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A PROSPECTIVE STUDY TO COMPARE CONVENTIONAL CHEMORADIOTHERAPY WITH CONCOMITANT BOOST CHEMORADIOTHERAPY IN CARCINOMA OF ORAL CAVITY

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ABSTRACT

Background : India accounts for the highest incidence of lip and oral cancer in the world. In early stages,surgery and radiation therapy are curative treatments,while locally a locally advanced carcinoma requires a multidisciplinary management. A major cause of failure in advanced rapidly growing tumors is accelerated repopulation.To overcome this problem ,various accelerated fractionation radiotherapy techniques are used.

Aim : To compare the outcome,feasibility,tolerability of concomitant boost chemoradiotherapy over conventional chemoradiotherapy

Materials and methods: From November 2018 to June 2020,64 patients from J.K.Cancer institute,Kanpur were enrolled in this study.prospective comparative study was done to find out the difference in all groups

Results : out of 59 eligible patients,31 were assigned to arm A(conventional chemoradiation) and 28 were assigned to arm B (concomitant boost chemoradiation). Out of 31 patients in arm A, 15(48.4%) had complete response(CR),8 (25.8%) had partial response (PR),4(12.9%) had stable disease (SD) and 4(12.9%) had progressive disease (PD).In arm B ,out of 28 patients,14(50%) had complete response,6(21.4%) had partial response,6(21.4%) had stable disease and 2 (7.1%) had progressive disease.

Conclusion : Concomitant boost chemoradiotherapy had a response comparable to conventional chemoradiotherapy with moderate efficacy and acceptable toxicity.It can be used as alternative to conventional chemoradiotherapy in limited resource setting where the total duration can be minimized and workload can be reduced.

Key words: oral cavity–concomitant boost technique–conventional chemoradiotherapy

1 INTRODUCTION

Head and neck cancer is the 7th most common type of cancer and 8^{th} most common cancer related death in the world, more than 8 lakhs new cases of head and neck cancer are diagnosed each year.In India head neck cancer is the most common cancer in men, About 1.93 lakhs new cases of head neck cancer are diagnosed and 1.14 lakhs deaths occurred due to head neck cancer, per year in India.India contributes to up to 15.6% of the global cancer burden and 12.1% of global cancer deaths.(globocon 2018)[1] India accounts for the highest incidence of lip and oral cancer in the world with over 1,00,000 cases registered annually. . Approximately 30 to 40 % patients present with early stage I/II disease. These patients are treated with curative intent using single modality treatment either radiation or surgery alone. A non operative approach is favoured for patients in which surgery followed by either radiation alone or radio-chemotherapy may lead to severe functional impairment. One of the most important cause of failure is accelerated repopulation of tumor cells , which usually starts around the 4^{th} week of radiotherapy. To combat this 60cGY of daily extra dose is needed. Hence to increase local control and survival, several strat-

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egy of altered fractionation has been tried. Work of Maciejewski [2] and Withers [3], 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.[4-7] 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. [8]

Accelerating the radiation schedule involves shortening the overall duration of therapy to less than the 7 weeks used in a conventional schedule. The key element is the reduction in the overall time. One problem with a fractionated course of radiation is that tumor regeneration can occur during a course of treatment, reducing the probability of cure. Several studies have attempted to determine the dose of radiation necessary to overcome the effects of tumor regeneration.. Withers et alanalyzed the dose equivalent of regeneration during therapy. They suggested that tumor clonogens undergo an accelerated repopulation after a certain period of time, and that an additional 0.6 Gy is required for each day of therapy beyond the time when repopulation sets in.[9] It was estimated that this phenomenon of accelerated repopulation begins in the fourth week of a conventionally fractionated schedule, based on a retrospective analysis of local control rates in tonsillar carcinomas achieved at different international centers using a variety of fractionation schedules.[10] Unfortunately, simply adding this supplementary dose to overcome repopulation could potentially increase late effects on normal tissue. An alternative method was to shorten the time of therapy to prohibit accelerated repopulation from occurring. Multiple fractions per day might not be required if one could deliver larger doses per fraction to the tumor only, while maintaining lower doses per fraction to subclinical disease and normal tissues. Tworandomized trials, in Denmark[11] and Poland,[12] evaluated conventional therapy with five fractions per week, compared to accelerated regimens using six to seven fractions per week. Totaldose and fraction size remained the same, resulting in a shortening of treatment time by 1 or 2weeks.

Radiation for head and neck cancers involves delivery of both a planned dose to the gross tumor and a lesser dose to sites of microscopic or subclinical disease. Conventional radiation delivers 50 to 54 Gy to these subclinical sites, and then the radiation portals are reduced in size to deliver the "boost" to the gross disease. Concomitant-boost therapy delivers this boost on the same days that the therapy to subclinical disease is given. As the boost is given on the same day as a second daily fraction, the dose per fraction is lowered.

2 MATERIALS AND METHODS

This study enrolled total of 64 patients from November 2018 to June 2020 registered in J.K.Cancer institute,Kanpur. Prior to the onset of therapy,the patients were thoroughly informed about all the aspects of the study and regulatory requirements that needed to be satisfied for informed consent. All the patients underwent an extensive pretreatment evaluation ,which included a medical history,a complete physical examination,a complete blood count and routine biochemistry panel,CT or MRI scans of the head and neck,chest radiography.Histologically proven cases of squamous cell carcinoma of bulky T2 and locally advanced(T3,T4) were selected.patients are staged according to AJCC staging system(2018). The eligible patients were between 20 and 70 years and had an karnofsky performance status >70.

