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# Submandibular Gland Sparing Radiotherapy for Locally Advanced Head and Neck Squamous Cell Cancers: Xerostomia Outcomes

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**Abstract**

*Aim:* To spare the contralateral submandibular gland in head and neck cancers using IMRT and to compare them with the contralateral unspared group of head and neck cancers also on IMRT but in whom sparing of cSMG is not possible because of various factors and to access xerostomia outcomes in these two groups. *Materials and methods:* It is a prospective and comparative intent to reduce toxicity levels in 30 patients presented to our hospital of locally advanced head and neck cancers and treated with IMRT and concurrent chemotherapy and their follow-up. All patients with stage I, II / IV Head and Neck cancers to be treated with bilateral head and neck IMRT. Appropriately selected patients with favourable primary tumor characteristics and no definite contralateral neck disease treated with cSMG- sparing. *Results:* Post treatment after 2 months where a score of 2 was seen in 13.3% of patients in the cSMG sparing was done against 30% of the control group. At the end of 4 and 6 months from commencement of treatment were 3.3% and 3.3% respectively in the study group and,16% and 6.6% in the control group. The difference at 2 and 4 months was clinically significant but statistically could not be proved. This significant difference was observed due to the lower dryness felt by the patients at rest in the cSMG spared arm. Pre irradiation MR sialography with secretion stimulation could not help predict severity of radiation induced xerostomia. Whereas post irradiated MR imaging revealed submandibular gland secretion response in submandibular gland spared arm and revealed that submandibular gland secretion response is most influential to radiation induced xerostomia grading clinically whereas statistical significance could not beproved. This difference was seen when grade 2 and 3 response was seen in base liner SG vs post RT rSG in both IMRT (36% and 30%) and conventional arms (43% and 40%respectively). *Conclusions:* The useof IMRT with daily imaging and time required for careful selection of patients and properexecution of the treatment may lead to questions regarding the time and the costrequired for execution of this type of planning.

**Keywords:** Cancer; Submandibular; Xerostomia; Radiotherapy.

## Introduction

Cancer of the head and neck is one of the most common cancers in India affecting both males and females [1]. In India, head and neck constitutes 25% to 30% in males and 15% in females. Pharyngeal cancers constitute 17.2% of all head and neck cancers [2]. The patients of head and neck cancers should be dealt with by a multi - disciplinary team comprising specialist surgeons, oncologists, pathologists, radiologists and palliative care doctors, together with dieticians, speech and language therapists and clinical nurse specialist. Surgery and radiotherapy with or without chemotherapy are most frequently used therapeutic modalities in head and neck cancers. Radiotherapy with or without chemotherapy offer higher rates of organ preservation, and for some cancers, where function is important, it is the treatment of choice. The choice of treatments depends on individual factors, including patient preference. Surgery or radiotherapy has shown good comparable results in early stage cancers (T1,T2). For advance stage disease (stage III / IV) with large primary tumors

and or regional nodal involvement, the primary curative modalities are surgery, radiotherapy and chemotherapy. Whenever two modalities show similar results in terms of control and survival, quality of life and cosmesis becomes important. Standard conventional radiotherapy protocol calls for a total dose of 66–70 Gy, 2 Gy per fraction, once daily for five days a week for 6–7 weeks. The conventional RT to head and neck cancers typically involves irradiation of major salivary glands and large area of normal mucosal irradiation. It leads to mucositis, dysphagia and xerostomia. Xerostomia [3] is most prevalent late side effect of head and neck malignancy. Also xerostomia is cited by patient as major cause of decreased quality of life. When treating HNSCC with curative intent the greatest challenge is to deliver a sterilizing dose to tumor bed without causing excessive damage to surrounding normal tissue using conventional RT techniques. Careful planning of RT fields with appropriate blocks for critical anatomical structures is essential, hence the adverse effects on normal tissue are dependent on total dose delivered, the fractionation schedule, the volume treated and the fields employed. An adverse effect to normal tissue is the major treatment limiting factor in RT. The radiation induced adverse events manifest as either acute reactions (i.e. occurring within 90 days of RT) or late/ delayed reactions (i.e. occurring months to years after RT). The acute reaction includes mucositis, difficulty in swallowing food & xerostomia. The delayed effect includes nocturnal dry mouth, difficulty in swallowing food, speech, dental caries, periodontitis & osteoradionecrosis.

