Concomitant Boost on Saturdays in Radiotherapy for Locally Advanced Oral Cavity and Oropharyngeal Cancers

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ABSTRACT

Introduction: Head and neck cancer is a major health problem in Asia, especially in the Indian subcontinent. Study aimed to assess the response of concomitant boost radiotherapy against the concurrent chemoradiotherapy in locally advanced oral cavity and oropharyngeal cancers and to compare the toxicity in terms of oral mucositis in both treatment groups.
Material and methods: Total 60 patients were enrolled and randomly allotted to arm A (n=30) that received concurrent chemoradiotherapy and arm B (n=30) that received concomitant boost radiotherapy without any concurrent chemotherapy.
Results: The response at 6 weeks in both treatment arms was comparable (p value- 0.721), the toxicity in terms of mucositis (p value-0.133) also came out to be comparable in both arms.
Conclusion: The observations made in our study helped us arrive at a conclusion that concomitant boost radiotherapy without concomitant cisplatin has a response comparable to the conventional chemoradiotherapy regimen with not significantly higher cases of oral mucositis

Keywords: Concomitant Boost, Saturday Boost, Chemoradiotherapy, Mucositis, Oral Cavity, Oropharyngeal Cancers.

INTRODUCTION

More than 2 lakh new cases of head and neck cancer are diagnosed each year. India contributes to upto 7.8% of the global cancer burden and 8.33% of global cancer deaths.[1] India accounts for the highest incidence of oropharyngeal cancer in the world with over 1,00,000 cases registered annually.[2] In locally advanced head and neck cancers, the chemoradiotherapy has been identified as a standard therapeutic method in patients with locally advanced squamous cell carcinoma of the head and neck.[3] Work of Maciejewski[5] and Withers[6], showed that with increasing overall time the total dose to cure a tumour of the head and neck area had to be raised, this was attributed to repopulation, which may not be important until the third week of a course of treatment. Accelerated regimens with shortened overall duration of treatment were therefore investigated with the aim of reducing the time in which cellular repopulation could occur. Several randomised clinical trials have shown an increase in local control using accelerated or hyperfractionated radiotherapy.[7-10] A meta-analysis showed that altered radiotherapy with new fractionating schedules, achieved an increase of 7% in local control and 3% in survival at 5 years.[11] Taking into account these considerations, attempts have therefore been made to improve the therapeutic ratio by studying and testing various altered fractionation schedules. Concomitant boost can be given in three forms. In the first variant, the boost dose is delivered in the initial part of the treatment. In the second variant, it is given at the end of the treatment and in the third variant, it is delivered throughout the treatment.[14] We chose to study the concomitant boost technique in which we planned to give treatment on boost field every Saturday of each week during treatment.

MATERIAL AND METHODS

This was a single institution, prospective, randomized study conducted at the Department of Radiotherapy, Guru Gobind Singh Medical College and Hospital, Faridkot over a period of one year (April 2015-May 2016). A total number of 60 patients were enrolled in the study. Inclusion Criteria for the study included histologically proven oral cavity and oropharyngeal squamous cell carcinoma (excluding cancer of upper and lower lip). Stage III – IV A (Locoregionally advanced disease), Good performance score (ECOG<3), Written and signed consent for enrollment into the study. Exclusion Criteria for the study includes Stage IV B disease, prior treatment with radiotherapy or chemotherapy, any other malignancy (synchronous/metachronous), pregnant or breast-feeding women. Arm A denotes Concurrent chemoradiotherapy (conventionally fractionated radiotherapy+weekly cisplatin) Arm B denotes concomitant boost radiotherapy without concurrent chemotherapy. Baseline workup for the study provides a detailed history and physical examination including complete head and neck examination was conducted in each case and recorded on a prescribed proforma. Investigations considered after proper individualization includes- local examination- Per-oral and neck examination, ENT Evaluation - IDL / DL / Triple Endoscopy (as indicated), histopathology (Biopsy from primary site) and or Cytopathology from neck nodes, Complete hemogram, Routine biochemistry investigations (RFT/LFT/Serum Electrolytes/RBS), Chest X-ray (Postero-anterior view). Imaging modalities are CECT / MRI face and neck, Dental evaluation. All Patients were treated by teletherapy machine using either Co-60 gamma rays or 6-MV photons (Cobalt 60 teletherapy unit-equinox) following simulation at the simulix (Elekta) machine with 2D technique in Department of Radiotherapy at Guru Gobind Singh Medical College and Hospital, Faridkot. ARM A Patients received radical radiotherapy with conventional fractionation to a total dose of 66Gy in 33 fractions (200cGy per fraction), five fractions per week (Monday to Friday) over a period of 6.5 -7 weeks with two parallel opposed lateral portals using shrinking field technique. 66Gy/33 fraction was given as follows:-

