Acta Oncologica, 2015; 54: 1310–1316

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Toward a more patient-specific model of post-radiotherapy saliva secretion for head and neck cancer patients

LAURA TUOMIKOSKI[1], MIKA KAPANEN[1,2], JUHANI COLLAN[1], JANI KEYRILÄINEN[1,3], KAUKO SAARILAHTI[1], VENLA LOIMU[1], TIINA SEPPÄLÄ[1] & MIKKO TENHUNEN[1]

[1]*HUCH Comprehensive Cancer Center, Department of Radiation Oncology, Helsinki University Central Hospital, Helsinki, Finland,* [2]*Department of Medical Physics, Tampere University Hospital, Tampere, Finland and* [3]*Department of Oncology and Radiotherapy, Turku University Hospital, Turku, Finland*

ABSTRACT

Background. Reduction of saliva secretion is a common side effect following radiotherapy (RT) for cancer of the head and neck region. The aim of this study is to predict the post-RT salivary function for individual patients prior to treatment and to recognise possible differences in individual radiosensitivity.
Material and methods. A predictive model for post-RT salivary function was validated for 64 head and neck cancer patients. The input parameters for the model were salivary excretion fraction (sEF) measured by 99mTc-pertechnetate scintigraphy, total stimulated salivary flow and mean absorbed dose for the major salivary glands. SEF values after RT relative to the baseline before RT (rEF) were compared among the patients using the distance ΔrEF between single gland rEF and the corresponding expected value at the dose response curve.
Results. A significant correlation ($R = 0.86$, $p = 0.018$) was found between the modelled and the measured values of stimulated salivary flow six months after RT. The average prediction error for the saliva flow rate was 6 ml/15 min. A linear relationship between ΔrEF for the left and the right parotid glands was observed both six ($R = 0.53$) and 12 ($R = 0.79$) months after RT. The average of absolute values of ΔrEF was 0.20 for parotid glands and 0.22 for submandibular glands.
Conclusions. The salivary flow model was validated for 64 patients. The results imply, that one explanation for the discrepancies between the predicted and the measured salivary flow rate values and the common variations found in ΔrEF for the parotid glands may be differences in patients' individual response to radiation. However, quantitative extraction of individual radiosensitivity would require further studies in order to take it into account in predictive models.

During recent years, there has been a growing concern about the preservation of salivary gland function of head and neck cancer patients undergoing radiation therapy (RT). Xerostomia is a common side effect of RT for head and neck cancer and it has been shown to reduce the quality of life [1]. Due to the implementation of intensity-modulated radiation therapy (IMRT), it has become possible to reduce the absorbed dose in the major salivary glands without compromising the tumour control, usually enabling at least partial preservation of the salivary gland function [2,3]. Dose response analysis based on large patient populations have been performed in order to derive dose tolerance values for the salivary glands to be used in treatment planning [4]. Nevertheless, the effect of RT on salivary function is difficult to predict on individual patient level [5]. Therefore, there is a need for a patient-specific predictive model for post-RT salivary function, which could be used in the optimisation of treatment plans for head and neck region.

Several methods have been reported in the attempt of quantifying the post-RT reduction of salivary gland function. Direct measurements have been realised by collecting saliva via spitting or using suction cups. However, a quantification of the total saliva secretion does not provide information on the function of the individual glands. Magnetic

Correspondence: L. Tuomikoski, Comprehensive Cancer Center, Department of Radiation Oncology, Helsinki University Central Hospital, PO Box 180, 00029 HUS, Helsinki, Finland. Tel: + 358 50 427 1302. Fax: + 358 9 4717 6181. E-mail: laura.tuomikoski@hus.fi

(Received 16 May 2015; accepted 25 June 2015)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.3109/0284186X.2015.1067717

resonance (MR) sialography [6], diffusion-weighted MR imaging [7,8] and 11C-methionine positron emission tomography (PET) [9] have been proposed for determining the post-RT glandular function. Another method of analysing the function of the single glands is quantitative 99mTc-pertechnetate salivary scintigraphy. Valdés Olmos et al. were the first to report the use of scintigraphy in the quantification of radiation-induced decrease of salivary gland function [10]. Later, several studies have used scintigraphy to determine dose-volume response for salivary glands [11–14].

