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A Prospective Study to Assess the Effectiveness and Safety of Radiation Therapy for Oral Cavity and Oropharyngeal Cancer Using Contralateral Submandibular Gland-Sparing Radiation Therapy

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ABSTRACT
Submandibular glands (SMGs) take up 95% of everyday salivary circulation. Therefore, sparing of SMG in intensity-modulated radiation therapy (IMRT) may help to optimize the patient-reported xerostomia results. Smaller organs like the SMG tend to be spared less often due to the technical difficulty of doing so, coupled with their close proximity to target lymph node groups suspected of harboring disease. The contralateral SMG (cSMG)-sparing radiation therapy has been adopted with a potential aim to improve xerostomia and other toxicities but the impact on treatment outcome is unsure. Submandibular glands-sparing IMRT was offered either as definitive or post-surgery adjuvant therapy according to clinical indicators for patients with squamous cell carcinoma of oral cavity and oropharynx who had unilateral neck node involvement only. Patients were assessed weekly during radiotherapy and at 6 weeks, 3 months and at 6 months after completion of the radiation for treatment response and evaluation of xerostomia and other toxicities. The mean dose (Gy) to the cSMG was 33.68. 25.7% of patients had Grade 2 acute xerostomia exactly after radiotherapy, 3 months after radiotherapy this reduced to 2.9% and 6 months after radiotherapy, no patients developing Grade 2 acute xerostomia ($P<0.01$). Patients who received radiotherapy, with or without chemotherapy, after surgery did not experience recurrence in the whole follow-up period. After 6 months, 57.1% of patients who underwent definitive concurrent chemo radiotherapy exhibited complete response. cSMG-sparing IMRT can significantly reduce rates of xerostomia while maintaining similar levels of tumour control among patients with well-lateralized oropharyngeal and oral cavity carcinoma.

INTRODUCTION

India has the second highest incidence of head and neck carcinoma. Males with a mortality of 12·3% Cancers of lip oral cavity are the leading cancer (16·1%) Xerostomia[1], or dry mouth (reduced or absent salivary flow), is one of the most common sequelae after irradiation, especially in patients with head-and-neck cancers. Xerostomia leads to dental caries, pharyngeal discomfort, altered taste and difficulty chewing and swallowing, which causes nutritional deficiency and subsequent weight loss. Therefore preservation of the salivary glands to the extent possible during a course of radiotherapy may enhance post radiotherapy quality of life[2,3]. The parotid and submandibular glands (SMGs) are the main contributors to salivary flow. The parotid gland, however, is mainly serous so its saliva lacks the mucin that gives an impression of moisture[5]. Therefore, mere preservation of the parotids cannot reliably be associated with an improvement in xerostomia. However, the SMGs contribute 65%-90% of unstimulated saliva and almost 95% of salivary flow in 24-h periods and its secretion is high in mucin[4]. As such, this approach to SMG-sparing IMRT may optimise patient-reported xerostomia outcomes. The SMG is quite small and because it is very close to some target lymph node groups, it is technically very difficult to spare the SMG. In that regard, it is always rare to be able to spare the ipsilateral SMG in patients undergoing radiotherapy for an oral cavity and oropharyngeal carcinoma as its location directly about the primary and/or grossly involved lymph nodes that are subjected to a tumoricidal dose of 66-70 Gy[5]. On the other hand, the contralateral SMG (cSMG) may not need to be included in the target volume if the cSMG is not involved to achieve a comparable treatment outcome while reducing the incidence of radiation-induced xerostomia. We examined the impact of cSMG-sparing RT on treatment results, xerostomia and other acute toxicities in this study[4].

