The Effect of Radiotherapy on the Excretion and Concentration Functions of the Salivary Glands

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ABSTRACT

Salivary glands are often exposed to radiation during head and neck cancer radiotherapy (RT). In this study, the effect of radiation doses on concentration and excretion functions of salivary glands was investigated in patients receiving RT. Twenty-five patients were prospectively evaluated. The 99m Technetium (^{99m}Tc)-pertechnetate salivary gland scintigraphy was performed to each patient before RT (pre-RT) , at the end of RT and 3rd month after RT (3rd month). Submandibular and parotid glands were separately evaluated. Scintigraphic evaluation of the submandibular glands didn't show any significant difference in mean cumulative doses on the concentration function at pre-RT, end of RT and 3rd month (p= 0.572). In excretion function there was a significant difference between pre-RT and 3rd month (p< 0.001); the end of RT and 3rd month (p= 0.006). When the dose was above 40 Gy, mild-moderate deterioration in the excretion function and when the dose was between 50-60 Gy, severe dysfunction was observed. For parotid glands; significant difference between pre-RT and end of RT (p< 0.001); pre-RT and 3rd month (p< 0.001) in concentration function was observed. When the dose was above 40 Gy, dysfunction was evident. Statistically significant difference was found in parotid glands' excretion function, between pre-RT and end of RT (p< 0.001); end of RT and 3rd month (p= 0.009); pre-RT and 3rd month (p< 0.001). With doses above 20 Gy, mild to moderate dysfunction and above 40 Gy, severe dysfunction was seen. For submandibular gland although the mean cumulative dose and the concentration function were not significantly related, the excretion function was significantly affected. There was a significant correlation between the mean cumulative dose of the parotid gland and its concentration and excretion functions.

Keywords: Salivary glands, Radiotherapy, 99m Technetium (Tc)-pertechnetate salivary gland scintigraphy, Excretion function, Concentration function

INTRODUCTION

Head-neck tumors constitute about 3% of all cancer types and are the most common 6th cancer type in the whole world.[1,2] Radiotherapy (RT) plays an important role as a treatment method in almost all phases of head-neck cancers. However, RT can cause significant side effects. Salivary glands are usually irradiated in patients receiving RT for head-neck cancers, and side effects develop from RT. The main mechanisms causing damage to salivary gland cells are apoptosis, necrosis and autophagia. The basic mechanism for radiation damage and function loss is thought to be apoptosis rather than necrosis and autophagy.[3] As a result, after RT, loss of function in the salivary gland and, consequently, decreased salivary flow, decreased salivary pH, electrolyte and immunoglobulin alterations, changes in the oral flora occur.[4,5] One of the methods to measure the function of the parotid and submandibular gland is ^{99m}Tc-pertechnetate salivary gland scintigraphy.[6,7] It uses the absorption and excretion properties of radioisotopes such as ^{99m}Tc in salivary glands for functional evaluation.[8,9]

The ^{99m}Tc is seized and secreted easily in the ductal epithelium of the salivary glands so it allows us to obtain quantitative information about the function of the secretion gland.[10,11] In this way, the discharge and concentrating function of the gland is measured objectively. Vades Olmos et al. have shown that the first effect of radiation is on the discharge function. In the late period, concentration function is affected.[12] There are a few studies about RT doses and its effects on the function of the glands. We aimed in this study to assess how the RT doses affect the concentration and excretion functions of salivary glands in head-neck cancer patients and contribute future pharmacological intervention with sialagogues for xerostomia in patients who underwent RT.

PATIENTS AND METHODS

Study Group

For this study, 25 patients who underwent RT in the head-neck region between August 2012-January 2014, fulfilling the study eligibility criteria, were prospectively evaluated.

Patient selection criteria: Patients with good performance (ECOG 0-2), who underwent RT in the head-neck area with T1-4 N0-3 M0 stage, with no neck dissection, and no renal dysfunction for salivary gland scintigraphy were included in the study.