The starting point for this work was the salivary flow model reported by Tenhunen et al. [13]. The individual flow model was based on salivary gland excretion fraction (sEF) measurements by scintigraphy, and mean dose response curves for sEF in a larger patient population. In their research the authors found a substantial correlation between the measured and the predicted values of stimulated salivary flow rates six months after RT relative to the baseline. However, the sample size was limited (n = 20), and the predictivity of the model remained still too low on the individual patient level. In the present study we aimed at refining and validating the model for a larger patient population (n = 70). Instead of looking at the relative changes of the salivary flow over time, we now concentrated on the absolute quantities of the salivary flow rates. Another goal for this study was to investigate if the large inter-patient variation of post-RT sEF values, which has also been present in other studies, could be explained by a biological factor, such as individual radiosensitivity.

Material and methods

Patients

The study population consisted of 70 head and neck cancer patients who received RT in Helsinki University Central Hospital (HUCH) during the years 2006–2008 (50 patients) and 2012–2013 (20 patients) (Supplementary Table I, available online at: http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1067717). The study protocol was approved by an Ethics Committee of HUCH. All the patients were treated bilaterally using thermoplastic mask fixation to a total dose of 50–70 Gy (fractional dose 2 Gy), using IMRT with 6 MV photons and at least weekly portal imaging. For one patient the post-RT measurement files were unavailable for the analysis. Five patients were also excluded from the salivary flow model due to unsuccessful or incomplete set of measurements. Mean absorbed doses to parotid and submandibular glands had a range of 5–64 Gy and 21–73 Gy, respectively. Details of planning target definition and treatment planning can be found elsewhere [2,13].

Total saliva secretion and scintigraphy measurements

The stimulated function of the salivary glands was investigated by two different methods before the initiation of RT and both six and 12 months after RT. The methods in use were direct measurement of the stimulated total saliva secretion by collecting saliva in a measuring glass while chewing a piece of paraffin wax, and measurement of sEF for individual salivary glands using quantitative 99mTc-pertechnetate scintigraphy with a lemon juice stimulus. Both methods have been previously reported in detail by Tenhunen et al. [13].

The sEF values, determined by scintigraphy, were calculated separately for each of the four major salivary glands using the following equation:

$$sEF = \frac{C_{\max} - C_{\min}}{C_{\max} - C_{bg}} \tag{1}$$

where C_{max} and C_{min} are the detected counts in the salivary gland region of interest (ROI) before and after the lemon juice stimulus, respectively, taken as the average of four successive 30 second imaging frames. C_{bg} is the number of counts in the background ROI contoured in the brain, normalised by the relation of salivary gland and background ROI areas. Relative excretion fraction (rEF) at time t after RT was calculated from the ratio rEF = sEF(t)/sEF(t = 0), where sEF(t = 0) represents the baseline measurement before RT. The salivary glands which were not functioning properly before RT were excluded from the analysis. This was done by omitting glands with baseline sEF(t = 0) values lower than sEF_{mean} − 2*(standard deviation) (threshold values sEF(parotid) = 0.04, sEF(submandibular) = 0.07). In addition, negative rEF values resulting from non-functional glands were set to zero.

The absolute flow model

In the individual salivary flow model [13] the relative total salivary flow under stimulation was calculated from a weighted sum of the expected relative ejection fractions for all functioning major salivary glands. The weighting coefficients for each gland were derived by assuming that the volume of saliva secreted by a single gland in response to the stimulation is directly proportional to the count difference in ROI before and after stimulation, given by the subtraction $\Delta C = C_{max} - C_{min}$. Hence the proportion of single gland saliva output m of the total saliva production could be determined using the equation. $m = \Delta C_i / \sum_{all\_glands} \Delta C_k$. The sum was calculated for all functioning glands.

