SINGLE INSTITUTE BASED PROSPECTIVE RANDOMISED STUDY ON THE EFFECT OF PAROTID STEM CELL SPARING IMRT IN HEAD AND NECK CANCER

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Abstract-

AIM: Our study aims at analysing the concept of preserving the function of parotid gland more efficiently when stem cell region of parotid gland is spared.

OBJECTIVES: The primary objective was to test the hypothesis that if stem cell region of parotid is spared, it better preserves parotid gland function by using EORTC QLQ H&N- 35. The secondary objectives were 1) To assess the patient rated day and night time xerostomia between two arms subjectively by using Groningen Radiation induced Xerostomia Questionnaire ,2) To compare the mean dose to the both parotids, both superficial lobes, both deep lobes and both stem cell region between the arms.

METHODS: Prospective randomized study done in 100 patients of head and neck cancer. Patients with diagnosis of head and neck carcinoma with confirmed histology of squamous cell carcinoma, undergoing definitive radiotherapy treatment with bilateral cervical nodal irradiation with concurrent chemotherapy with Cisplatin are included. All the 100 patients were randomized to two groups: whole parotid sparing without stem cell sparing or whole parotid sparing with parotid stem cell sparing group. Then patients were routinely followed up for grading the symptoms of Xerostomia/ Dry Mouth, which was done subjectively by using EORTC QLQ H& N 35 and Groningen Radiation Induced Xerostomia Questionnaire before starting RT, on completing RT, at 3 months and 6months post completion of RT.

INTRODUCTION:

Xerostomia is the very common and irreversible side effect of radiotherapy to head and neck cancer.The concept of IMRT then came up with main rationale to reduce radiation dose to the whole parotid gland there by reducing xerostomia. But modern studies emerged with the concept that around the main salivary ducts of parotid where the first branch of stensen ducts arises, stem cell/progenitor cells are resided. This is suggested by the data from irradiated rats and human parotid gland. In order gain higher salivary output and further reduction in xerostomia, efforts were made to spare this specific region using IMRT.

RESULTS: A significant p value <0.0001 was found for the difference in mean dose to bilateral whole parotid and mean dose to bilateral stem cell between study arm and control arm. No patients had dry mouth before starting radiotherapy. There is no statistically significant difference reported in experiencing dry mouth after completing radiotherapy, at 3month post radiotherapy and 6month post radiotherapy when comparing study arm and control arm. Even for dry mouth in day time or night time, there was no significant difference shown.

CONCLUSION: Dose to parotid and parotid stem cell region will be one of these factors that affects xerostomia. The effect of submandibular gland dose and dose to other OARs such as oral cavity (where the sublingual and minor salivary glands reside) on xerostomia were shown by some studies. But these factors were not analysed and assessed in our study. So the concept of parotid stem cell sparing rather than whole parotid sparing alone is not proven to be promising in preserving salivary gland function from our study.

Key words: **Head and neck cancer, Xerostomia, Parotid, Parotid stem cell region, c Kit + cells.**

INTRODUCTION:

The most common long-term side effect of RT in many of the survivors of HNC is Xerostomia or dry mouth syndrome, which causes decrease in the quality of life (QoL) after treatment. Salivary gland is formed of well-vascularized system of acini and ducts. The salivary parenchyma is made up of clusters of secretory acinar cells. These cells contribute to most of the protein in saliva. Reabsorption of sodium and chloride by the ducts produces a hypotonic solution and this saliva is transported into the oral cavity by the ductal system (1).

Radiation leads to selective membrane damage of acini causing deficient water secretion leading to thick viscous saliva initially and as there is radiation induced cellular apoptosis. The newly formed cells are ill-equipped to secrete saliva due to poor micro vasculature and thus compromised blood supply (1). Within 24 hours following radiation, parotid gland injury is clearly expressed. Death happening to serous acinar cells is the most prominent alteration. Normally these cells show limited mitotic activity and also are highly specialized and long-lived cells. Therefore, interphase cell death is the mode of rapid killing of these cells after irradiation (2).

Xerostomia occurs because RT usually involves administering a high radiation dose to bilateral salivary glands when they are present in the radiation fields. The volume, consistency and pH of the secreted saliva were altered due to radiation induced damage

to the salivary glands. As a result, saliva which was thin in consistency changes to a thick secretion and the neutral salivary pH becomes acidic (3).

