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# Comprehensive assessment of xerostomia in patients receiving radiation for head and neck cancer

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*Original Article*

## Abstract

**Purpose:** Xerostomia is a well known complication of radiation for head and neck cancer. It causes significant impairment of Quality Of Life (QOL).Comprehensive assessment is possible with the help of scintigraphy, Dose-volume histogram (DVH) parameters as well as QOL questionnaire. **Methods:** Thirty patients of head and neck cancer undergoing radiation were assessed for xerostomia. Scintigraphic assessment of parotid gland function was done before and at six weeks after radiation. QOL questionnaire was administered before, during, and at six weeks after radiation as well as at two years of follow up. Dose received by parotids were correlated with scintigraphic and QOL outcomes. **Results:** Mean parotid gland volume and dose received were 24.9 cc and 45.3 Gy respectively. Mean Salivary Excretion Factor (SEF) decreased from 54.1 to 12 at six weeks after radiation. QOL scores worsened from first week (mean value: 2.37) of radiotherapy (RT) to fourth week (mean value: 15.50, $p < 0.0000$) , remained same till completion of RT (mean value: 17.57, $p = 0.1063$) and at six weeks after radiation (mean value:16.10, $p = 0.2519$ ). There was a significant decrease in QOL scores between post RT six weeks versus two years follow up ($p < 0.0000$). Mean parotid dose and QOL scores correlated at six weeks ($p < 0.0000$), whereas no correlation was found between SEF and QOL. **Conclusion:** Comprehensive assessment of parotid gland function with Scintigraphy, QOL questionnaire and its correlation with dose volume parameters is helpful in quantifying xerostomia. Even though radiation induced xerostomia persisted for a long time after radiation, it did not translate to decreased QOL.

**Keywords**: Scintigraphy; Xerostomia; Quality of Life; Head and Neck Cancer; Radiotherapy

## 1. Introduction

Over 200,000 cases of head and neck cancers occur each year in India accounting for 30% of all cancers in males and 11 to 16% of all cancers among females. More than half of them present with locally advanced disease.[1] Over the years, the treatment of head & neck cancer has changed from radical surgery to organ or function preserving multimodality approach. Radiation has an important role in definitive as well as adjuvant context. Xerostomia is one of the most important sequelae of radiation, which interferes with the Quality Of Life (QOL) of the patient. Exact incidence is unclear since grading; definition and radiation fields vary, but ranges from 60% to 100%.[2] It lasts for up to several months to years and may or may not recover, depending on the volume of salivary glands irradiated, the total radiation dose and individual patient variation.[3] With the advent of computed tomography (CT) based planning, quantification of dose received by parotid is possible. The different ways of assessing parotid gland function are scintigraphy[4], QOL questionnaire[5, 6, 7] among many others. Although enough data is available on each of these, a combination of these would be ideal and the data is sparse.[8] In this study, an attempt is made to correlate dose volume characteristics of parotid with subjective as well as objective assessment of xerostomia.

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## 2. Methods and Materials

This prospective study was conducted between December 2011 & May 2013 in which thirty patients of head and neck cancer were included. Sample size was decided in consultation with the biostatistician, with a power of 80% & alpha error of 5%. Inclusion criteria were biopsy proven patients undergoing definitive or adjuvant radiation with both parotids in the field of irradiation. Patients who had tumors of parotid, history of drug intake causing xerostomia, previous parotid surgery and earlier irradiation were considered as exclusion criteria.

**Table 1:** Questionnaire to assess xerostomia

| | Questions | No | Mild | Severe |
|---|---|---|---|---|
| 1 | Do you have pain in your mouth? | | | |
| 2 | Do you have any dryness in your mouth? | | | |
| 3 | Do you have trouble in eating? | | | |
| 4 | Do you have problem swallowing liquids? | | | |
| 5 | Do you have problem chewing solid food? | | | |
| 6 | Do you have problem swallowing solid food ? | | | |
| 7 | Have you choked when swallowing? | | | |
| 8 | Do you have sticky saliva? | | | |
| 9 | Do you have problem with your sense of taste? | | | |
| 10 | Do you have problem with your sense of smell? | | | |
| 11 | Do you have trouble enjoying your meals ? | | | |
| 12 | Do you have cough? | | | |
| 13 | Do you have trouble in talking? | | | |

Following informed consent and investigations, all patients were treated as per the department protocol. This included immobilization, CT simulation with 3 - 5 mm cuts, contouring and treatment either with 3 dimensional conformal radiation therapy (3DCRT) or intensity modulated radiation therapy (IMRT). For patients with adjuvant intent, a dose of 60 Gy and for patients with definitive intent 66 - 70 Gy with two Gy per fraction over six to seven weeks was given. Dose received by parotids was obtained from dose volume histogram (DVH) parameters. Patients also received neoadjuvant or concurrent cisplatin chemotherapy. Scintigraphic evaluation of parotid was done prior to radiation and at six weeks after completion.