The dose response relationship for rEF was assumed to be shaped as a sigmoidal function described by the equation:

$$rEF = \frac{1}{1+(\frac{D_{mean}}{D_{50}})^k} \quad (2)$$

where D_{mean} is the mean glandular dose, D_{50} is the dose for a 50% reduction in sEF and k represents the steepness of the curve. Parameters D_{50} and k were determined by non-linear fitting in Matlab software (version R2009a, MathWorks, Natick, MA, USA). In the construction of the model previously reported values of D_{50} and k were used (Table I), which were derived from a different patient population than the one used in this work. The absolute flow model was then presented by the equation:

$$F_{calc}(t) = F_{meas}(0) \times \sum_i m_i \times rEF(D_{mean,i}) \quad (3)$$

Only the saliva production of the parotid and the submandibular glands are included in the model, thus ignoring the excretion from the sublingual and the minor salivary glands. Here $F_{calc}(t)$ is the total stimulated salivary flow after RT as predicted by the equation, and $F_{meas}(0)$ is the directly measured stimulated total salivary flow before RT. This model was used to calculate the absolute value of salivary flow six months after RT for 64 patients.

Table I. The parameters D_{50} and k with 95% confidence intervals from non-linear fitting of sigmoidal dose-response function for relative excretion fraction (rEF) six (6M) and 12 (12M) months after RT are reported for the present study. The corresponding values reported by Tenhunen et al. [13] were used in the absolute flow model. The non-functional glands before RT were excluded, and the number of glands used in fitting is indicated by n.

Present values	D50 (Gy)	k	n
Parotid glands 6M	35.5 ± 6.4	2.7 ± 1.5	112
Parotid glands 12M	43.0 ± 14.1	3.5 ± 2.8	87
Submandibular glands 6M	40.3 ± 2.4	6.0 ± 1.7	87
Submandibular glands 12M	41.4 ± 4.3	4.7 ± 1.9	65
Tenhunen et al.	**D50 (Gy)**	**k**	**n**
Parotid glands 6M	40.3 ± 13.3	2.6 ± 1.8	38
Parotid glands 12M	39.2 ± 11.0	2.3 ± 1.5	28
Submandibular glands 6M	37.3 ± 6.5	4.5 ± 2.6	30
Submandibular glands 12M	38.5 ± 5.8	3.0 ± 1.4	22

Evaluation of inter-patient variation in scintigraphic measurements

One goal of the research was to investigate if such differences could be found in the scintigraphy measurement data that could indicate different levels of individual radiosensitivity among the patients. For this purpose the measured values of rEF were compared to the mean sigmoidal dose response curve. Separate dose response curves were determined for the parotid and the submandibular glands. Only the salivary glands with D_{mean} of 10–50 Gy were included in the analysis, since we expected the possible differences in individual radiosensitivity to emerge in medium dose levels where the sEF is changing as a function of glandular dose.

Measurements of salivary function are prone to different factors, such as the consistency of the stimulus, that may cause unrealistic results, and hence a further exclusion was made, omitting values $rEF > 1.3$ to remove outliers. A subgroup of patients was formed, where the D_{mean} for the both parotid glands ranged between 10 and 50 Gy. In this subgroup ($n = 38$) the effect of the mean systematic residual patient positioning error to the D_{mean} of the glands was evaluated from portal images and the D_{mean} values were corrected accordingly. The salivary glands finally included in the analysis are visualised in Figure 1. The initial number of major salivary glands measured with scintigraphy six months after RT was 205. After the exclusion of non-functional glands in the baseline and the glands with $rEF > 1.3$, 188 glands were left in the analysis. Of these 132 were within the dose range of 10–50 Gy.

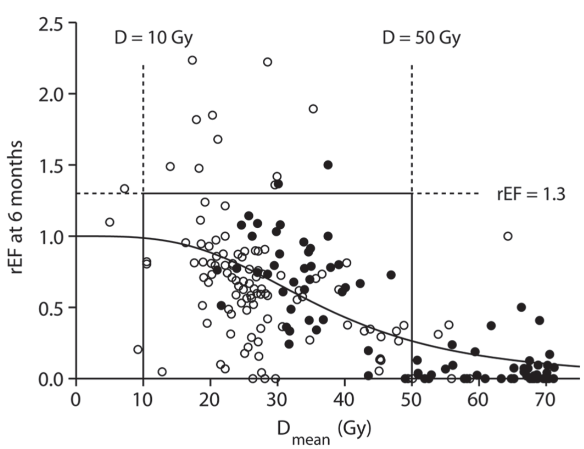

Figure 1. The relative excretion fraction (rEF) six months after RT measured for the major salivary glands using scintigraphy was plotted against the mean absorbed dose (D_{mean}) for the glands. The solid line represents the sigmoidal dose-response function fitted to the sample consisting of both parotid (open symbols) and submandibular (coloured symbols) glands. Only the glands with $rEF < 1.3$ and D_{mean} 10–50 Gy were included in the analysis of individual radiosensitivity.