In order to restrict radiation exposure to adjacent normal structures to radiation targets, three-dimensional radiotherapy planning and dose delivery techniques, such as IMRT have been used. Inverse-planning algorithm allows selective sparing or dose reduction to adjacent healthy tissues without compromising dose delivery to the tumour. Retention of salivary output and amelioration of xerostomia can be achieved with this technique by substantial dose reductions to contralateral parotid and submandibular glands (4).

By using IMRT**,** magnitude and volumes of high doses in OARs were significantly reduced. The mean doses to all major salivary glands, most notably the contralateral parotid (receiving on average 32% of the prescribed dose) were significantly lower in the conformal plans than the standard radiation plans. The mean dose to the uninvolved oral cavity also tended to be lower in the conformal plans (5).

But xerostomia may occur despite advanced Parotid sparing IMRT, but a partial improvement of salivary secretion may occur (5). Then there emerges the concept of salivary gland stem cells. The advantage of IMRT is directed toward the personalized radiation treatment plan to each head and neck cancer patient, that may or may not affect specific regions of parotid gland which harbours epithelial stem/progenitor cells and its unique environment (6).

Sca-1+/c-Kit+ mouse salivary gland cells isolated by Fluorescence activated cell sorting have the capacity to transdifferentiate into pancreas and liver lineages. The stem cell markers such as Sca-1, cKit and Musashi-1 are looked for and salivary gland cells expressing these markers were cultured in vitro as Salispheres. Intra-glandular transplantation or injection of an in vitro cultured cKit + cell population containing salivary gland stem cells, resulted in restoration of salivary gland function and morphology in long term (7).

The stem /progenitor cell containing salispheres cultured from human SGs have the potency for self-renewal and differentiation and thereby the rescue of saliva production. Hence it was proven that c-Kit1 cell derived salispheres were capable of organoid differentiation in vitro and rescued saliva production in vivo (8).

AIM:

This study aims at analysing the concept of preserving the function of parotid gland more efficiently when stem cell region of parotid gland is spared.

OBJECTIVES:

1. To test the hypothesis that if stem cell region of parotid is spared, it better preserves parotid gland function, by comparing the patient rated dry mouth between two arms (parotid stem cell sparing and whole parotid sparing groups) subjectively by using EORTC QLQ H&N- 35.
2. To assess the patient rated day and night time xerostomia between two arms subjectively by using Groningen Radiation induced Xerostomia Questionnaire.
3. To compare the mean dose to the both parotids, both superficial lobes, both deep lobes and both stem cell region between the arms.

MATERIALS AND METHODS:

This study was conducted at the Department of Radiation Oncology, Apollo Speciality Hospital, Teynampet, Chennai. This was a Prospective randomized study. Simple randomization was the type of randomization used in our study. With control versus study groups, the side of the coin (Head for control and tail for study group) determines the assignment of each subject.

INCLUSION CRITERIA:

Diagnosis of head and neck carcinoma (oral cavity, oropharynx, hypopharynx, nasopharynx and larynx subsites) with confirmed histology of squamous cell carcinoma undergoing definitive radiotherapy treatment with bilateral cervical nodal irradiation, Mean prescription dose 66Gy, Age >18 years and < 70 years, KPS>70, Concurrent chemotherapy with Cisplatin, Non-metastatic disease.

EXCLUSION CRITERIA:

Prior history of radiotherapy to head and neck region, Patients who are not willing to give consent, Recurrent cancer, Parotid tumours.

After staging work up, patients were counselled and an informed consent was obtained. Patients will be positioned on a flat couch with neck rest and immobilized thermoplastic mask. A radiotherapy planning CT scan of the head and neck region in 3 mm slice thickness from the base of the skull to superior mediastinum was obtained. The CT scan images were transferred to the Eclipse Treatment Planning System (Version 13). The patients were randomized to control arm (Parotid sparing group without stem cell sparing) and study arm (Parotid sparing group with stem cell sparing) using simple randomization. Contouring done in axial images and reviewed in sagittal and coronal planes.

