. For example, Cha et al. registered a recovery of about 50% of secretory function after irradiation with 60Gy during 5 to 8 months after finishing radiotherapy [35]. Roesink observed some recovery of function of parotids at 1 year after radiotherapy in scintigraphy assessment [5].

Conclusions

The amount of SEF in parotid glands measured 6 weeks after radiotherapy clearly reflects the dose-response relationship of irradiated salivary tissue. 6 months later changes of SEFs are an indication of partial recovery of parotids.

The results of sparing salivary glands can be optimised in the future; that is, a further reduction of xerostomia can be achieved by using improved IMRT techniques and focusing on sparing major and minor salivary glands.

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