To enable a comparison of salivary glands with different mean absorbed doses, the difference between the measured rEF value and the corresponding value at the mean sigmoidal dose response curve was calculated for each gland i by the following equation:

$$\Delta rEF = rEF_{measured}(i) - rEF_{mean}(D_{mean,i}) \qquad (4)$$

Using Equation 4 the normal dose response of a gland resulted in a difference ΔrEF close to 0. For the salivary glands with rEF lower than the population mean value ΔrEF was negative, and if measured rEF value was higher than the population mean, ΔrEF was positive.

The ΔrEF values for the left and the right parotid glands six months after RT were compared to investigate whether both glands of the same patient gave similar results relative to the population mean. The same comparison was repeated for the measurements performed 12 months after RT.

We also divided patients into three different groups based on mean ΔrEF value (ΔrEF_{mean}) calculated using all four major salivary glands. The patients were sorted in ascending order based on ΔrEF_{mean}, and three groups of equal size with low, medium and high ΔrEF_{mean} were formed. For these groups the sigmoidal dose response function was re-fitted pooling both parotid and submandibular glands together and keeping k parameter as a constant.

Pearson's correlation coefficient was used to evaluate linear correlation between the modelled and the measured salivary flow values, and the p-values were obtained by two-tailed t-test.

Results

The sigmoidal dose response curve described by Equation 2 was fitted in the entire patient population, resulting in D_{50} and k parameters comparable within the range of their uncertainties to the historical values used in the construction of the model (Table I). The absolute salivary flow for the stimulated total saliva secretion six months after RT was calculated using the historical parameters reported in Table I. A significant correlation was found between the modelled and the directly measured salivary flow values six months after RT ($R = 0.86$, $p = 0.018$) (Figure 2). The mean absolute difference between the predicted and the measured values was 6 ml/15 min.

In Figure 3 the distances ΔrEF between rEF values for individual glands and the mean dose response function are plotted pairwise for the left and the right parotid gland of the same patient. A linear correlation was found between the ΔrEF values for the right

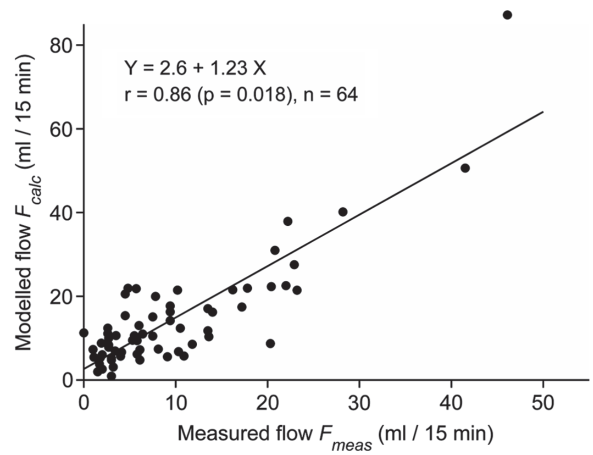

Figure 2. A significant linear correlation was seen between the modelled absolute salivary flow (F_{calc}) and the measured values of salivary flow (F_{meas}) six months after RT.

and the left parotid glands, and there were patients with both ΔrEF values (right and left parotid gland) clearly above or below average (Figure 3A). The comparison was repeated for the measurements performed 12 months after RT and for the same glands at both times (six and 12 months) of measurement (Figure 3B and C).

The average of absolute values of ΔrEF was 0.20 for parotid glands and 0.22 for submandibular glands. The three patient groups of low, medium and high ΔrEF_{mean} had an average ΔrEF_{mean} value of -0.25, 0.02 and 0.24, respectively. For these groups the sigmoidal dose response function was re-fitted, resulting in D_{50} values of 23, 36 and 42 Gy for the low, medium and high ΔrEF_{mean} groups, respectively.