This would compromise on the outcome of the patient with respect to the long term physiological functioning and quality of life [4]. Acute reactions occur during the course of RT because of direct tissue injury and possible secondary bacterial irritation, inflammatory reactions in the mucosal, epidermal and glandular tissues within the radiation field leading to acute mucositis, dermatitis & xerostomia which may become dose limiting. Oral mucositis usually develops within seven to fourteen days after chemotherapy or radiation therapy is initiated. Mucositis secondary to radiation results from repeated tissue damage from daily treatments. It begins to manifest at doses of 10 to 20Gy (one to two weeks of therapy) and is limited to the field of radiation. Initial signs may include mucosal whitening due to transient hyperkeratinization followed by erythema or erythema may occur first. Ulceration then occurs typically at doses over 30Gy. The potential sequelae of mucositis consists of severe pain, increased risk for local and systemic infection, compromising oral and pharyngeal function, oral bleeding thateffects quality of life leading to increased duration of hospitalization and cost of care [6].

However, chronic xerostomia remains a vexing and common clinical problem that impairs the quality of life of surviving patients. Sparing of salivary glands isessential to minimize xerostomia [10].

Parotid-sparing intensity-modulated radiation therapy (IMRT) is standard radiotherapy technique for patients with squamous cancers of the head and neck region. However, parotid saliva lacks mucins that maintaina patient's subjective sense of hydration, and preserving the parotids alone has inconsistently translated to improvements in xerostomia [7]. We conducted this study to report the outcomes in patients with locally advanced

head and neck SCC treated with bilateral neck IMRT at our institution. We divided the patients into cSMG-spared and cSMG-unspared groups in order to compare the incidence of xerostomia.

**Materials**

Study design: prospective and comparative intent to reduce toxicitylevels

Study population: 30 patients presented to our hospital of locallyadvanced head and neck cancers and treated with IMRT and concurrent chemotherapy and their follow-up. Study period: Dec 2015- May 2017

Study patients- Al l patients with stage I, II / IV Head and Neck cancersto be treated with bilateral head and neck IMRT. Appropriately selected patients with favourable primary tumor characteristics andno definite contralateral neck disease treated with cSMG- sparing

IMRT Arm A: - patients of head and neck cancers (cSMG spared) with contralateral level IB nodal level not targeted for elective RT and cSMG had planning object ve (dose range 15.6-56.2) Arm B: -cSMGunspared- all other patients

Pat ients with nodal involvement limi ted to U/L neck and who had ananatomically favourable primary tumor were considered for cSMG spared group

Radiotherapy: TD: 60-66Gy, DD: 200cGy /day in single fraction and Technique: IMRT

*Inclusion Criteria*

- Age: - 25-80 yrs

- Performance status (0-2)

- Biopsy proven cases of squamous cell cancer

- Patients informed consent

- Patienst for definitive chemo-RT in head and neck cancers T1-4, N0-3 AJCC stage III-IV

*Exclusion Criteria*

- Patients with poor performance status

- Patients not consenting for study

- Patients with recurrent disease

- Patients with early stages AJCC stage I-II

- Patients receiving unilateral treatment for well lateralized tumors

- Patients in whom the disease is crossing the midline

- Patients with involvement of contralateral nodes

The patients with advanced disease localized to one side and not involvingcontralateral nodes will be taken in the cSMG spared arm and the ones withdisease crossing midline and involving contralateral nodes in cSMG unsparedarm. CT simulation will be done for all the patients The plan of treatment is IMRT with concurrent chemotherapy (weekly cisplatin)