The performance evaluation of the patients was based on the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) scale.[13] The characteristics of the patients are shown in Table 1.

Chemotherapy protocols of patients: The Chemotherapy (CT) status of other patients is shown in Table 2.

Table 1. Patient and tumour characteristics

Characteristics	n (%)
Gender	
Female	5 (20)
Male	20 (80)
ECOG	
0	13 (52)
1	11 (44)
2	1 (4)
Primary Site	
Nasopharynx	10 (40)
Oropharynx	1 (4)
Hypopharynx	3 (12)
Larynx	4 (16)
Oral cavity	3 (12)
Others	4 (16)
Tumor histology	14 (56)
Undifferentiated carcinoma	6 (24)
Diffuse B cell lymphoma	2 (8)
Malignant epithelial tumour	2 (8)
Insular carcinoma	1 (4)
Primary tumor size (*)	
T1-2	9 (36)
T3-4	14 (56)
Regional lymph node involvement (*)	
N0	6 (24)
N1	6 (24)
N2	9 (36)
N3	2 (8)
Tumor stage (*)	
I	–
II	3 (12)
III	11 (44)
IVA	6 (24)
IVB	3 (12)

(*) For 2 patients diagnosed with lymphoma only the stage (Ann Arbor) is provided

Plan Evaluation

RT was performed using the IMRT technique for all patients included in the study. Dose distributions obtained through the virtual environment through the planning tomography of the patients who were completed treatment and the dosages of submandibular and parotid glands from dose-volume histograms were recorded. Quantitative scintigraphic measurement was performed at the beginning of treatment, at the end of treatment and at 3rd month after treatment.

Table 2. CT schema

	Number of the patients	Percentage of the patients
CT before RT	5	20
CT simultaneously with RT	22	88
CT after RT or CRT	7	28

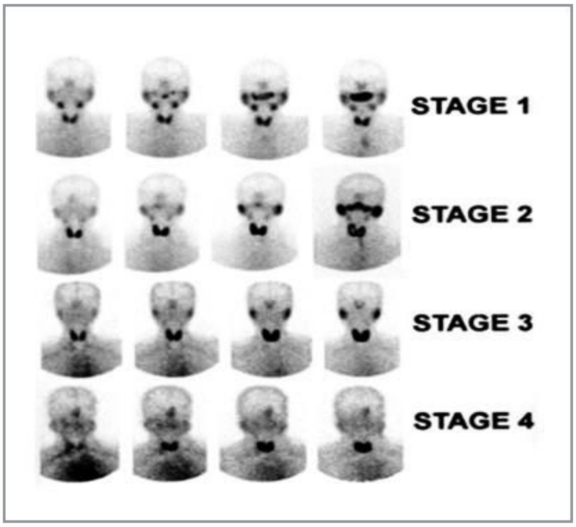

Figure 1. Visual evaluation of salivary gland scintigraphy

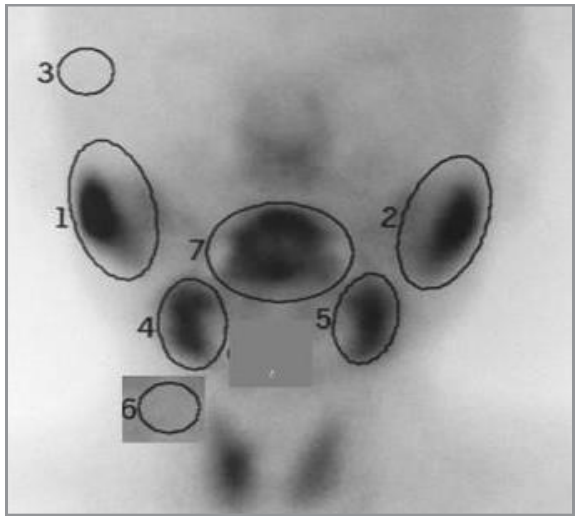

Figure 2. Determination of areas of interest for each salivary gland and ground

Evaluation of the Salivary Gland Scintigraphy

Patients were administered 370 MBq (10 mCi) ^{99m}Tc-pertechnetate in the supine position. The head and neck were monitored via dynamic follow-up of one minute (128x128 matrix) during 40 minutes as so they are included in the imaging area. In the 20th minute, 5 cc of lemon juice was given orally. For both parotid and submandibular glands, the ROI (Region Of Interest) was drawn. The time-activity curve was obtained. The evaluation was performed in two ways visually and numerically, and all evaluations were made by the same nuclear medicine specialist.