Discussion

In this research, we aimed at validating the absolute salivary flow model in a sample of 64 patients with head and neck cancer. The absolute flow model was used for 64 patients with a good correlation between the modelled and the measured salivary flow. Compared to the earlier form of the model [13], the addition of the absolute value of baseline salivary flow before RT improved the correlation between the modelled and the measured values. Large inter-patient variations were still observed in the predicted salivary flow rates, and the mean absolute deviation between the calculated and the measured values was 6 ml/15 min. Therefore, we also investigated patient-specific variation in the scintigraphy measurements. For this purpose, the distances of the rEF values for the individual glands from the mean dose response curve were calculated in order to see if the glands of an individual patient behave similarly. Our analysis suggests that there is a common pattern of reaction of individual glands (Figure 3). Hence, there may be

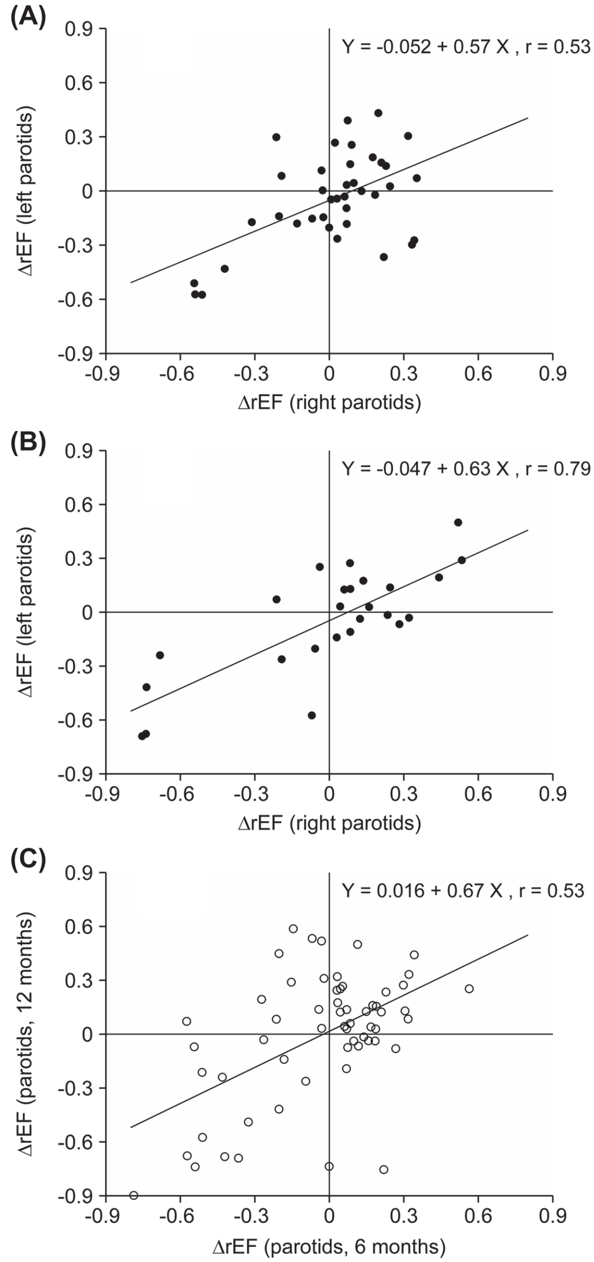

Figure 3. The distance of the measured rEF values from the mean dose-response curve (ΔrEF) A) six months and B) 12 months after RT are presented for the right and the left parotid glands, here one symbol in the plot represents one patient. C) For each gland also the ΔrEF values at six and 12 months after RT were compared.

a common factor, such as patient-specific sensitivity, explaining the similar deviation of separate glands from the mean dose response curve when compared to each other at the same time point, and even at two different time points. It is not probable that some other unknown and uncontrollable random factor, like variable stimulus, day-to-day variation of the patient's response to stimulus or any scintigraphic analysis-specific variation, causes similar effect on both glands on both sides and times. Hence, we believe that this result is indirect evidence for some patient-specific sensitivity that each gland follows.