While on treatment patient will be evaluated for xerostomia using thequestionarre method based on four criteria 1. Subjectice 2. Objective 3. management of xerostomia 4. analytical. Then grading the pts accordingly into four grades from grade 1-4 At the end of treatment patients again will be assessed at the intervals of 2 months and the grade of xerostomia will be assessed using:

1. Questionarre method

2. MR Sialography

When all the investigations were within the normal limits, patient's written consent was taken after explaining the nature of the disease, its treatment options and side effects in the own vernacular language.

*Radiation Technique*

The principles of target selection and IMRT planning followed are as per the general consensus of target delineation in head and neck cancers (105). The delineation of the level II region was given importance due to its close proximity tothe submandibular gland. These nodes can be divided into the subdigastric (jugulodigastric) nodes, located below the level at which the posterior belly of thedigastric muscle crosses the jugular vein and the more cranially located nodes belowthe base of skull. The subdigastric nodes are the main nodes involved when contralateral metastasis occurs, whereas the more posteriorly located nodes are at risk bilaterally in cases of cancer of the nasopharynx and in the neck side that contains other Level II-III metastasis [106]. A slightly smaller margin was given on the cSMG spared IMRT plans between the CTV and PTV so that the posterior part of the submandibular gland which forms the anterior border of the level II region does notreceive higher dose.

While defining target volumes, the planning target volumes (PTVs) were created using a uniform margin of about 0.5cm from the clinical target volume (CTV) which accounts for the daily setup errors which were monitored based on daily kV portal imaging and not allowed to be beyond 1-1.5mm. Contouring of the two major salivary glands- the parotids and submandibular glands was given utmost importance and done based on anatomic atlases.

*Contouring of the parotid glands*

The parotids are the largest set of salivary glands and due to their radiolucency areusually easily picked up distinctly on CT imaging. Its laterally placed position alsomakes it easy to demarcate the gland based on the structures around it. The cranial most part of the parotid gland (orange outline) starts at the level of the mandible (black arrow with blue outline), lies infero-lateral to the masseter muscle. The caudal most part of the parotid as seen in the CT cut ends inferior to the submandibular gland and lies superior to the sternocleido mastoid msucle.

*Contouring of the submandibular gland*

The submandibular glands are the next largest salivary glands and are placed moremedially compared. They start just along the level of the ramus of the mandible andthen extend inferiorly.

They are a little difficult to demarcate from the adjacent muscle (pterygoid) as they have similar lucency. Hence, an MRI is a better modality of imaging to visualise the submandibular gland but, on CT imaging the submandibular gland can be identified based on the anatomic location relative to its adjacent structure, that is, the cranial ofthe myolohyoid muscle.

The right submandibular gland (green outline) as seen on this CT cut starts along with the cranial most portion of the mylohyoid muscle (light blue outline). The right parotid is also seen infero-lateral to the submandibular gland with masseterpresent laterally.

The caudal end of the submandibular gland (green outline) is easier to demarcate as itdoesn't have any muscles in close proximity. It ends at the level of the mid portion of thehyoid bone

Other anatomic structures around this part of the submandibular are the digastric muscle placed posteriorly and sternocleido mastoid muscle infero-laterally.

*Dose prescription*

The dose prescription includes all the targets delineated in PTV to receive TD-66Gy at 220cGy/ fraction for five days a week/70Gy at 220cGy/ fraction. With the help ofin house planning systems (VARIAN), inverse IMRT plans were analysed and executedonce target dose homogeneity is achieved. An optimized IMRT plan was thus generatedwhich included the dose given to the delineated PTVs as per the RTOG protocol alongwith an optimization goal to try and constraint the dose to the swallowing structures. Thesalivary glands that were contoured were given dosimetric constraints-with the meandose of parotid gland <30Gy and the mean dose of submandibular gland <39Gy. Nocompromise to the primary target PTV was allowed while sparing these structures andfor achieving optimum dosimetric goals.