MATERIALS AND METHODS

A prospective, single-arm study among patients with histopathologically proven squamous cell carcinoma of oral cavity and oropharynx with radiological and/or clinical evidence of unilateral neck node aged 20-70 years with adequate hepatic, renal, haematological parameters and Eastern Cooperative Oncology Group score of 0-2. Patients with bilateral neck node involvement, head-neck malignancies of other sites, recurrent or metastatic disease and those with previous history of any other malignancy or radiotherapy were excluded from the study. The Institutional Ethical Committee approved the study. The patients who met the inclusion and exclusion criteria described above received IMRT sparing the contralateral submandibular gland. Pre Treatment Evaluation All study patients received preradiotherapy dental prophylaxis/evaluation prior to treatment to manage underlying dental pathology. Both arms being beside the body, head extended, shoulder retracted, and immobilization with four-clamp thermoplastic mask were done with CT Scan in supine position at the time of computerized tomography-based simulation Planning. Radio-opaque balls were used to create the reference line Axial images were obtained for all patients with 3-mm sections summit to midthorax. These images were then reconstructed in three dimensions by the system and were sent to the VARIAN treatment planning system. The planning CT scan was done delineation of tumor and contouring was done followed by planning Gross tumor volume (GTV)-All gross primary tumor (s) and involved lymph node (s) as determined by physical, pathological examination and imaging (only in the nonsurgical case). GTV and adjacent volume of subclinical microscopic malignancy which comprised CTV [clinical target volume] Planning target volume (PTV)-PTV was defined by outlining the margins that need to be added around the CTV to account for organ, tumor patient motions, errors in beam and patient set-up and all other uncertainties. Organ at risk (OAR)-The OARs contour to maximize the passing dose during the radiation therapy planning which includes parotid gland (right and left), spinal cord, mandible, cervical oesophagus, brain stem, optic nerve (right and left), optic chiasm, cochlea (right and left), larynx, thyroid, eyeball (right and left), lens (right and left) and cSMG. Dose The dose was administered via the sequential boost approach. CTV-High (high-risk CTV)-66 Gy conventional fractionation in 33 fractions over 6.5 weeks in patients with gross disease CTV-Intermediate (intermediate-risk CTV)-60 Gy in 30 fractions over 6 weeks (conventional fractionation). CTV Low (low-risk CTV)-50 Gy in 25 fractions (5 weeks, conventional fractionation). Postoperative setting CTV-Intermediate-60 Gy/30/6 weeks CTV-Target-50 Gy in 25 fractions over 5 weeks. Those with close/positive margins and/or extra-capsular nodal spread were boosted 63-66 Gy to the region. In order to avoid the sparing of cSMG, it should be delivered a mean dose of <36 Gy. The PTV expansion was restricted to 2-5 mmto minimize the coverage of salivary sparing. Among evaluation criteria for plans were PTV coverage, conformity and homogeneity (for boost), hotspot, OAR constraints, and OAR high-dose region. Plans were accepted if they covered $\geq$95% of the planning target volume (PTV) with $\geq$95% of the prescribed dose. We tried to minimize the Hotspots (outside PTV receiving dose >100%, which described as the area of 1.5cc volume in this study) well, particularly on the OARs. Dose-volume histogram

was used for the quantitative assessment of plans. Setup and verification and treatment The position was recreated on the treatment couch by utilizing device. Linear accelerator with photon beam was used to treat them. The isocenter was matched by shifting the couch with an accurate source to surface distance according to the planning system data. To mitigate the setup error, on board imaging was used to verify them. Comparison of Images were compared with digitally reconstructed radiographs derived during CT simulation and matched with bony landmarks on both images (MV-KV) After evaluating the field, three-dimensional shifts were derived by this technique. Follow-up-All patients were followed up weekly during radiotherapy highlighting preventive and early management of radiation-induced toxicity and at 6 weeks, 3 months and 6 months after completion of radiation. RT Oncologic Group scoring was used to assess treatment-related toxicities. In patients with definitive chemo radiotherapy, RECIST 1.1 was used to evaluate response. In this study, for treatment response assessment, we assess the recurrence of disease during the follow-up period (6 months) of this study for patients where resection of gross primary tumour is performed (with/without lymph node dissection., i.e., those who were without gross disease by the time of radiotherapy and therefore received postoperative adjuvant radiotherapy/ chemoradiotherapy). Surgical intervention was indicated for disease progression after definitive chemoradiotherapy, while in cases that surgery was not feasible or in case the patient developed metastasis, chemotherapy was administered. Chemotherapy was used for progressive disease in patients with postoperative radiation.