In the scintigraphy evaluation of the damage that occurred in the glands with doses of the submandibular and parotid glands, the right and left submandibular glands were evaluated separately. Likewise, the right and left parotid glands were evaluated separately.

Visual Evaluation: The patients were visually divided into 4 stages according to uptake and excretion of the salivary glands, and the increase in the visual stage showed an increase in the dysfunction of the gland. Visual evaluation of glands'function was shown in Figure 1.

Stage 1 (Normal): Normal uptake and normal excretion

Stage 2 (Mild to moderate dysfunction): Decreased uptake and delayed excretion, the oral activity is equal to the salivary gland activity in the 40th minute (end of study).

Stage 3 (Moderate-severe dysfunction): Significantly decreased uptake and delayed excretion, oral activity is lower than the salivary gland activity in minute 40.

Stage 4 (Severe dysfunction): Significantly decreased uptake, no excretion. The cardiac and background (ground) activity in minute 40 is higher than the salivary gland activity.

Numerical Evaluation: ROI was drawn through both parotid and submandibular glands and oral activity. The oral activity (7) ground activity of parotid glands (1-2) were drawn from the right zygomatic region (3), and the ground activity (6) of both submandibular glands (4-5) was drawn from the right lateral section of the neck by drawing ROI and shown in Figure 2.

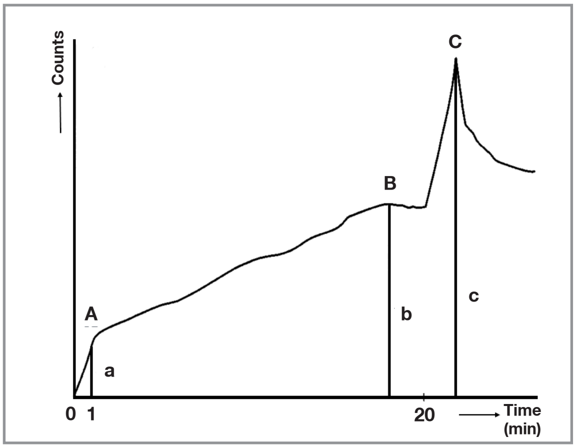

Figure 3. Schematic view of the time activity curve for oral activity in a normal salivary gland scintigraphy

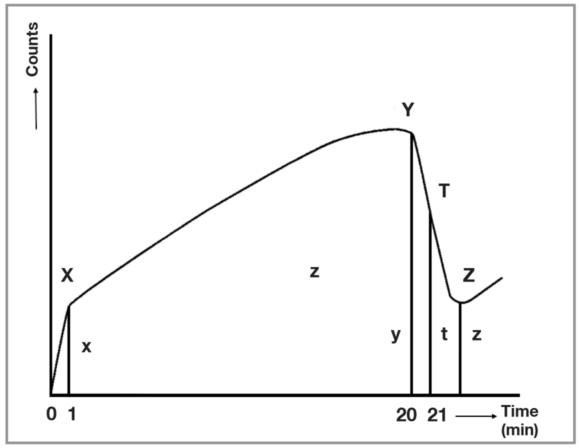

Figure 4. Gland activity-time curve in normal salivary gland scintigraphy (x axis: time [minute])

First, the ground activity was removed and the oral activity curve was drawn. Oral activity values before lemon stimulation (PRI: Prestimulatory index), oral activity after lemon stimulation (POI: Poststimulatory index) values were found in the time-activity curve which were drawn as Figure 3 and Figure 4.