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40Gy/20fr/4week to to the primary and draining lymph nodes (phase I) 20Gy/10fr/2weeks fractions to reduced field with spinal cord spared (phase II) 6Gy /3fr/3days boost (Additionally reduced portals with a margin of 2 cm around the original gross tumour.) (Phase III) ARM B Patients received radical radiotherapy as follows:-40Gy/20fr/4 weeks to the primary and draining lymph nodes (phase) +16Gy/8fr/8days to the reduced field with spinal cord spared (phase II). This totals to a dose of 56Gy/28fr/5.5weeks (200cGy per fraction) from Monday to Friday on cobalt teletherapy machine. 12Gy/ 5fr (240cGy per fraction) was given to the boost field, concomitantly on every Saturday of each week for 5 consecutive weeks on linear accelerator machine (Elekta synergy). Markings for boost field were made along with the phase 1 field. Radiation doses given in both the protocols were biologically equivalent as calculated by TDF table. In Chemotherapy ARM A- Patients received concurrent chemotherapy with cisplatin (35 mg/m^2) weekly. Chemotherapy was administered in the cancer day care ward on outpatient basis at Guru Gobind Singh Medical College and Hospital. ARM B Patients did not receive any chemotherapy. Monitoring for response and toxicity involves tumour response which was evaluated after completion of treatment by clinical examination and imaging investigations (CT/MRI head and neck region). The best tumour response at 6 weeks from completion of treatment was recorded and used for the assessment using RECIST criteria (Response evaluation criteria in solid tumours). Patients were monitored for mucosal reactions atleast weekly during radiotherapy. The severity of which was scored using the RTOG (Radiation Therapy Oncology Group) toxicity criteria. The first clinical follow up was scheduled at 6 weeks and thereafter every two month for rest of the year.

STATISTICAL ANALYSIS

SPSS version 21 was used for the statistical analysis. Chi square test was used for comparison of variables. Descriptive statistics was used to interpret the inferential data.

RESULTS

The baseline clinical characteristics of the patients included in the study have been summarised in [Table 1] to demonstrate comparability between the two treatment group. In our study most of the patients were able to complete the planned treatment on time. Out of the analyzable patients there were 7 patients (23%) and 9 patients (30%) in Arm A and Arm B respectively with prolongation of treatment which came out to be stastically insignificant (p value=0.260). As shown in [Figure 1]. As we compared oral mucositis as shown in [Figure 2], we observed that Grade II mucositis was seen in 12 patients (40%) in Arm A and 10 patients (33.3%) in Arm B. Grade III toxicity was slightly more in Arm B patients as compared to patients in Arm A. 5 patients (16.7%) and 10 patients (33.3%) in Arm A and Arm B respectively developed grade III mucositis. No patient in Arm A developed grade IV mucositis whereas 3 patients (10%) in Arm B developed grade IV mucositis. There was no significant difference in both treatment arms (p value=0.133). There was complete response in 18 patients (60%) in Arm A and 14 patients (46.7%) in Arm B. 8 patients (26.7%) and 10 patients (33.3%) in Arm A and Arm B respectively showed partial response. 4 patients (13.3%) in each arm had stable disease [Figure 3]. The disease progression was not seen in any patient in both arms, there was no statistical significance found in the response at 6 weeks in both the treatment groups (p value=0.721).