The GTV (gross tumour volume) includes the disease (primary tumour and clinically involved node) identified clinically and by imaging. CTV (clinical target volume) is obtained by 5mm expansion of GTV and areas of suspected subclinical disease such as regional lymphatics and nodes, lymphatic regions are contoured based on Gregoire et al. A PTV expansion of the CTV was created. The organs at risk such as spinal cord, pharyngeal constrictors were contoured. Parotid is delineated as OAR for both the groups (bilateral Superficial lobe, bilateral deep lobe and bilateral stem cell region were drawn separately based on study done by Van Luijk et al and Neven et al).

The enrolled patients received a prescription dose of 66Gy in 1.8Gy per fraction to the PTV P (primary and involved cervical nodal levels) and a dose of 54Gy in 1.8Gy per fraction to the PTV (uninvolved nodes) along with concurrent weekly Cisplatin.

Parotid as OAR: For Parotid sparing group without stem cell sparing, dose constraints given only to the whole parotid (D mean < 26Gy). For Parotid sparing with stem cell sparing group, dose constraints given to the whole parotid (D mean <26Gy) and to the

stem cell region (D mean 16 to 24Gy) were given. Treatment planning will be done on the Eclipse planning system by Varian. A highly conformal IMRT planning will be generated for both the groups.

Patients were routinely followed up for grading the symptoms of Xerostomia/ Dry Mouth, which was done subjectively by using EORTC QLQ H& N 35 (Question number 41: Do you have dry mouth? Likert scale 1-4) and Groningen Radiation Induced Xerostomia Questionnaire (Question number 1: Do you experience dry mouth during day time? and Question number 7: Do you experience dry mouth during night time? both Likert scale 1-4) before starting RT, on completing RT, at 3 months and 6months post completion of RT.

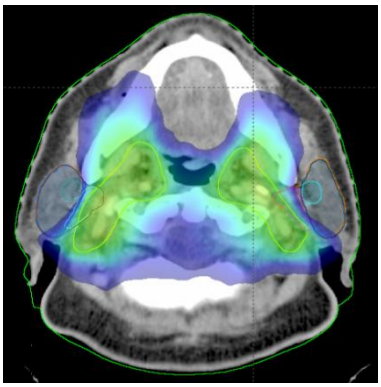

Figure 1: IMRT plan for Study arm (Parotid sparing with stem cell sparing)

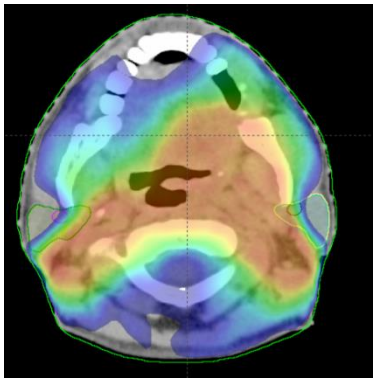

Figure 2: IMRT plan for control arm (Parotid sparing without stem cell sparing)

RESULT:

Total 100 patients were recruited for our study and each one was randomized to either study arm (Parotid sparing with stem cell sparing) or a control arm (Parotid sparing without stem cell sparing). One out of 50 patients in control arm developed recurrence at 3month so was excluded from the further follow up, so only 49 patients were taken for analysis in control arm at 3 months and 6 months. The study arm consisted of 50 patients, 44 of whom were male (88%) and 6 were female (12%). In the control arm, 41 out of 50 patients were male (82%) and 9 were female (18%).

	STUDY GROUP		CONTROL GROUP	
Male	44	88%	41	82%
Female	6	12%	9	18%
<40years	5	10	10	20
41-50 years	8	16	10	20
51-60 years	16	32	13	26
>61 years	21	42	17	34
Nasopharynx	2	4	1	2
Oral cavity	11	22	17	34
Oropharynx	12	24	8	16
Hypopharynx	19	38	18	36
Larynx	6	12	6	12
T1	1	2%	3	6%
T2	15	30%	13	265
T3	26	52%	28	56%

T4	8	16%	6	12%
N0	5	10%	9	18%
N1	12	24%	9	18%
N2	26	52%	28	56%
N3	7	14%	4	8%

Table number 1: Patient characteristics

At the time of enrolment into the study, none of the patients belonging to study or control groups reported dry mouth symptoms when analysed subjectively using EORTC Questionnaire (Question number 41) and GRIX Questionnaire (Question number 1 and 7).