Figure 3 represents; A: Vascular perfusion peak, B: Maximum activity point before stimulation. C: Maximum activity point after stimulation. a, b, and c show the count value at points A, B, and C, respectively. PRI= (b-a)/b*100 (%) and POI= (c-a)/c*100 (%)

Figure 4 represents; Vascular perfusion peak (X) at minute 1, maximum activity in the salivary gland at minute 20 before stimulation (Y), the salivary gland activity (T) on the minute 21, the minimum activity in the salivary gland after stimulation (Z). x, y, z, and T represent the count value at the points X, Y, Z, and T, respectively.

Secondly, the time-activity curves of both the submandibular gland and parotid glands were obtained by removing the ground activity. Upon these curves, the accumulation on minute 20 (A20), maximum secretion (MS), uptake rate on minute 20 (A20UR) and the secretion rate (SV) were calculated for each salivary gland for each imaging, according to the following formulas for the right and left submandibular and parotid glands;

A20 (%)= (y-x)/y*100 and MS (%)= (y-z)/y*100

A20UR= Uptake on minute 20/ground activity and SV (%/min)= (y-t)/y*100

Statistical Analysis

Analyzes were performed with IBM SPSS Packet version 24.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics for continuous (quantitative) variables are expressed as "mean", "standard deviation", "minimum-maximum and median" values, while categorical variables are expressed as number (n) and ratio (%). Categorical demographic characteristics of the patients were calculated by Chi-square and Fisher's exact test. Compliance of the variables to the normal distribution was evaluated by visual and analysis methods and parametric tests were used for the data matching the normal distribution, and parametric tests were used. Comparisons between two groups performed by Student-t Test and more than two groups were performed by ANOVA test. The Tukey test was used in comparisons between the binary groups. The paired sample T-test was used to compare measurement groups before and after treatment. $p < 0.05$ values were considered statistically significant.

RESULTS

Twenty five patients aged between 29-76 years (median age 57) were included in the study and the mean follow-up time of the patients was 4.6

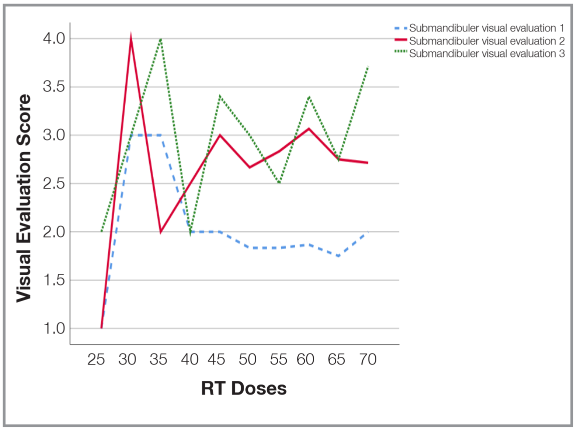

Figure 5. Visual evaluations stages the pre-RT (1), end of RT (2), and 3rd month (3) according to the submandibular dose groups

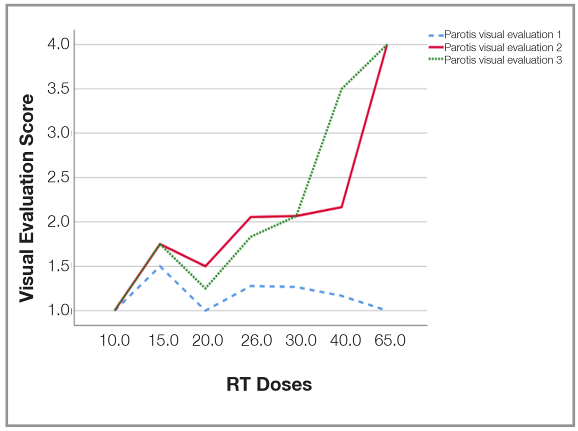

Figure 6. Visual evaluations stages pre-RT (1), end of RT (2), and 3rd month (3) according to the parotid dose groups

months (2-5.5 months). In 24 out of 25 patients, both the stimulated salivary amount measurement and the scintigraphic measurement were performed completely at the beginning of treatment, at the end of treatment and 3rd month follow-up. In one patient, at 3rd month follow-up measurement wasn't performed. 22 patients received CT simultaneously with RT. Three patients, of whom 2 with DBBHL and 1 with thyroid ca have been administered only RT.