In all patients, the prescription dose to the targets was considered as high priority and other critical organ dosimetric constraints were considered to be secondary exceptfor maximal spinal cord dose. The optimized IMRT strategy for sparing of the submandibular gland was implemented and for purpose of the study these dose prescriptions were considered to be clinically significant. For the whole structures and the parts that over lapped the PTVs, DVH analyses were performed and reported.

Dose specifications and constraints used for the two groups

*1. cSMGunspared IMRT (control group)*

Targets

- PTV66 for the radiological gross disease; prescribed dose 66Gy in 33 fractions

Noninvolved tissues and organs

- Parotid gland, mean dose <26Gy or <50% receive <30Gy
- Maximal dose to brain stem 54Gy
- Maximal dose to spinal cord 45Gy
- Maximal dose to mandible 70Gy

All the non-specific tissues outside PTVs: <1% to receive <110% of PTV60 dose

*2. cSMG spared group IMRT(study group)*

The dose specifications and constraints given are the same as that for Standard IMRT.

In addition, the constraint for submandibular gland mean dose of <39Gy was also to be followed.

*Chemotherapy*

- Patients who were deemed as fit for chemotherapy received weekly cisplatin (40mg/m2) for 5 weeks along with RT. If the patient developed toxicity due tochemo which resulted in hindrance to radiation, then the chemo was discontinued.

*Supportive care*

- Anti-emetics and adequate hydration both before and after chemotherapy was delivered following standard of care.
- Among patients having dysphagia which lead to decreased food intake orally, nasogastric tube intubation was initiated.

*Evaluation of xerostomia*

All the patients who were part of the study were periodically assessed during the treatment and at the end of treatment, the observer rated grading of xerostomia wasdone based on the CTCAE criteria. Then, the grading was repeated during the follow upperiod, 2 months, 4 months and 6 months after commencement of radiation therapy.

Subjective assessment of xerostomia was done using MR sialography based grading before and one week after the commencement of RT. These scores were systematically noted down and recorded for all the patients whowere part of the study and had come for regular follow up.

Data entry was done by using Microsoft excel 2007 version. Data analysiswas done by epi. info 7.2.1.0 version. For obtaining thep values chisquare test was used.

## Results

*Patient characteristics*

A total of 30 patients were considered for this study. Of these patients, 15 werein the study arm (cSMG spared IMRT) whereas 15 were in the control arm (unsparedarm).

All the patients were locally advanced cancers of oropharynx (20), hypopharynx (2) and oral cavity (8). The mean age of these patients was 59 yrs. 25 (75%) out of 30 patients received concurrent chemoradiation with weekly CDDP and 5 (25%) patients received RT alone.

Out of the 30 patients, 7 (23%) were found to be in stage III, 21 (70%) in stage IVA and 2 (6.6%) patients belonged to stage IV B.All the characteristics of the patients and tumors are detailed in with pie charts.

**Table 1:** Dose volume characteristics

| Ipsilateral parotid | Mean dose (in Gy) |
|---|---|
| Spared | 31 |
| Unspared | 30 |
| Contralateral parotid | |
| Spared | 24.2 |
| Unspared | 31.9 |
| Ipsilateral SMG | |
| Spared | 60 |
| Unspared | 60 |
| Contralateral SMG | |
| Spared | 37 |
| Unspared | 60 |

**Table 2:** Demographic distribution in study

| Age in years | Frequency | Percent |
|---|---|---|
| 33-39 | 2 | 6.67% |
| 40-49 | 9 | 30.00% |
| 50-59 | 11 | 36.67% |
| 60-69 | 6 | 20.00% |
| 70-79 | 2 | 6.67% |
| Total | 30 | 100.00% |
| Gender | | |
| Females | 2 | 6.67% |
| Males | 28 | 93.33% |