There is no statistically significant difference (p value >0.05) observed in patient reported Likert scale point for Dry mouth after completing Radiotherapy, at 3month and 6month between the two arms was analysed using EORTC H&N QLQ 35 question number 41. Even when patient reported Likert scale point for dry mouth during day time and night time patient rate xerostomia was analysed using GRIX questionnaire (Question number 1 and 7) after completing Radiotherapy, at 3month and 6month between the two arms, no significant difference was observed for patient rated xerostomia (p value >0.05)

COMPARING DOSES TO PAROTID AND PAROTID STEM CELL REGION BETWEEN TWO GROUPS

There was a statistically significant difference in the mean dose to the bilateral whole parotid, between study group and control group. D mean to the bilateral whole parotid in the study arm is 24.54+/-3.74Gy and D mean in control arm is 29.81+/-4.544Gy (p <0.0001). Comparing mean dose to the bilateral superficial lobe and bilateral deep lobe between two arms, statistically significant difference was found. Finally, there was a statistically significant difference in mean dose to the bilateral stem cell region between the two groups. D mean to the bilateral stem cell region in study group is 17.43+/-3.41Gy and in control group is 23.56+/- 4.68Gy (p<0.0001).

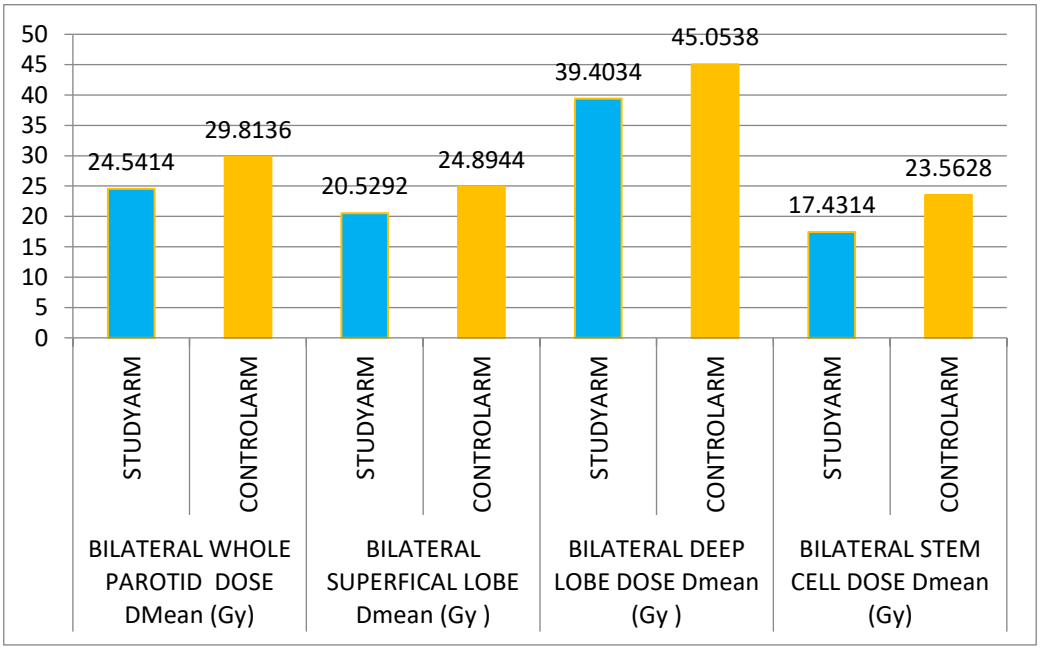

Figure 3: Comparison of dose to superficial lobe of parotid, deep lobe of parotid and stem cell region between two groups

COMPARING DOSES TO V15%, V30% AND V45% TO BILATERAL WHOLE PAROTID BETWEEN TWO ARMS

No statistically significant difference was observed between study and control arm on comparing mean dose to V15%, V30% and V45% to the bilateral whole parotid.