The median treatment dose of patients was 70 Gy (30-70 Gy). The median doses of the submandibular glands were 57 Gy (24-71 Gy) and for parotid glands were 27 Gy (11-66 Gy). The salivary gland function of the patients was evaluated visually and numerically by salivary gland scintigraphy.

Visual Evaluation Results

Visual Evaluation of Submandibular Glands

As a result of the visual evaluation of the submandibular glands, an increase in the stage was observed at the end of RT compared to pre-RT. In the third month evaluation, an increase in the visual stage was also observed compared to pre-RT and end of RT. The increase in dysfunction was evident at doses above 35 Gy for the end of RT, while dysfunction in the 3rd month was significant at doses above 40 Gy (Figure 5).

There was a significant difference between pre-RT, end of RT and the 3rd month measurements for the submandibular glands ($p< 0.001$). Visual evaluation at the end of RT and the 3rd month was significantly different from visual evaluation at pre-RT ($p< 0.001$). The difference between end of RT and the 3rd month was not statistically significant ($p= 0.181$). Namely, while the measurements' changes were significant in two groups than pre-RT, there was no significant difference between the end of RT and 3rd month measurements.

In summary, there was a significant change in the function of the gland between pre and end of RT in the visual evaluation of the submandibular gland. However, this change was not significant in the prolonged periods after RT.

Visual Evaluation of the Parotid Glands

As a result of the visual evaluation of the parotid glands, an increase in the stage was observed at the end of RT compared to pre-RT. In the 3rd month evaluation, there was an increase in the visual stage compared to pre and end of RT stages. This increase was evident at the dose of > 40 Gy for the end of RT, and severe dysfunction was present at ≥ 65 Gy. For the 3rd month, the increase in dysfunction was evident after the dose exceeded 30 Gy (Figure 6).

There was a significant difference between pre-RT, end of RT, and the 3rd month measurements ($p< 0.001$). Visual evaluation at the end of RT and the 3rd month was significantly different from visual evaluation pre-RT ($p< 0.001$). The difference between the end of RT and the 3rd month was not statistically significant (p= 0.953). Namely, while the changes of measurements were significant in two groups compared to pre-RT, there was no significant difference between end of RT and the 3rd month measurements. In summary, there was a significant change in the gland's function between the pre-RT and the end of RT period in the visual evaluation of the submandibular gland. However, this change was not significant in the prolonged periods after RT. With this feature, a similar and consistent result was observed with the visual evaluation of the submandibular gland.

Numerical Evaluation Results

A20 and A20UR values were used to determine the salivary glands' concentration (uptake) function in the scintigraphic numerical evaluation of the damage caused by the doses of the submandibular and parotid glands. MS, SV, POI, and PRI values were used to determine the salivary glands' excretion function.

Numerical Evaluation for Submandibular Glands

There was no statistical difference between mean cumulative doses of submandibular glands and A20 values at pre and the end of RT (p= 0.390), pre-RT and 3rd month (p= 0.572), as well as between end of RT and 3rd month periods (p= 0.911).

When comparing the mean cumulative doses of submandibular glands with A20UR values, a decrease in A20UR value was observed when the dose exceeded 40 Gy for the end of RT and 3rd month measurements. There was no significant relationship between the changes at pre-RT and the end of RT (p= 0.980), end of RT and the 3rd month (p= 0.061), and pre-RT and at the 3rd month periods (p= 0.229).