**Table 2:** Patient and treatment characteristics

| Variable | At 6 weeks post RT (%) | At 2 year follow up (%) |
|---|---|---|
| Sex | | |
| Male | 23 (77) | 11 (91.7) |
| Female | 7 (23) | 1 (8.3) |
| Age | | |
| 31-40 | 3 (10) | 1 (8.3) |
| 41-50 | 13(43) | 6 (50) |
| 51-60 | 7 (23) | 1 (8.3) |
| 61-70 | 7 (23) | 4 (33.3) |
| Site of malignancy | | |
| Nasopharynx | 2 (7) | 1 (8.3) |
| Oral cavity | 7 (23) | 2 (16.7) |
| Oropharynx | 6 (10) | 4 (33.3) |
| Hypopharynx | 7 (23) | 2 16.7) |
| Larynx | 5 (17) | 2 (16.7) |
| Others | 3 (10) | 1 (8.3) |
| Treatment given | | |
| Adjuvant RT CT | 4 (13) | 1 (8.3) |
| Radical RT CT | 26 (87) | 11 (91.7) |
| NACT | 5 (16.7) | |
| Radiation technique | | |
| IMRT | 7 (23) | 5 (42) |
| 3DCRT | 21(70) | 7 (58) |
| Conventional | 2 (7) | 0 |

Maximal uptake of the tracer without stimulus (a) and after stimulation with lemon juice (b) were recorded as counts per second (ct/s). Saliva Excretion Factor (SEF) was calculated using equation (a - b) / a.[4] SEF ratio was calculated by dividing SEF at post RT six weeks with SEF at baseline. To assess QOL associated with xerostomia, the most widely used questionnaire is QLQ - C30 and the QLQ – H & N35. But, in a country like ours with lot of diversity in language, culture and educational levels, such a valid questionnaire which can uniformly reflect QOL is challenging. Hence, a modified version similar to Benjamin *et al.*[9] was used to assess QOL weekly during RT, at six weeks post RT and at two years after completion of radiation (Table 1).

### 2.1 Statistical Analysis

The statistical software IBM SPSS 16 and 20 were used for analysis of the data. Paired t-test was used to find the significance of study parameters on continuous measurements and QOL scores across time. Unpaired t - test was used to test for significance between independent samples like right and left parotid glands. Mann - Whitney U test was used to find any difference between technique and QOL scores at two years follow up. Karl Pearson's correlation coefficient was used to find correlations between the various scintigraphic measures, QOL scores and parotid gland doses. P - value lower than or equal to the significance level of 5% was considered as statistically significant.

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**Table 3:** Change in scintigraphic measures with RT

| Change in aat 6 weeks after RT | | | | | | | |
|---|---|---|---|---|---|---|---|
| Time | Mean | SD | Mean difference | SD | %of change | Paired t | P value |
| Baseline | 2921.85 | 1528.15 | 945.69 | 930.07 | 32.37 | 7.8102 | 0.0000 |
| Post RT | 1976.15 | 1195.32 | | | | | |
| **Change in bat 6 weeks after RT** | | | | | | | |
| Time | Mean | SD | Mean difference | SD | %of change | Paired t | P value |
| Baseline | 1244.07 | 569.82 | -500.39 | 991.32 | -40.22 | -3.8772 | 0.0003 |
| Post RT | 1744.46 | 1068.45 | | | | | |
| **Change in SEF 6 weeks after RT** | | | | | | | |
| Time | Mean | SD | Mean difference | SD | %of change | Paired t | P value |
| Baseline | 54.06 | 16.09 | 42.05 | 19.10 | 77.79 | 16.9093 | 0.0000 |
| Post RT | 12.01 | 9.39 | | | | | |