RESULTS AND DISCUSSIONS

The mean age of the population studied was 52.08 years and the majority of patients were male (68.57%, 24 patients). In the study population, buccal mucosa was the predominant subsite of disease (45.72%) (Table 1). Most patients underwent adjuvant radiotherapy post-surgically. Of these patients, 22.9% of overall patients received concurrent chemoradiotherapy and 37.1% received adjuvant radiotherapy only. Definitive chemoradiotherapy was performed for 40 percentage patients. Mean doses to cSMG (mean±SD): 33.6886±2.09 Gy Minimum and maximum doses to the gland were 28.8 Gy and 36.3 Gy, respectively. In our report, immediately after treatment 27 (77.1%) patients had Grade 1 and 8 (22.9%) patients had Grade 2 skin toxicity. At 6 weeks, 24 (68.6%) of patients had grade 1 skin toxicity and none had grade 2 or higher toxicity. Grade 2 mucositis affected 42.86% of patients initially post-treatment, but dropped progressively with time, at 6 weeks 14.29% and at 3 months 0%. The most frequent acute complication during follow-up was grade 1 xerostomia. Immediately following the completion of treatment, 28.57% of patients had Grade 2 xerostomia, falling to 14.29% and 11.43%, respectively, at 6 weeks and at 3 months post-treatment. At 6 month follow up, seven (20%) patients had Grade1 xerostomia and only two (5%) patients had grade 2 xerostomia (table 2).

Table 1: Distribution of Baseline Characters

Parameters	Numbers	Percentages
Age distribution		
<40 years	1	2.85%
41-50 years	15	42.85%
51-60 years	12	32.28%
61-70 years	7	20%
Mean age	52.08	
Gender		
Male	24	68.57%
Female	11	31.43%
Site of lesion		
Buccal mucosa	16	45.72%
Gingivobuccal sulcus	9	25.72%
Tonsil	8	22.85%
Retromolar trigone	2	5.71%
ECOG score		
1	25	71.42%
2	10	28.58%

Table 2: Radiation Induced Acute Toxicities

Toxicity and grading	Immediately after treatment		After 6 weeks		After 3 months	
Mucositis						
Grade 0	0	0%	11	31.43%	31	88.57%
Grade 1	20	57.14%	19	54.29%	4	11.43%
Grade 2	15	42.86%	5	14.29%	0	0%
Acute xerostomia						
Grade 0	2	5.71%	6	17.14%	14	40%
Grade 1	23	65.71%	24	68.57%	17	48.57%
Grade 2	10	28.57%	5	14.29%	4	11.43%

All patients achieved a partial response (PR) at the end of therapy in the definitive chemoradiotherapy group, and no patient had recurrence of disease in the postoperative radiotherapy with/without chemotherapy group (Fig. 1).

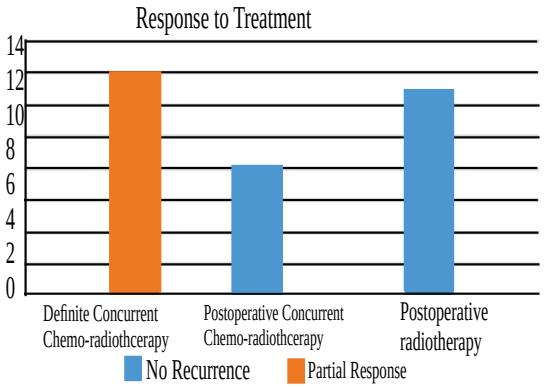

Fig. 1: Association of Treatment and Response Immediately after Treatment

Responses were identical to those found immediately after treatment, 6 weeks after therapy completion. P<0.0001 for association of response just after treatment and after 6 weeks regarding type of

radiotherapy. At 3 months after completion of treatment, 35.7% of patients treated with definitive Concurrent Chemo-Radiation (CTRT) exhibited complete response, while there was still no incident of disease recurrence in any of patients managed by postoperative radiotherapy with or without concurrent chemotherapy. There was also a statistically significant association between the mode of radiotherapy and response at 3 months (P<0.0001). Among patients treated with definitive chemoradiotherapy, this raised the rate of complete response to 57.1% but led to 14% developing progressive disease at 6 months. In the adjuvant RT/CTRT setting, there were zero cases of recurrence. Statistical analysis of response at 6 months according to the mode of radiotherapy was significant (P<0.0001) (Fig. 2).