When comparing the mean cumulative dose of submandibular glands with MS and SV values, there was a sharp decrease in doses between 50 and 60 Gy, but no significant change after 60 Gy. MS and SV values were different at pre-RT with end of RT (MS: p= 0.000 and SV: p= 0.002) and the 3rd month measurements (MS: p< 0.001 and SV: p< 0.001). Likewise, there was a difference between the 3rd month measurements and the end of RT values (MS: p= 0.024 and SV: p= 0.019). These values were found to be statistically significant.

When comparing the mean cumulative dose of submandibular glands with PRI values, there was a decrease at the end of RT values after the dose exceeded 40 Gy. There was a sharp decrease in the 3rd month values between 30-40 Gy, a moderate decrease between 50-70 Gy.

When comparing the mean cumulative dose of submandibular glands with POI values, there was a decrease at the end of RT values after the dose exceeded 40 Gy. There was a sharp decrease in the 3rd month values with doses above 50 Gy. While there was no statistically significant difference in PRI and POI values in pre-RT and end of RT (PRI:p= 0.125 and POI: p= 0.508), the difference between the end of RT and the 3rd month was found to be statistically significant (PRI: p= 0.009 and POI: p= 0.006). However, the difference between pre-RT and 3rd month values was also statistically significant (PRI: p< 0.001 and POI: p= 0.002).

Based on these findings, while there was no significant relationship between mean cumulative doses of submandibular glands and concentration function, there was a significant relationship between excretion function and mean cumulative doses. After the average cumulative dose of submandibular glands exceeded 40 Gy, it was seen an impairment in the gland's excretion function. When the dose was between 50-60 Gy, impairment in excretory function was severe.

Numerical Evaluation for Parotid Glands

While the mean cumulative dose of the parotid gland was > 40 Gy, as the dose increased, there was a sharp decrease in A20 values both at the end of RT and at the 3rd month. While there was a significant difference between the change of pre-RT and the end of RT (p< 0.001) and pre-RT and the 3rd month A20 values (p< 0.001), there was no statistically significant difference in the change between the end of RT and the 3rd month values (p= 0.953).

In the comparison of the mean cumulative doses of the parotid glands and A20UR values, there was no significant difference between the pre-RT and the end of RT (p= 0.970), the end of RT and the 3rd month (p= 0.222), and pre-RT and the 3rd month periods (p= 0.230)

When comparing the mean cumulative doses of the parotid glands with MS values, after the dose exceeded 40 Gy, there was a moderate decrease in MS values at the end of RT, while there was a sharp decrease after 40 Gy at the 3rd month. According to the measurements pre-RT, while there was a significant difference at the end of RT (p< 0.001) and 3rd month changes (p< 0.001), no significant difference was found in the 3rd month measurements compared to the end of RT (p= 0.440).

Comparing the mean cumulative doses of the parotid glands with SV values, there was a sharp decrease at the end of RT and 3rd month values with doses above 20 Gy, whereas there was a moderate decrease in the 40-60 Gy. In the evaluation of SV measurements for parotid glands, statistically significant differences were found between pre-RT and the end of RT (p< 0.001); the end of RT and the 3rd month (p= 0.031); pre-RT and the 3rd month (p< 0.001).

Comparing the mean cumulative doses of the parotid glands with PRI and POI values, when the dose was above 40 Gy, there was a sharp decrease in PRI and POI values both at the end of RT and at the 3rd month. The 3rd month values were lower than pre-RT and the end of RT values. While there was no significant correlation between pre-RT and the end of RT values (PRI: p= 0.120 and POI: p= 0.500), statistically significant differences were found between the end of RT and the 3rd month (PRI: p= 0.009 and POI: p= 0.006) pre-RT and the 3rd month values (PRI: p< 0.001 and POI: p= 0.002).

Based on these findings, it is possible to say that there is a deterioration in the parotid gland's concentration function at doses above 40 Gy. When the dose is above 40 Gy, there is a severe impairment of the excretion function, and this impairment is quite evident in the 3rd month. While there is no significant relationship between the end of RT and pre-RT values, there is a statistically significant relationship between the end of RT and 3rd month values.