Volumes of Bilateral parotid gland	**STUDY GROUP**		**CONTROL GROUP**		**P value**
	Mean dose	**Std deviation**	**Mean dose**	**Std deviation**	
V15%	46.896	5.204	46.515	5.144	0.713
V30%	35.527	6.432	34.605	6.283	0.470

V45%	26.857	5.067	25.950	4.414	0.342

Table 2: Comparing dose to V15%, V30% and V45 % to bilateral whole parotid between two arms

COMPARING NUMBER OF PATIENTS REPORTED LIKERT SCALE POINT > 2 FOR GRIX QUESTIONNAIRE FOR DAY TIME AND NIGHT DRY MOUTH AND DOSE TO STEM CELL REGION:

Even though there is a significant difference between study group and control group with respect to dose to the stem cell region (17.43+/- 3.42Gy in study group and 23.56+/-4.68Gy in control arm with p value =0.00), no significant difference in the Likert point scale >2 for GRIX questionnaire Dry mouth in day time and night time is found between the arms.

Variables		**Mean dose to stem cell region (Gy)**	**GRIX: Dry mouth during day time with Likert scale point >2**	**GRIX: Dry mouth during night time with Likert scale point >2**
Study group	After completing RT	17.4314+/-3.41879Gy	7	15
	At 3 months		2	1
	At 6 months		0	0
Control group	After completing RT	23.5628+/-4.68490Gy	8	18
	At 3 months		2	2
	At 6 months		0	0

Table 3: Comparing dose to bilateral stem cell region and number of patients reported Likert scale point >2 for the GRIX questionnaire during day time and night time.

DISCUSSION

A notable difficulty with irradiation of head-and-neck cancer is the large number of organs at risk in close proximity to the target, including the salivary glands. This results in severe consequences for the quality of life of these patients (9). Introduction of intensity-modulated radiation therapy technique for the treatment of HNC replaced 3D-conformal radiation therapy techniques, which resulted in much better dose conformity and sparing of the OARs and, therefore, less radiation-induced toxicity (10).

In **Van Luijk et al's** study, they determined that salivary production is most strongly associated and predicted by dose to a specific sub volume of gland. This sub volume was found to be located around the dorsal edge of the mandible. Several data from parotid glands of rat and mouse were consistent with this sub volume. This sub volume anatomically correlates with the region where first branching of Stensen's duct occurs.

It is also established that rather than conventional mean dose to the entire gland, post treatment parotid function is predicted more accurately by radiotherapy dose to this region in a fivefold cross-validation procedure. Only the cells biopsied from this region could be grown in the sphere assay. These results also indicate that clinical outcome corelates with the dosage to the region of major ducts (11).

Nevens et al studied whether xerostomia can be limited by sparing of the contralateral superficial parotid lobe in HNC treated with RT. This study is based on the concept that location of SC region is in the vicinity of major ducts in superficial lobe, which was shown by Groningen group. Retrospectively after planning, superficial and deep lobes of parotid gland were delineated by one observer. Superficial lobe was outlined and defined as the parotid tissue lateral to the retromandibular vein. In this study, statistically significant difference with p value of 0.04 was noticed between group in which superficial parotid lobe of contralateral side could be spared and group in which even the superficial lobes of both sides could not be spared. Hence even if both or one parotid gland sparing from high dose irradiation is not possible, sparing of superficial lobe of contralateral parotid gland will result in decreased xerostomia during 6 month and 12 months follow up time. So it was concluded that when an entire parotid gland cannot be spared, delineating and sparing superficial lobes of both parotid glands limit xerostomia in HNC patients treated with RT (12).

Following the study by Van Luijk et al, there emerged the concept of parotid stem cell sparing IMRT technique for enhanced reduction the xerostomia. c- Kit is known to be progenitor cell marker / salivary gland cell marker and are distributed around the ducts of human parotid gland. When these ducts were included in radiation field in rats, that lead to gland dysfunction with reduced saliva production due to loss of regenerative capacity. There are not many studies based on this concept and the one and only study was done by Steenbakkers et al.