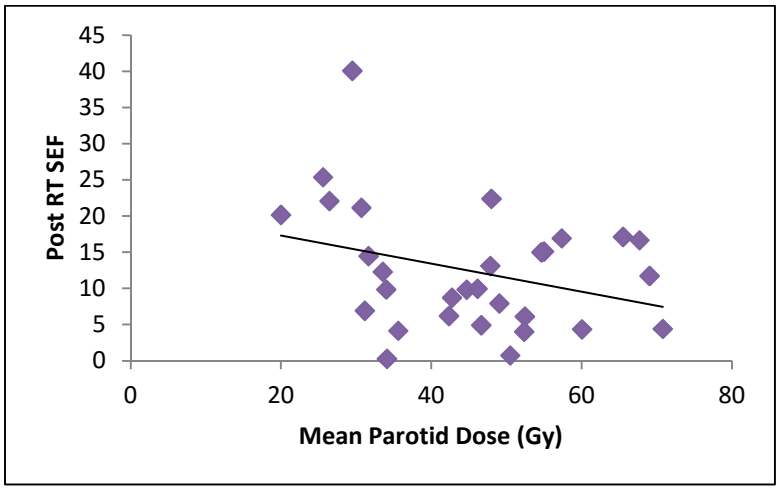


**Figure 1:** Graph showing correlation of Post RT SEF with Mean Parotid Dose. SEF reduced from 54.06 to 12.01 indicating 77.79% reduction following radiation. (r = -0.3113, p = 0.0163)

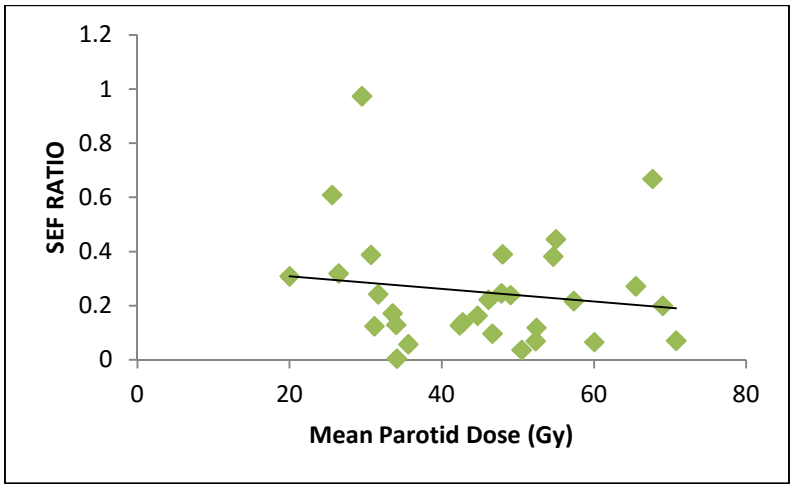


**Figure 2:** Graph showing correlation of SEF ratio with Mean Parotid Dose. SEF ratio in our study was 24.8 indicating the parotid were functioning at 75% of their initial activity post irradiation (r = -0.3730, p = 0.0036).

## 3. Results

A total of 30 patients of head & neck cancer were accrued and the study population included 23 (77%) men and seven (23%) women. The age of the patients ranged from 33 to 70 years with a median of 49.5 years. There was an equal distribution between oral cavity, oropharynx and hypopharynx. Out of 30 patients, four patients underwent surgery and were treated with adjuvant radiation. Two patients were carcinoma tongue and underwent wide local excision and neck dissection. One patient had metastasis of unknown origin and underwent modified radical neck dissection while the fourth patient underwent R2 resection for middle ear carcinoma. Five patients received three cycles of cisplatin based neo adjuvant chemotherapy followed by definitive RT. Out of 30 patients, 21 were treated with 3DCRT, seven with IMRT and two with conventional technique (Table 2). At two years follow up out of 30 patients, 12 were alive for analysis. The mean dose received by the parotid glands was 45.3 Gy, ranging from 16.4 Gy to 72 Gy without any variation between the sides. The mean parotid gland volume was 24.9 cc with no significant variation between the sides. In scintigraphy the mean maximal uptake of the tracer prior to RT ranged from 789 ct/s to 7980 ct/s with a mean of 2921 ct/s with no significant differences between the two sides. This uptake dropped to 1976 ct/s post RT. The post stimulus nadir, b, prior to RT ranged from 304 ct/s to 2890 ct/s with a mean of 1244 ct/s, which has become 1744 ct/s post radiation. The SEF value calculated from a and b is 54.1 with Standard Deviation (SD) of 16.1. The SEF has come down to 12 with a SD of 12 at six weeks post RT. The change in SEF six weeks post RT is 77.79% which is statistically significant (p = 0.0000) (Table 3).