**Table 3:** Staging in study subjects

| Ajcc Stage | Frequency | Percent |
|---|---|---|
| III | 7 | 23.33% |
| IVA | 22 | 73.33% |
| IVB | 1 | 3.33% |
| Total | 30 | 100.00% |
| N STAGE | | |
| N1 | 7 | 23.33% |
| N2 | 14 | 46.67% |
| N3 | 1 | 3.33% |
| N0 | 8 | 26.67% |
| T STAGE | | |
| T2 | 1 | 3.33% |
| T3 | 11 | 36.67% |
| T4 | 8 | 26.67% |
| T4a | 10 | 33.33% |

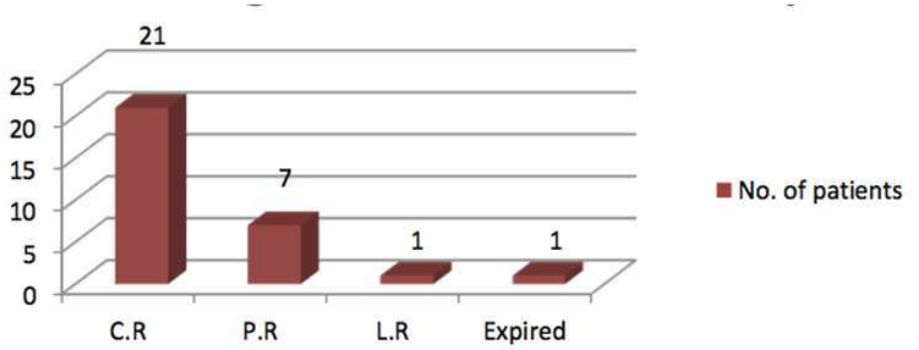


**Fig. 1:** Distribution of study population according to their status of recovery.

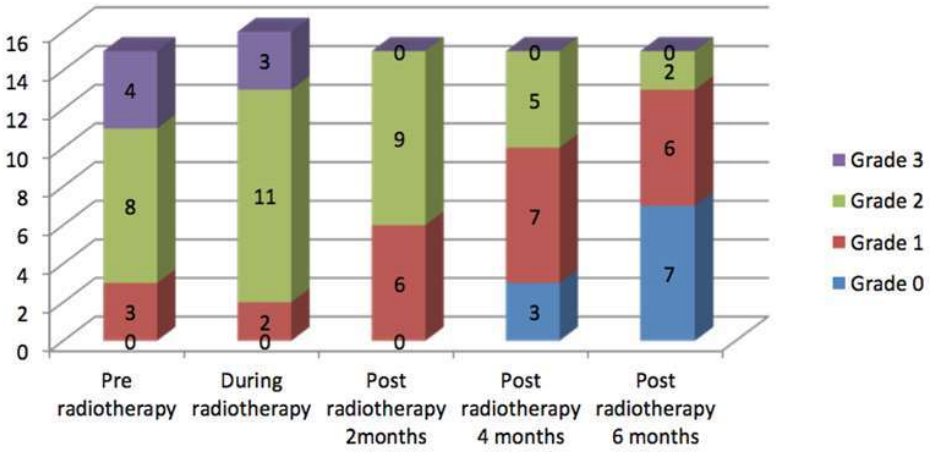


**Fig. 2:** Grading of xerostomia in the sudy population during different stages of conventional therapy

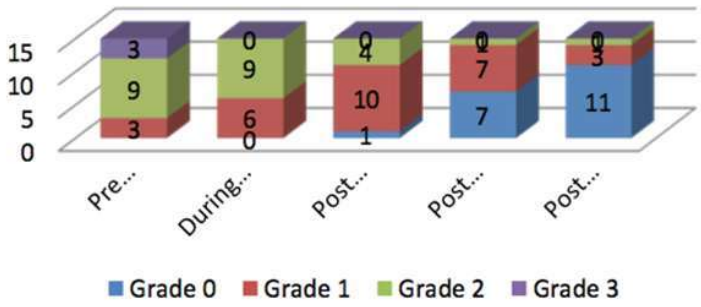


**Fig. 3:** Grading of xerostomia in the sudy population during different stages of IMRT.

**Table 4:** Sialography findings

| | | Grade 1 | Grade 2 | Grade 3 | P-value |
|---|---|---|---|---|---|
| Baseline rsG | IMRT | 4 | 6 | 5 | 0.5021 |
| | Conventional | 2 | 9 | 4 | |
| Baseline nssG | IMRT | 1 | 8 | 6 | 0.3919 |
| | Conventional | 0 | 11 | 4 | |
| Baseline ssG | IMRT | 3 | 11 | 1 | 0.5049 |
| | Conventional | 2 | 13 | 0 | |
| PostRTrsg | IMRT | 6 | 9 | 0 | 0.1353 |

| | | Grade 1 | Grade 2 | Grade 3 | P-value |
|---|---|---|---|---|---|
| PostRTssg | Conventional | 3 | 9 | 3 | 0.234 |
| | IMRT | 5 | 10 | 0 | |
| PostRTnssg | Conventional | 3 | 10 | 2 | 0.06 |
| | IMRT | 0 | 12 | 3 | |
| 2 months | Conventional | 0 | 8 | 7 | 0.1406 |
| | IMRT | 1 | 10 | 4 | |
| 4 months | Conventional | 0 | 6 | 9 | 0.1184 |
| | IMRT | 7 | 7 | 1 | |
| 6 months | Conventional | 3 | 7 | 5 | 0.3292 |
| | IMRT | 11 | 3 | 1 | |
| | Conventional | 7 | 6 | 2 | |

**Table 5:** Xerostomia among IMRT & Conventional at different time intervals

| Grade 2 patients during MR sialography | nsSG | | sSG | | Rsg | |
|---|---|---|---|---|---|---|
| | PRE RT | POST RT | PRE RT | POST RT | PRE RT | POST RT |
| Conventional Arm | 10 | 7 | 12 | 10 | 8 | 9 |
| IMRT ARM | 8 | 12 | 11 | 10 | 6 | 9 |