Steenbakkers et al showed that in stem cell sparing radiation therapy, function of salivary gland was not preserved significantly. This study showed mean dose to parotid as 28+/-8.6Gy in standard arm and in stem cell arm, the mean dose achieved was 27+/-7.5Gy. For stem cell region in standard arm, dose (median) was 22Gy and 14Gy in study arm. The primary end point was found to be negative, ie between the SCR -RT and SCRT, no difference in prevalence of ≥75% reduction in stimulated parotid gland salivary production was found. Ipsilateral salivary gland function was found to be consistent with dose to both SCR regions while contralateral relative parotid function was associated only with mean dose to contralateral SCR region at 6month post treatment. Multivariable analysis showed that day time xerostomia was strongly predicted by dose to the contralateral SCR region at 12 months and 24 months post treatment. This suggested that if contralateral gland is damaged by the dose to contralateral SCR, xerostomia will be more pronounced and thus never compensates to the loss of function of the ipsilateral parotid gland. No significant association between dose to SCR region and patient rated night time xerostomia was found. Also Moderate-to-severe patient-rated xerostomia assessed by the question "Do you have a dry mouth?" was not associated with dose to the SCR regions (13).

PARSPORT trial compared the incidence of grade 2 xerostomia between patients who were treated with 3DCRT and IMRT technique. The dose to contralateral parotid was significantly less in IMRT group with p <0.0001. The mean dose to contralateral parotid and ipsilateral parotid in IMRT arm were 25.4Gy (23.2-28) and 47.6Gy (39.6-54.5) respectively. In 3DCRT, the mean dose achieved for both contralateral and ipsilateral parotid is 61Gy (54.6-63.8Gy) (14).

Another study by **Hsiung et al** evaluated parotid function in parotid sparing IMRT in Carcinoma Nasopharynx. This study showed significant preservation of the parotid function with IMRT. In 3DCRT group, 72.1Gy was the mean total dose to parotid while in IMRT group, it was 69.3Gy (15). **Kwong et al** study on IMRT in earlystage Nasopharyngeal cancer patients, the mean parotid dose achieved was between 32.2Gy to 46.1Gy (average 38.8Gy) (16).

In our study, mean dose to bilateral whole parotid ranges between 20.60Gy to 28.28Gy (average mean dose of 24.54Gy). This mean dose is less when comparing with above mentioned studies.

Zheng et al conducted a study on preserving parotid stem cell during IMRT in 80 patients of Carcinoma Nasopharynx. Patients were assigned into two groups, in which one group is a restricted group where dose to parotid ducts were limited and the other group where no restriction of dose to parotid ducts region were given. This study compared difference in the parotid ducts and overall volume dosimetry of parotid glands between two radiotherapy plans. There is no statistically significant difference in mean dose and V30 between two groups. But lower V20 and higher V45 was noted in restricted group than the regular group. D mean to Left parotid gland is 31.55+/-0.77Gy while right parotid gland is 31.03+/- 0.93Gy. V20%, V30% and V45% for left parotid gland were 78.77+/- 3.22Gy, 43.26+/-3.13Gy and 24.64+/-2.72Gy. V20%, V30% and V45% for right parotid gland were 75.82Gy +/-4.64Gy, 42.45+/-3.73Gy and 22.69+/-3.09Gy (39-18).In our study, D mean to bilateral whole parotid showed significant difference between the whole parotid with stem cell sparing arm and whole parotid without stem cell sparing arm. But we couldn't reach a significant difference in V25%, V30% and V45% between two arms(17).

No significant difference was found between the study group and control group for the patient reported Likert scale point for EORTC QLQ questionnaire for dry mouth and GRIX questionnaire for dry mouth during day time and night time after completing RT, at 3month post radiotherapy and 6month post radiotherapy. Fewer number of patients in study arm had dry mouth during day time with Likert scale point >2 than control arm, but the difference was not statistically significant. No difference found between two arms for the patient rated Likert scale point for GRIX questionnaire –Do you have dry mouth during day time?

There was a significant difference in mean dose to the bilateral parotid gland, bilateral superficial lobe, bilateral deep lobe and bilateral stem cell between two arms. Mean dose to the parotid and stem cell region was significantly less in study arm than control arm. But in our study, this difference was not proved to result in better preservation of parotid gland function and thereby reducing xerostomia.

Parotid glands play a major role in salivary secretion during eating and oral stimulation. Submandibular gland contributes to more than 70% of unstimulated or resting salivary output that helps in maintaining hydration of oral mucosa (18).