DISCUSSION

In our study, we examined the difference between the deterioration of the functions of the parotid and submandibular glands with the doses of the glands in patients receiving radiotherapy in the head-neck area by taking the measurements of salivary gland scintigraphy before RT, at the end of RT and at the 3rd month after RT.

As a result of the scintigraphic evaluations, when the cumulative mean dose of the parotid gland is above 40 Gy, there is deterioration in both concentration and excretion function. Chen et al., found a strong relationship between the mean parotid dose and the excretion of the parotid gland after RT, in the 1st and 2nd year. They investigated the relationship with the patient or treatment related factors (age, tumor region, surgery and CT), but showed that the only factor associated with the excretion of the parotid gland was the mean parotid dose.[14] Many studies show that the maximum dose of the gland should be between 31-43.9 Gy to preserve the function of the parotid gland.[15,16,17] In our study, significant deterioration was detected in the excretion function of the parotid gland with doses 40 Gy and above as a result of the prospective evaluation.

While there was no significant difference between the average cumulative doses of the submandibular glands and the concentration function, a significant difference was found between the excretion function. After the mean cumulative dose of the submandibular glands exceeds 40 Gy, there is a sharp decrease in the excretion function of the gland, and the deterioration of the excretion function is found severe while the dose is between 50 Gy-60 Gy. Vades Olmos et al. have shown in their study that the first effect of radiation is on the discharging function. In the late period, the deterioration in the concentration function is added.[12] Since we don't have long-term follow-up results in our study, there is no further examination of the deterioration in the concentration function. If the follow-up time was longer, it would be possible to see deterioration in the concentration function. In this study, it was stated that the most sensitive and first affected function of the major salivary glands was ejection fraction.[12] The threshold dosage for the submandibular glands is higher than the threshold dose previously specified for the parotid gland (26 Gy). These findings show us that the submandibular glands are less radiosensitive than the parotid gland. Parotid glands are the most radiosensitive salivary glands. The functional changes in the parotid gland depend on the RT dose and the irradiated RT volume.[18] Olmos et al. showed that there is a decreased excretion in the salivary glands in low to moderate doses but normal acinar secretion.[12] In high doses, it has been shown that secretion function is being inhibited by the loss of isotope uptake towards the salivary glands. This data supports the assertion that the dramatic decrease in the amount of saliva after the first few fractions of RT is dependent on a cause other than acinar destruction.[19]

In patients receiving concomitant CT, the deterioration rate of the salivary gland function in both end of RT and at the 3rd month, was higher compared to the patients who don't receive CT. Kosuda S. et al., in their follow-up using salivary gland scintigraphy, showed that the CT alone does not cause changes in the discharge rate of the salivary gland, but when the CT is combined with RT, it increases RT-associated salivary gland damage. Compared to RT alone, they demonstrated that there is a significant decrease in salivary discharge rate in CRT.[7]

The strengths of our study is its prospective aspect. The contours and scintigraphic evaluations were performed by a single researcher to reduce the interobserver differences. In addition, objective parameters were used to assess the salivary gland functions in our study.

The limitations of this study are the relatively small sample size and the short follow-up period. Longer-term follow-ups with larger sample sizes in future studies may be useful in understanding the factors that affect the prediction of salivary gland dysfunction.

Conclusion

There is a significant difference between the mean cumulative doses of the parotid gland and the deterioration of both concentration and the excretion function. Although there is no significant difference between the mean cumulative dose of the submandibular gland and the concentration function, there is a significant difference between the excretion function. Longer follow-up is necessary to demonstrate deterioration in the concentration function.

When compared to the RT alone, the CRT has been shown to have a significant decrease in salivary discharge rate. However, in our study, since there are three patients who didn't undergo CT, more patients should be evaluated to obtain statistically significant results. Although this study is efficient in terms of guiding pharmacological treatments about salivary secretion in the future, studies with larger patient groups are needed.

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