| Grade 3 patients during MR sialography | | | | | | |
| Conventional Arm | 4 | 7 | 0 | 2 | 4 | 3 |
| IMRT ARM | 6 | 3 | 1 | 0 | 5 | 0 |

*Assessment of xerostomia*

The grading for xerostomia based on the CTCAE criteria was done three times. Post treatment after 2 months where a score of 2 was seen in 13.3% of patients in the cSMG sparing was done against 30% of the control group. At the end of 4 and 6 months from commencement of treatment were 3.3% and 3.3% respectively in the study group and, 16% and 6.6% in the control group. The difference at 2 and 4 months was clinically significant but statistically could not be proved. This significant difference was observed due to the lower dryness felt by the patients at rest in the cSMG spared arm.

*Interpretation:* This, questionnaire and the result clearly indicates that the saliva was better preserved in the cSMG spared arm which resulted in significantly lower scores in the questions.

*Assesment of xerostomia from MR sialography:* Preirradiation MR sialography with secretion stimulation could not help predict severityof radiation induced xerostomia. Whereas post irradiated MR imaging revealed submandibular gland secretion response in submandibular gland spared arm and revealed that submandibular gland secretion response is most influential to radiation induced xerostomia grading clinically whereas statistical significance could not be proved. This difference was seen when grade 2 and 3 response was seen in baseliner SG vs post RT rSG in both IMRT (36% and 30%) and conventional arms (43% and 40% respectively).

## Discussion

Although there has been improvement in salivary flow rates by parotid sparing IMRT and it is now considered technique for treating patients with locally advanced head and neck cancers, like hypopharynx and oropharynx, it may still fall short with respect to the patient rated xerostomia. And this has been proved to have a significant impact on quality of life of patients [8].