Different normal tissue complication probability models for salivary function have been compared in literature [13,15–18]. In our analysis, the dose response function for salivary gland rEF was assumed to follow a sigmoidal shape, although the use of linear models or a dose threshold model have also been reported in literature [19]. The value of D_{mean} was assumed to correlate with post-RT sEF values since salivary glands are considered as parallel organs. In the salivary flow model, fitting parameters from Tenhunen et al. [13] were used. These parameters were consistent within their error margins with the corresponding values calculated for the present patient population. However, small deviation in D_{50} values may contribute to some extent to the prediction error of the model. In the creation of the subgroup of patients for the analysis of individual gland behaviour relative to the mean dose response curve several exclusion criteria were used. Only the glands with D_{mean} value between 10 and 50 Gy were included. Within this range sEF values are expected to change as a function of mean dose, and this range is also supported by the varying TD50 range presented by Buus et al. [20]. The glands which were non-functional in the baseline measurement were ignored in the analysis, as very low baseline sEF values often caused abnormally high rEF values (rEF$>>$1) due to large proportion of noise in the sEF values. Additionally, values rEF$>$1.3 were excluded. By these selections the rEF values for the included glands were symmetrically located above and below the mean dose response curve, and no clear outliers were included (Figure 1). The values of rEF$>>$1 suggest that RT improves the function of the salivary gland, which might happen due to decreased tumour compression and/or altered tissue anatomy and physiology caused by RT and/or altered stimulus response after surgery (baseline sEF) and RT in some patient cases. In our analysis the glands with rEF$>>$1 would appear as radioresistant, but as these values are most likely produced by a completely different phenomenon, they were excluded.

In our study some patients showed systematically low or high ΔrEF values six months after RT for both parotid glands. This could be explained by three possible reasons: 1) the variations are related to the measurement technique; or 2) the individual patients react differently to the lemon juice stimulus given during the scintigraphy; or 3) the post-RT sEF is affected by varying individual responses to radiation. The possible problems related to the measurement technique include the consistency of the lemon juice stimulus and any such variation in the performance of the gamma camera or sEF definition that could lead to incorrect value for sEF. When ΔrEF values for the same parotid glands at six and 12 months after RT were compared, usually the same patients had similar values of ΔrEF for the parotid glands at both times of measurement. Hence, we concluded that the differences found in ΔrEF values between patients were not generated by transient instabilities in the measurement technique. Saliva production can be influenced by many different factors at the time of measurement. These include previous smoking, eating and drinking, and use of certain pharmaceuticals. However, by using relative EF values instead of single sEF values, we can at least partly overcome the problem of patients reacting differently to the stimulus, assuming that the factors, such as smoking, that may influence saliva production remain the same between the measurements. In our protocol eating, drinking and smoking were prohibited one hour before measurements. We also repeated the pairwise analysis of left and right parotid glands using a narrower dose range of 15–45 Gy as inclusion criteria for the glands. A clearly improved correlation was seen, as the glands in 45–50 Gy dose range have low values of rEF, including a large relative effect from the inaccuracy of the measurement technique.

In addition, we performed an experiment of dividing patients into three different groups based on ΔrEF_{mean} value calculated using all four major salivary glands. This analysis gives an idea of the variation in the data and D_{50} doses due to possible patient-specific sensitivity to radiation. However, these data include the overall uncertainty of the method, and the contribution of radiosensitivity cannot be exclusively extracted.

Typical variations in the scintigraphic measurement results have been estimated in literature. In a study by Firat et al. [21], applying a similar technique as was used in our institution, a standard deviation (SD) of 0.09–0.14 in sEF was observed in different age groups of normal subjects for both parotid and submandibular glands. A maximum SD of 0.14 in sEF corresponds to 0.2 deviation in rEF. As the variance in sEF also includes possible inter-patient variations in the reaction to the stimulus, which is eliminated in rEF, we estimate 0.2 to be an upper limit for the variation in rEF. In our scintigraphy data, the standard error for the fit of the sigmoidal dose response curve was 0.42 for parotid glands. This suggests that there remains a large component of variation that cannot be explained by the measurement technique. We believe that this variation can partly be due to differences in radiosensitivity.