### 3.1 Correlation of scintigraphy with dose and volume

The post RT SEF was significantly correlated with mean parotid dose (r = - 0.3113, p = 0.0163) (Figure 1) but not with mean parotid gland volume. Significant correlation was also observed between the SEF ratio at six weeks and mean parotid gland dose (r = - 0.3730, p = 0.0036) (Figure 2). No significant correlation was found between the scintigraphic measures a, b, Baseline SEF, SEF change and mean parotid gland dose.

### 3.2 Correlation of QOL scores with dose and volume

QOL scores worsened significantly from the first week of RT to fourth week (p = 0.0000) and remained same with no statistically significant change till completion of RT (p = 0.1063), post RT six weeks (p = 0.2519) and improved at two years follow up. There is a significant decrease in QOL scores between week seven of RT versus two year follow up (p = 0.0000) and post RT six weeks versus two year follow up (p = 0.0000) (Figures 3 & 4). There is no statistically significant difference between the two radiation techniques. (p = 0.7443).

The mean parotid dose and QOL are significantly correlated at six weeks (r = 0.3116, p = 0.0004) (Figure 5). No significant correlation was found between the post RT SEF, SEF change or SEF ratio with QOL scores at six weeks.

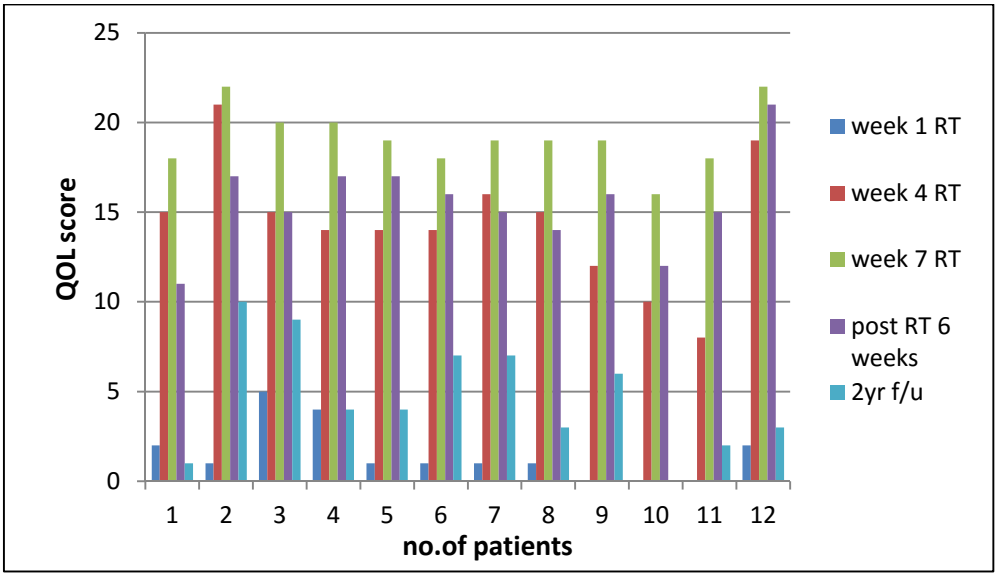


**Figure 3:** Bar diagram showing QOL scores of twelve patients. There was a significant decrease in QOL scores between post RT six weeks versus two years follow up (p = 0.0000)