In the present study, patients treated with cSMG sparing bilateral neck IMRT, the mean dose cSMG could be limited 37Gy. Based on both observer and patient rated xerostomia scores, it was found that xerostomia was significantly lower in the cSMG spared group compared to the control group, independent of parotid sparing. There are concerns that there could be increase in risk of marginal recurrences with aggressive cSMG sparing as adequate coverage of target volumes could be compromised [9]. There has been a study where recurrences were noted in the area where parotid sparing was done. Hence, the patient selection criteria should be very stringent and is to be followed with utmost care. As, reducing the side effects of treatment is important, it still only plays second fiddle to curing of the disease.

This is a CT cut of a case of Ca oropharynx where the growth is just crossing the midline. This increases the chance of marginal miss and recurrences if cSMG sparing is attempted because of close proximity of the

**Table 6:** Our study in comparision with other studies

| Study | N | Definitive RT | Mean cSMG (Gy) | Disease outcome | Late xerostomia |
|---|---|---|---|---|---|
| Univ of Washington | 76 | 86% | 30.7 | No per-SMG recurrence | 23%grade 2+ at 6months,N o permanent grade 3+ |
| Helsinki Univ,Finland[9] | 50 | 49% | 27.8 | No peri-SMG recurrence | No permanent grade+ |
| VU Univ.Med.Ctr., The Netherlands[10] | 20 | 100% | 34.1 | No peri-SMG nodal recurrence | No reported |
| Univ.of Michigan[11] | 17 | 100% | 43 | No contralateral level I recurrence | No grade 3+ |
| Centre Eugene Marquis, France[12] | 8 | 100% | 33.8 | No peri-SMG recurrence | No grade 3+ |

lesion with the level IB region/submandibular gland.

Though the cSMG sparing could be challenging because of the areas at risk lying inclose proximity with the organ that is being attempted to be spared, there have been anumber of studies where this has been attempted with no recurrence in the regionwhere the sparing was done. The table-5 above shows a list of major studies that have been conducted where cSMG sparing IMRT was used safely.

The most important area on which this study was focussed on was the subjective and objective assessment of xerostomia. This was carried out with a validated Xerostomia Questionnaire using the CTCAE grading for the subjective assessment and MR sialography grading for objective assesment. The results obtained through the patient reported outcomes of the impact dryness had on the QoL indicated that sparing of contralateral submandibular gland resulted in significant improvement in the symptoms in many patients of the study arm clinically though it did not project statistically.

Few limitations of this study are the small sample size and the non-randomized design which may have lead to some bias. Another limitation was the duration of the study, as longer follow-ups would have projected statistical significance as xerostomia is a late effect. However, the clinical improvement in both the observer rated xerostomia after 6 months and the MR sialography based grading show that using the technique of intensity modulation and proper planning, there can be significant reduction in the one of themain side effects of radiation therapy in Head and Neck cancers. This difference couldbe appreciated when number of patients having grade 2 and 3 were seen andcompared in both the arms based on pre RT and post RT finding.

## Conclusion

This was a prospective study where the patients under went careful selection based on tumor characteristics and were planned using IMRT. The follow up was meticulous andthe result obtained showed significant improvement in xerostomia clinically butstatistically could not be appreciated, by limiting the dose received by the contralateral submandibular gland along with the parotid.

A multivariate analysis by taking compounding factors with a larger sample sizecan improve the strength of the study. Longer follow up can also shed light on the recurrence/ failure rates in both the arms. Although it has proven its benefit inxerostomia clinically but for proving significance large sample size is needed. The useof IMRT with daily imaging and time required for careful selection of patients and proper execution of the treatment may lead to questions regarding the time and the costrequired for execution of this type of planning. So, it could be worth while to do a study which calculates cost/ benefit ratio to better understand the application of this treatment in Indian scenario

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