Furthermore, systematic positioning errors in the longitudinal direction during RT would affect D_{mean} values for both parotid glands in a similar way, which could cause a patient to appear as radiosensitive or resistant in Figure 3, when considering only the ΔrEF values for parotid glands. Therefore the mean systematic patient positioning errors were defined according to the bony structures close to the glands, and the D_{mean} values, which were subsequently used in calculation of ΔrEF, were adjusted accordingly. Uncertainty in the delivered D_{mean} values for the salivary glands due to changes in patient anatomy has been recognised in literature [22,23]. In a recent study [23] the delivered glandular doses were compared to the planned doses for the parotid glands, with a median increase of 0.9 Gy. Complex setup deviations were identified as one major cause for the large dose discrepancies observed in this study (−4.9–8.4 Gy), as the large dose differences were already present at the first treatment fraction. In our analysis, we eliminated the mean effect of the setup deviations in parotid D_{mean}. Hence, the possible errors in D_{mean} values in the present analysis are mainly due to possible shrinkage and shifting of the glands. For this an average movement of 3 mm toward midline has been reported, which in a previous analysis performed in a fraction of our patient data corresponded to a 1.2 Gy dose increase [24]. In the study by Hunter et al., an analysis of dose response relationships showed a large dispersion of the salivary output values after RT for both planned and actually delivered doses, and there was no difference in the ability to predict post-RT salivary output using the planned or the delivered doses. This finding supports the idea that the large variations also seen in our rEF values are rather affected by some other factors, such as radiosensitivity, than the possible inaccuracies in D_{mean}.

In conclusion, the absolute salivary flow model was validated for 64 patients. A considerable inter-patient variation was observed for the predicted salivary flow rates, and hence the variations in scintigraphy data were further investigated. Using an indirect reasoning we believe that one possible explanation of the common variations found in ΔrEF for parotid glands are differences in patients' individual response to radiation. As there are no established methods to predict radiosensitivity before RT, the optimal way of defining radiosensitivity in order to improve predictions of post-RT salivary flow remains a topic for further studies.