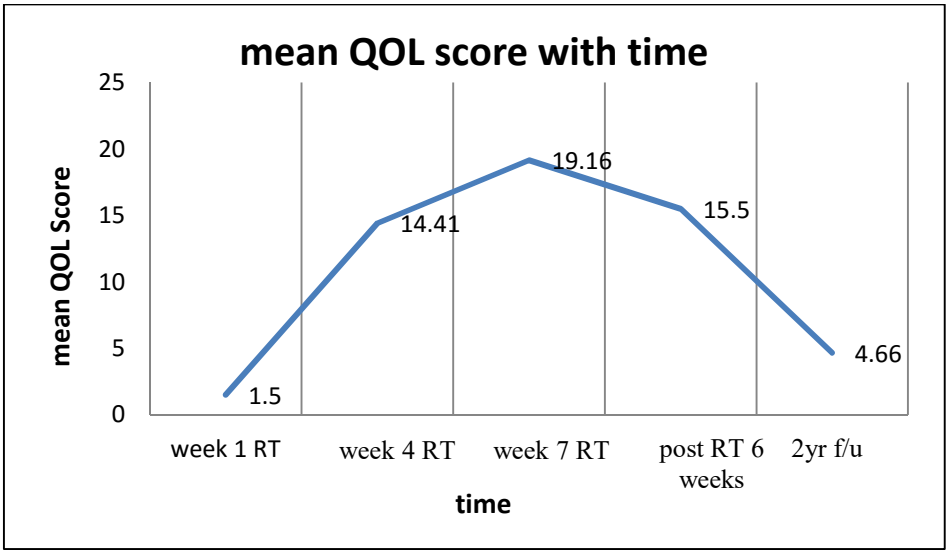


**Figure 4:** Line diagram showing mean QOL score with time

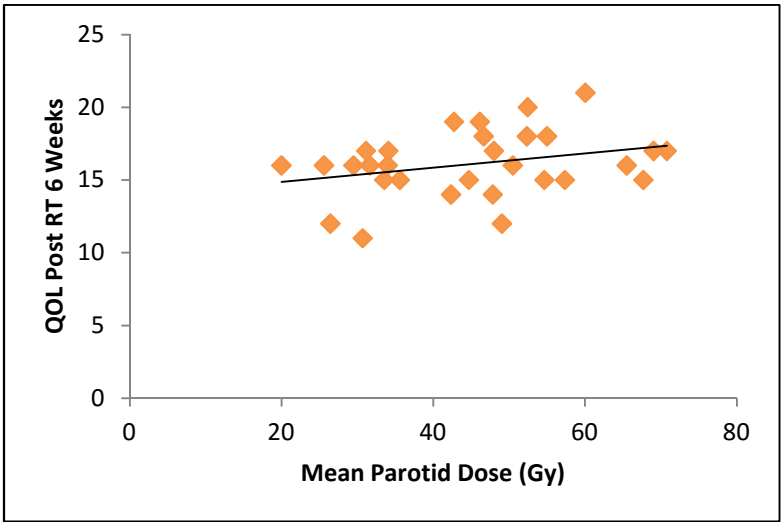


**Figure 5:** Correlation of QOL at six weeks with mean parotid dose (r = 0.3116)

## 4. Discussion

The present study was designed to correlate dose volume parameters of parotid gland with scintigraphy objectively as well as with QOL questionnaire in head and neck cancer patients receiving RT. Majority of the patients in the present study belonged to the age group of 40 - 60 years, mean age being 51.8 years (range 33 - 70 years). In a similar study by Roesink *et al.*[4] the mean age was 57 years which consisted of elderly population compared to our study. The mean volume of parotid gland was 23cc (SD 8), which is comparable to 24.9cc (SD 8.7), in a study by Van Rij *et al.*[10] The volume of the right and left parotid glands were found to be similar.

The mean dose of radiation received by parotid glands was 45.3 Gy (SD 14.4) across all techniques. The mean parotid dose in those treated with IMRT was 30.8 Gy, which is similar to the 30.02 Gy by Chao *et al.*[11] though marginally higher compared to 28 Gy by Van Rij *et al.*[10] who studied the xerostomia related QOL in patients treated with parotid sparing IMRT. The mean parotid dose using 3DCRT technique by Chao *et al.*[11] ranged from 40Gy to 44.5 Gy (SD 14) when compared to dose in our study which was 49.44 Gy (SD 13.4). This difference might be because of the differences in the dose prescription, as majority of the cases in their trial were post - operative, treated to a dose of 60Gy while in our study most of the patients were treated with definitive RT to a dose of 66 - 70Gy. A well - known study by Emami *et al.* suggested TD 5 / 5 of 32 Gy and TD 50 / 5

of 46 Gy for more than 2 / 3 parotid irradiation with severe xerostomia as an endpoint. As per quantec data, mean parotid dose of 25 Gy is associated with minimal grade four xerostomia.[12] Ours is an observational study and no efforts were done to spare the parotid glands.