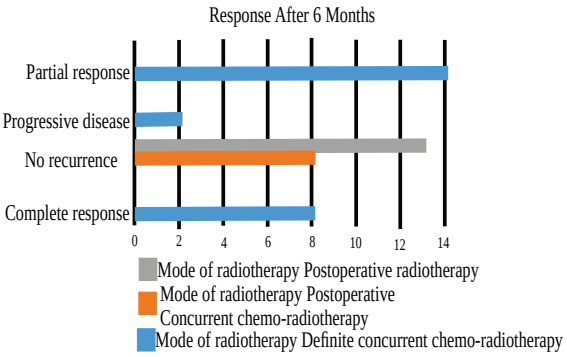

Fig. 2: Association of Treatment and Response after 6 Months of Treatment

To prevent xerostomia, it is crucial to maintain an appropriate function of the SMG since they can contribute to as much as 90% of the unstimulated salivary output. Concurrent avoidance of acute radiotherapy induced toxicities along with tumour control avoiding cSMG induced dry mouth is possible by delivering submandibular gland sparing radiotherapy[4]. In our study, most of our patients were in the age group of 41-50 years 42.85%, while the groups of 51-60 and 61-70 years were close to each other 32.28% followed by 20% respectively (Table 1). The average age for the present study was 52.08 years with minimum age was of 35 years and maximum age of 65 years which was comparable to studies done by different authors. The proportion of male patients in the study population (68.57%) was consistent with the reported incidence and prevalence of oral cavity and oropharyngeal cancers according to gender[6,7]. In oral cavity cancers, most of our patients were carcinoma buccal mucosa (45.72%) (Right side-24.72% and left side-21%) followed by Gingivobuccal sulcus (left-14.3% and right-11.4%) and Retromolar trigone (right-5.7% and left-2.9%). Sparing of the submandibular gland is not possible in patients with carcinoma of oral tongue or floor of mouth, as this disease requires definitive bilateral nodal irradiation[9], which was excluded in the study population. We excluded tonsil primary (right tonsil-8.6% and left tonsil-14.3%) in oropharyngeal carcinoma as in case of any midline tumour or tumour encroaching toward midline sparing of SMG can jeopardize tumour control due to the tendency for such tumors to involve bilateral neck nodes[10]. Such patients predominated (80%) in our study to comprise the Stage III oral cavity cancer and oropharyngeal cancers[11]. Those who were nonwilling for surgery/ unfit for surgery/inoperable cases, they are managed by definitive CTRT (40% of the study population) and the rest population who underwent surgery were managed by adjuvant radiotherapy (37.1%)/CTRT (22.9%) depends on their indication. Indications with mean dose of cSMG was 33.68 Gy (minimum mean dose-28 Gy and maximum-36 Gy in the study population) with cSMG-sparing IMRT radiation. Similar to the study done by Robin[9] However, sparing of the SMGs is technically challenging compared to parotid tissue sparing and may be associated with increased risk because these small glands are embedded within the level Ib lymph nodes and adjacent to II lymph nodes that may harbour disease. Nonetheless, IMRT enabled smg dose reduction without compromising target coverage, leading to less RT toxicity due to highly conformal nature of this mode of RT. After finishing radiotherapy, Grade 2 skin toxicity was seen in only 22.9% of cases and no Grade 3 toxicity was reported. No patient developed neurologic toxicity of Grade 2 or higher on follow up at 6 weeks, 3 months and 6 months. Of 40% of the patients had Grade 2 toxicity on immediate completion of radiotherapy, this dropped to 8.6% on follow-up at 3 months and at 6 months there were no patients with mucositis (Table 2). Grade 1 acute xerostomia (dryness of mouth) was found in 65.71% of cases and Grade 2 in 28.57%, immediately after the completion of radiotherapy. Over the next 3 and 6 months of follow-up acute dryness of mouth gradually disappears and at 6 months 88.57% of patients were free from any signs of xerostomia and only 2.9% of cases showed Grade 2 toxicity (Table 2). SMG-sparing IMRT significantly decreased late Grade 2 acute dryness of mouth. A study by Gensheimer *et al.* Late xerostomia (Grade 2 or above) was significantly less common in the cSMG spared group (up to 24 months after RT)[4]. None of the patients experienced a recurrence event within 6 months after surgery aside from postoperative radiotherapy with or without chemotherapy. The rest of the patients were treated with definitive CTRT and all patients immediately after treatment had accounted as partial response and after 3 months, which increased to 57.1% after 6 months complete

response was encountered with 14% of patients had progressive disease . All of these cases had progression in the region of the high-dose but not within the spared SMG itself or in its immediate area. Other studies like Robin *et al.,* Collan *et al* and Saarilahti *et al.* reported analogous results with a 31-month follow-up[8,9,12].

CONCLUSION

To achieve less xerostomia without sacrificing tumour control, it is possible to spare the cSMG in patients with well-lateralized oropharyngeal and oral cavity carcinoma by keeping the mean dose below 36 Gy.

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