DISCUSSION

Concomitant boost radiotherapy was taken in the study keeping in mind the radiobiological aspects of accelerated fractionated radiotherapy.[16] Concomitant boost radiotherapy has shown a better response than conventionally fractionated radiotherapy in various studies done till date.[12,13,17-19] Most successful treatment schedules attempt to administer the highest possible doses during the shortest possible time without doing much damage to the normal tissues and vital organs at risk. Out of 60 patients enrolled, 58 patients successfully completed the treatment (30/30 in arm A and 28/30 in arm B). One patient defaulted and one patient expired during treatment, both of which were enrolled in arm B. So these patients could not complete the treatment and hence were not evaluated for response. In our study all the patients were examined on weekly basis and acute toxicity in terms of oral mucositis were noted and graded on the basis of RTOG toxicity criteria. Oral mucositis developed in almost all patients during the treatment. Grade II toxicity was seen in 12 patients (40%) in arm A and 10 patients (33.3%) in arm B. GradeIII toxicity was more in arm B patients as compared to patients in arm A. 5 patients (16.7%) and 10 patients (33.3%) in arm A and arm B respectively developed grade III oral mucositis. No patient in arm A developed grade 4 oral mucositis whereas 3 patients (10%) in Arm B developed grade 4 oral mucositis. There was no significant difference in oral mucositis in both treatment arms (p value=0.133). These results were similar to the study by Rishi A, Ghoshal S et al in which 50 patients (46%) out of 110 patients developed grade II oral mucositis in concomitant boost arm as compared to 64 patients (62%) in chemoradiotherapy arm whereas 60 patients (55%) and 48 (38%) patients in concomitant boost arm and chemoradiotherapy arm developed grade III oral mucositis, and no patient in any arm showed grade IV oral mucositis.[15] In our study, during first week of treatment no patient developed oral mucositis. In second week one patient in arm B developed grade II-IV oral mucositis. By third week 13 patients (43.3%) in arm A and 14 patients (46.7%) in arm B developed grade II-IV oral mucositis. And by fourth and fifth week each 43.3% patients in arm A and 73.3% patients in arm B developed grade II-IV oral mucositis. The grade III toxicity led to no treatment interruptions and was manageable on outpatient basis but grade IV toxicity that was seen in Arm b patients led to treatment interruptions and required hospital admission. The RT was restarted only after reduction in oral mucositis by atleast one grade. The hospitalized patients were managed by i/v fluids and supportive therapy and were advised to maintain proper oral hygiene and to do saline/benzydamine gargles 6 to 8 times a day. Majority of patients in our study completed the planned treatment on time. Prolonged treatment time, for the purpose of this study was defined as completing treatment with a delay of more than 5 days. Patients who were able to complete their treatment within the stipulated time plus a 5 day allowance for logistical problems and public holidays were considered to have completed on time. There were 7 patients (23%) and 9 patients (30%) in Arm A and Arm B respectively with prolongation of treatment which

Baseline Characteristics	Arm a (conventional Chemoradiation)% out of 30 patients		Arm B (concomitant Boost)% out of 30 patients		P value	Significance
Age:					0.714	Ns
31-40	13.3		13.3			
41-50	23.3		26.7			
51-60	26.7		26.7			
61-70	30		33.3			
71-80	0		0			
81-90	6.7		0			
Mean age±SD	57.033±12.397		54.633±11.48			
Range	35-85		32-66			
Gender					0.739	Ns
Male	80		83.3			
Female	20		16.7			
Residence					0.080	Ns
Rural	83.3		63.3			
Urban	16.7		36.7			
Site					0.791	Ns
Oral cavity	60.0		63.3			
Oropharynx	40.0		36.7			
Subsite					0.844	Ns
Tongue	16.7		20			
Buccal mucosa	20		26.7			
Alveolar ridge	6.7		10			
Floor of mouth	0		0			
Retromolartrigone	10		3.3			
Tonsil	10		13.3			
Base of tongue	20		16.7			
Vallecula	0		3.3			
Hard palate	6.7		13.3			
Soft palate	0		0			
Posterior wall of Oropharynx	10		3.3			
Addictions	Yes	No	Yes	No		
Alcohol	36.7	63.3	60	40	0.791	Ns
Smoking	66.7	33.3	56.6	43.3	0.426	Ns
Tobacco	33.3	66.7	26.7	73.3	0.573	Ns
Opium	3.3	96.7	10	90	0.301	Ns
Stage					0.284	NS
III	30		43.3			
IVA	70		56.7			

Table-1: Baseline characteristics of patients

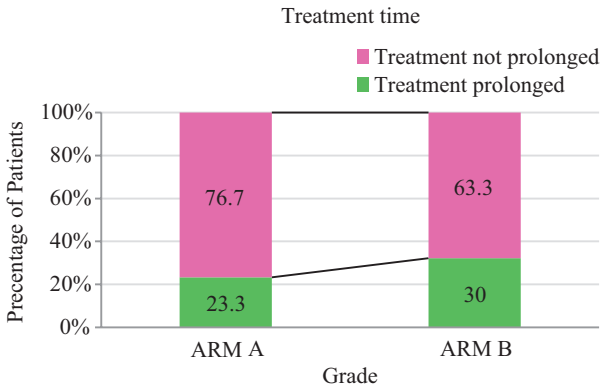

Figure-1: Representation of patients with prolonged treatment time in both treatment arms.