Acknowledgements

We would like to thank PhD Jorma Heikkonen for his contribution to the analysis of the scintigraphic measurements, and the Finnish Cancer Foundation and the Finnish Cancer Organisations for the financial support.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Lin A, Kim HM, Terrell JE, Dawson LA, Ship JA, Eisbruch A. Quality of life after parotid-sparing IMRT for head-and-neck cancer: A prospective longitudinal study. Int J Radiat Oncol Biol Phys 2003;57:61–70.
[2] Saarilahti K, Kouri M, Collan J, Hämäläinen T, Atula T, Joensuu H, et al. Intensity modulated radiotherapy for head and neck cancer: Evidence for preserved salivary gland function. Radiother Oncol 2005;74:251–8.
[3] Collan J, Kapanen M, Mäkitie A, Nyman H, Joensuu H, Tenhunen M, et al. Submandibular gland-sparing intensity modulated radiotherapy in the treatment of head and neck cancer: Sites of locoregional relapse and survival. Acta Oncol 2012;51:735–42.
[4] Deasy JO, Moiseenko V, Marks L, Chao KS, Nam J, Eisbruch A. Radiotherapy dose-volume effects on salivary gland function. Int J Radiat Oncol Biol Phys 2010;76:S58–63.
[5] Beetz I, Steenbakkers RJ, Chouvalova O, Leemans CR, Doornaert P, van der Laan BF, et al. The QUANTEC criteria for parotid gland dose and their efficacy to prevent moderate to severe patient-rated xerostomia. Acta Oncol 2014;53:597–604.
[6] Astreinidou E, Roesink JM, Raaijmakers CP, Bartels LW, Witkamp TD, Lagendijk JJ, et al. 3D MR sialography as a tool to investigate radiation-induced xerostomia: Feasibility study. Int J Radiat Oncol Biol Phys 2007;68:1310–9.
[7] Dirix P, De Keyzer F, Vandecaveye V, Stroobants S, Hermans R, Nuyts S. Diffusion-weighted magnetic resonance imaging to evaluate major salivary gland function before and after radiotherapy. Int J Radiat Oncol Biol Phys 2008;71:1365–71.
[8] Doornaert P, Dahele M, Ljumanovic R, de Bree R, Slotman BJ, Castelijns JA. Use of diffusion-weighted magnetic resonance imaging (DW-MRI) to investigate the effect of chemoradiotherapy on the salivary glands. Acta Oncol 2015;54:1068–71.
[9] Buus S, Grau C, Munk OL, Bender D, Jensen K, Keiding S. 11C-methionine PET, a novel method for measuring regional salivary gland function after radiotherapy of head and neck cancer. Radiother Oncol 2004;73:289–96.
[10] Valdés Olmos RA, Keus RB, Takes RP, van Tinteren H, Baris G, Hilgers FJ, et al. Scintigraphic assessment of salivary function and excretion response in radiation-induced injury of the major salivary glands. Cancer 1994;73:2886–93.
[11] Roesink JM, Moerland MA, Hoekstra A, Van Rijk PP, Terhaard CH. Scintigraphic assessment of early and late parotid gland function after radiotherapy for head-and-neck cancer: A prospective study of dose-volume response relationships. Int J Radiat Oncol Biol Phys 2004;58:1451–60.
[12] Münter MW, Hoffner S, Hof H, Herfarth KK, Haberkorn U, Rudat V, et al. Changes in salivary gland function after radiotherapy of head and neck tumours measured by quantitative pertechnetate scintigraphy: Comparison of intensity-modulated radiotherapy and conventional radiation therapy with and without amifostine. Int J Radiat Oncol Biol Phys 2007;67:651–9.
[13] Tenhunen M, Collan J, Kouri M, Kangasmäki A, Heikkonen J, Kairemo K, et al. Scintigraphy in prediction of the salivary gland function after gland-sparing intensity modulated radiation therapy for head and neck cancer. Radiother Oncol 2008;87:260–7.
[14] Bussels B, Maes A, Flamen P, Lambin P, Erven K, Hermans R, et al. Dose-response relationships within the parotid gland after radiotherapy for head and neck cancer. Radiother Oncol 2004;73:297–306.
[15] Houweling AC, Philippens ME, Dijkema T, Roesink JM, Terhaard CH, Schilstra C, et al. A comparison of dose-response models for the parotid gland in a large group of head-and-neck cancer patients. Int J Radiat Oncol Biol Phys 2010;76:1259–65.
[16] Blanco AI, Chao KS, El Naqa I, Franklin GE, Zakarian K, Vicic M, et al. Dose-volume modeling of salivary function in patients with head-and-neck cancer receiving radiotherapy. Int J Radiat Oncol Biol Phys 2005;62:1055–69.
[17] Ortholan C, Chamorey E, Benezery K, Thariat J, Dassonville O, Poissonnet G, et al. Modeling of salivary production recovery after radiotherapy using mixed models: Determination of optimal dose constraint for IMRT planning and construction of convenient tools to predict salivary function. Int J Radiat Oncol Biol Phys 2009;73:178–86.
[18] Beetz I, Schilstra C, Burlage FR, Koken PW, Doornaert P, Bijl HP, et al. Development of NTCP models for head and neck cancer patients treated with three-dimensional conformal radiotherapy for xerostomia and sticky saliva: The role of dosimetric and clinical factors. Radiother Oncol 2012;105:86–93.
[19] Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA. 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 1999;45:577–87.
[20] Buus S, Grau C, Munk OL, Rodell A, Jensen K, Mouridsen K, et al. Individual radiation response of parotid glands investigated by dynamic 11C-methionine PET. Radiother Oncol 2006;78:262–9.
[21] Firat F, Cermik TF, Sarikaya A, Berkarda S. Effects of gender and age on the quantitative parameters of [99mTc] pertechnetate salivary gland scintigraphy in normal subjects. Nucl Med Commun 2006;27:447–53.
[22] Ho KF, Marchant T, Moore C, Webster G, Rowbottom C, Penington H, et al. Monitoring dosimetric impact of weight loss with kilovoltage (kV) cone beam CT (CBCT) during parotid-sparing IMRT and concurrent chemotherapy. Int J Radiat Oncol Biol Phys 2012;82:e375–82.
[23] Hunter KU, Fernandes LL, Vineberg KA, McShan D, Antonuk AE, Cornwall C, et al. Parotid glands dose-effect relationships based on their actually delivered doses: Implications for adaptive replanning in radiation therapy of head-and-neck cancer. Int J Radiat Oncol Biol Phys 2013;87:676–82.
[24] Kapanen M. Accuracy of absorbed dose in external photon beam radiotherapy: What level is sufficient and how to approach it? [dissertation] University of Helsinki, Report Series in Physics, HU-P-D163. Helsinki: Helsinki University Press; 2009. p. 56–7.

Supplementary material available online

Supplementary Table I available online at: http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1067717