Several studies had shown that mucous salivary glands such as submandibular and sublingual gland are lessly affected by the early effect of ionizing radiation than serous glands (parotid). Vacuolar degeneration happens in serous acini glands even after single dose of radiation. But no acute histologic change occurs in mucous acini gland. In parotid, fibrosis is predominating while in submandibular gland, adiposis is of more characteristic. (19)

Valdez et al studied about differential radiation effects on major salivary gland such as Parotid, submandibular and sublingual glands. In this study, they demonstrated the clinical dysfunction of submandibular and sublingual salivary gland in terms of impaired resting and stimulated flow rates after radiation therapy. Sialochemical changes were also noted submandibular and sublingual salivary gland (19).

Jellema et al assessed the association between mean dose to salivary gland and dose to oral cavity with patient rated moderate to severe xerostomia and sticky saliva in 157 patients of head and neck cancer with bilateral neck irradiation. The mean dose to parotid was 24.2Gy, mean dose to submandibular gland was 46.7Gy and mean dose to oral cavity was 9.1Gy. A significant association was found between xerostomia at 6 months and mean dose to parotid gland, submandibular gland and oral cavity in a univariate logistic regression analysis. But in multivariate analysis, the significant association was proven only between xerostomia at 6 months and mean dose to parotid gland and submandibular gland (20).

There was association between patient rated sticky saliva at 6months with mean dose to parotid and submandibular gland in the univariate analysis. In the multivariate regression analysis, the only factor that was significantly associated with patient rated sticky saliva at 6months was mean dose to submandibular gland. This study thus concluded that in head and neck cancer patients who underwent radiation, risk of xerostomia was influenced by both mean dose to parotid and mean dose to submandibular gland. Sticky saliva depends mainly on mean dose to submandibular gland (20).

Study by Dijkema et al also suggests that the saliva is contributed by major and minor salivary glands including the sub-mandibular glands. This study showed that day time xerostomia and night time xerostomia is associated with salivary production by parotid

gland and submandibular gland respectively, after 1year of post radiotherapy treatment. However, these structures (minor salivary gland and sub- mandibular glands) are not considered as OAR`s in our Radiotherapy practice and effect of submandibular gland on xerostomia is not included in our study. (21)

Fried et al done a study in 244 patients of oropharyngeal carcinoma to assess the relationship between mean dose to oral cavity and patient rated xerostomia and dysgeusia. In this study they found that mean dose to oral cavity was significantly associated with xerostomia at 6 months post chemoradiotherapy. Among the substructures of the oral cavity, floor of mouth shown association with patient rated xerostomia at 6 months. This results can be accepted because sublingual salivary glands are present in floor of mouth and submandibular gland is immediately adjacent to it (22). But these factors also were not considered and analysed in our study.

Limitations of our study includes reference study is the first and only study conducted in humans to assess the effect of parotid stem cell sparing radiotherapy in head and neck cancer. Therefore presently, there is insufficient data regarding parotid stem cell sparing radiotherapy.The short follow up period is a limitation of this study. The patients should be ideally followed up for a minimum of 2 years so as to know the effect on xerostomia. In our study, only mean doses to combined (bilateral) whole parotid, combined superficial lobe, combined deep lobe and combined stem cell region were considered, so the effect of sparing the contralateral superficial lobe of parotid has not been assessed separately. Also attempts to analyses the association between dose to contralateral stem cell region and day time xerostomia was not done in our study.Concurrent cisplatin as a confounding factor has not been taken in to consideration in this study.Other factors affecting xerostomia such as dose to submandibular glands and dose to oral cavity were not assessed in our study.

CONCLUSION:

Xerostomia in head and neck cancer patients who were treated with radiotherapy is a multifactorial condition. Dose to parotid and parotid stem cell region will be one of these factors that affects xerostomia. The effect of submandibular gland dose and dose to other OARs such as oral cavity (where the sublingual and minor salivary glands resides) on xerostomia were shown by some studies. But these factors were not analysed and assessed in our study. So the concept of parotid stem cell sparing rather than whole parotid sparing alone is not proven to be promising in preserving salivary gland function from our study. Also further prospective trails are needed to evaluate the significance of parotid stem cell sparing in head and neck cancer radiotherapy.

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