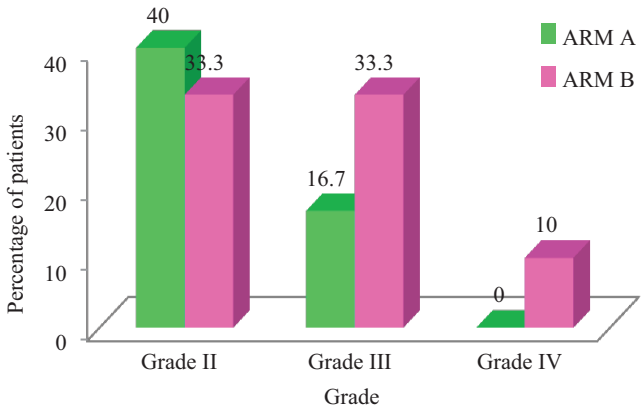

Figure-2: Comparision of oral mucositis in both treatment arms.

came out to be statistically insignificant (p value=0.260). The response to treatment, in our study, was assessed at 6 weeks after therapy according to RECIST criteria. Radiological (CT) findings were employed for response assessment. Out of 30 patients in Arm B one patient defaulted after 4rth week and one patient expired. The response assessment of these two patients could not be done. For rest 58 patients (30 in Arm A and 28 in Arm B) the response was evaluated. There was complete response in 18 patients (60%) in arm A and 14 patients (46.7%) in arm B. 8 patients (26.7%) and 10 patients (33.3%) in arm

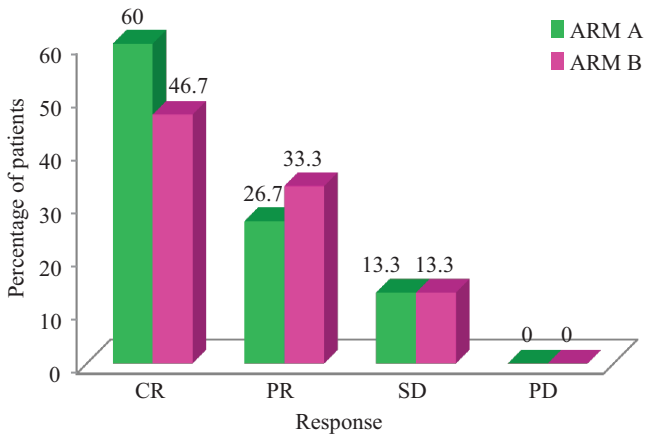

Figure-3: Representation of response at 6 weeks in both treatment arms.

A and arm B respectively showed partial response. 4 patients (13.3%) in each arm had stable disease. The disease progression was not seen in any patient in both arms. The complete response for locoregional disease in both treatment arms was comparable (p value=0.721). Similar results were seen in the study by Rishi A, Ghoshal S et al where 74% patients in concomitant boost arm showed complete response as compared to 68% patients in chemoradiotherapy arm and the difference was statistically insignificant.[15] In a study by K Shrivastava, M Shrivastava et al[14], out of 40 patients, 30 patients (75%) in concomitant boost arm and 24 patients (60%) in conventional chemoradiotherapy arm had complete response and the rest of the patients had partial response except for one patient in chemoradiotherapy arm who showed no response. In patients with residual tumour, disease recurrence, or progression of disease, salvage surgery or palliative treatment was offered depending on the performance status of the individual patient, symptoms and previous treatment, after multidisciplinary tumour board meeting.

The follow-up of the present study was relatively short and prevents us from commenting on the long term disease free survival, overall survival, and a more comprehensive evaluation of the late toxicities too. Another limitation of our study was the relatively smaller sample size and consequently, subgroup analyses could not be materialised.

CONCLUSION

The observations made in our study helped us arrive at a conclusion that concomitant boost radiotherapy without concomitant cisplatin has a response comparable to the conventional chemoradiotherapy regimen with not significantly higher cases of oral mucositis. But the need of the hour is that studies with larger sample sizes and longer follow-up should be instituted for further validation of the feasibility of concomitant boost radiotherapy and to get significant results so that we are able to consider concomitant boost radiotherapy as a routine practice in treatment of locoregionally advanced oral cavity and oropharyngeal carcinomas in future.

Abbreviations

RT-Radiotherapy, CT-Computed tomography, Fr-fraction, IDL- Indirect Laryngoscopy, DL-Direct Laryngoscopy, RTOG-Radiation Therapy Oncology Group, RECIST-Response evaluation criteria In Solid Tumors.

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