Scintigraphy was performed once at baseline and once at six weeks post RT. The mean maximal uptake of the parotid glands before RT was 3329 ± 1675 counts per second (ct / s) (range, 914 –10,656) in a trial by Roesink *et al*. studying the early and late parotid gland function using scintigraphy.[4] The same in our study was found to be 2922 ± 1528 ct / s (range, 789 - 7980). The same wide range of maximal uptake across different parotid glands was reflected in our study also.

The SEF was 54.06 (SD 16) prior to RT, which means that more than half of the accumulated activity in the parotid gland was excreted out on stimulation. This is similar to 48 - 53.5% observed in other studies.[5, 13] This factor reduced to 12% (SD 9.4) after six weeks post RT which relates to a 77% reduction in the gland's ability to eject the accumulated activity which is significant. It was 10.7% at the end of one month as noted by Hsiung *et al.*[13], while it was 18.7 (SD 20.1) at six weeks by Roesink *et al.*[4] Though the former study had results similar to ours, the difference with the latter study might be because of the large spread of data with wide SD. The other reason could be the lesser mean dose of 33 Gy to the parotids in their patients.

The ratio obtained between the initial and the post RT SEF explains the proportion of functional salivary gland function post RT. The mean SEF ratio is 24.8 in our study, indicating the parotid were functioning at 75% of their initial activity post irradiation. Considering SEF ratio limit of 45% to assess for toxicity as suggested by Roesink *et al.*[4], at six weeks post RT 86.4% of 59 evaluated parotid glands had significant loss of function. This is similar to 88% in their study. The SEF ratio also correlated with the mean parotid dose. QOL questionnaire showed a significant worsening right from the first week of RT indicating the acute component of parotid gland's response. The change in scores was maximum from second to fourth week and by fifth week had reached a peak with no significant worsening after that. We found that there was no significant difference in the scores between fourth week of radiation and six weeks following RT. This can probably be explained by the pain component due to the mucositis which peaks during fourth to fifth week of RT dominating the patients concern after fourth week. The mucositis reduces significantly by sixth week post RT and leaves the patient with dryness of mouth as a significant morbidity. Lent soma scale is also used by some authors for assessing xerostomia. Even though it is more specific, it is predominantly an observer based system and hence less frequently used.[14]

There is a significant correlation found between the post RT SEF and the mean parotid gland dose (p=0.0163) similar to Roesink *et al.*[4] we also found significant correlation for SEF ratio and mean parotid gland dose at six weeks (p = 0.003). Significance was also found at 12 - 24 months after RT in several studies[4, 5] probably, the acute functional impairment correlates with the late toxicity implying the early changes are a predictor of long term sequelae. Significant correlation between the mean parotid gland dose and QOL scores (p = 0.04) was found in our study similar to Pow *et al.*[6] who studied xerostomia in nasopharyngeal cancer patients.

No correlation was found between any scintigraphic parameter and QOL at six weeks. This might be because of the still dominant acute effects of radiation at six weeks, more appropriate time to assess would be beyond six months to one year.However,, interestingly parotid gland sparing did not significantly improve dry mouth in a study by Chen *et al.*[5] indicating no correlation between the two. Even in other studies, using parotid flow rates to measure functional status of parotid glands, no significant correlation was found between the QOL scores and flow rates.[6, 7, 8]

It is interesting to note that, though the other scores recovered at two years follow up, the dry mouth remained the same from completion of therapy even though it did not impact on overall QOL score, which is similar to the study done by Benjamin *et al.* [9] and Ringash *et al*.[15]

The chief merit of our prospective study is that we analyzed not only the subjectively using QOL Questionnaire and objectively using scintigraphy but also correlated them with DVH parameters. This enables us to understand the variables and complex interactions that interplay in causing radiation toxicity and to deliver better healthcare to the patients. The major limitation of our study is the restricted sample size and no scintigraphic assessment at two years follow up. Another scintigraphic assessment at two years would have provided a better understanding of parotid gland recovery.

## 5. Conclusion

Comprehensive assessment of parotid gland function with Scintigraphy, QOL questionnaire and its correlation with DVH parameters is helpful in quantifying xerostomia. Even though radiation induced xerostomia persisted for a long time after radiation, it did not translate to decreased QOL. The dose received by the parotid glands has a direct correlation with xerostomia, hence efforts to reduce the dose to parotid by IMRT probably further reduces dryness which may improve QOL

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## Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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