Patients with prior history of radiation,surgery or chemotherapy,poor general condition with karnofsky performance status <70,pregnant or lactating women,associated medical condition such as renal disease,liver or heart disease were excluded from this study.

All the eligible patients were assigned to two arms

Arm A : conventional fractionation (2Gy per fraction),5 days a week ,shrinking the field anterior to the spinal cord after 46Gy. Total of 70 Gy was given with concurrent cisplatin 100 mg/m2 3 weekly.

Arm B: In concomitant boost radiation,large field of 45Gy (1.8Gy per fraction)was given daily for 5days a week for 5 weeks. Remaining 27Gy was given as boost field at an interval of 6hours in the last three weeks of treatment. Total of 72 Gy was given along with concurrent cisplatin 100 mg/m2 3 weekly.

All the patients included in the study will be carefully and regularly assessed weekly during treatment. Radiation reactions will be assessed by Radiation Therapy Oncology Group (RTOG) criteria. Tumor response (both primary and nodal response) will be assessed by RECIST(1.1) response criteria 2 months after completion of Radiotherapy by clinical examination as well as radiological assessment by CT Face and Neck . All the patients will be assessed two weeks after the completion of treatment, to detect acute complications like mucositis, skin reaction and are followed monthly upto minimum of 6 months and then 3 monthly. At every visit, each patient will be clinically evaluated for local control of disease and treatment related complications and also will be assessed for any evidence of distant metastasis during each follow up. The data thus obtained will be assessed, analyzed and compared to find out difference in all the groups in terms of tumor response and toxicity .

3 RESULTS

In our study total number of patients enrolled in arm A and arm B was 32 each,out of which 1 patient from arm A and 4 patients from arm B defaulted from the treatment and are excluded from this study.31 patients in arm A and 28 patients in arm B were included for this study.

Table 1. Distribution of patients in two different groups

Characteristics		Arm A (n=31)		Arm B (n=28)	
		No.	%	No.	%
Sex	Male	27	87.1	27	96.4
	Female	4	12.9	1	3.6
Age –Range		30-68years		28-61 years	
Residence	Rural	17	54.8	13	46.4
	Urban	14	45.2	15	53.6
Site	Tongue	12	38.7	9	32.1
	Buccal mucosa	13	41.9	15	53.6
	RMT	3	9.7	1	3.6
	Hard palate	1	3.2	1	3.6
	Alveolus	2	6.5	2	7.1
Stage	II	6	19.4	5	17.9
	III	6	19.4	7	25
	IV	19	61.3	16	57.1

In our study sex wise distribution in both arms were maximum in male. Chi-square = 1.652, df = 1,P value = 0.09952, not significant . Age wise distribution in Arm A was maximum in age group 41 to 50 & 51-70years, Whereas in Arm B, maximum in the age group of 31 to 40 years . Range in arm A was between 30-68 years and in arm B was between 28-61 years.Chi-square = 1.47, degrees of freedom = 3, P value = 0.6893, not significant. Residence wise distribution in Arm A was more in rural i.e. 17 (54.8%) than in urban i.e. 14 (45.2%). However in Arm B was more in urban 15 (53.6%) than in rural 13 (46.4%). Chi-square = 0.4164, df = 1,P value = 0.2594, not significant. In our study ,maximum involved site was buccal mucosa followed by tongue. Chi-square = 1.423, df = 4, P value = 0.8403 , not significant . Our study showed stages of cancer in patient of Arm A was more is stage fourth i.e. 19 (61.3%), followed by stage second i.e. 6 (19.4%) & stage third 6 (19.4%) each. In Arm B showed maximum in stage fourth 16 (57.1%), followed by stage third 7 (25%), stage second were 5 (17.9%).Chi-square = 0.2731, df = 2, P value =0.8723, not significant .(Table 1)

Table 2. Histologic differentiation

Characteristics		Arm A		Arm B	
		No.	%	No .	%
Histologic differentiation	Well	23	74.2	21	75
	Moderate	6	19.4	7	25
	Poor	2	6.5	0	0
Total		31	100	28	100

In our study,histological differentiation of well,moderate and poor in arm A was 74.2%,19.4% and 6.5% respectively,whereas in arm B, well differentiated was 75%,moderate was 25% . (Table 2)

Our study showed that the duration of the treatment was 7-9.4 weeks in Arm A and 5-6.4 weeks in Arm B . In Arm A the dermatitis first was 87.1%, second was 9.7% and third was 3.2% in comparison to Arm B the first was 71.4%, second was 17.9% and third was 10.7%. Chi-square=2.396 ,df=2 ,P value=0.3018 ,not significant . In Arm A the mucositis first was 51.6%, second 45.2% and third was 3.2% in comparison to Arm B the first was 21.4%, second was 64.3% and third was 14.3%. Chi-square=6.71 ,df= 2 ,P value=0.03490 ,significant .(Table 3).Maximum incidence of grade 2 toxicity was seen in the 4^{th} week in arm B.

Table 3. Duration of treatment in weeks ,skin and mucosal toxicity

		Arm A		Arm B	
		No.	%	No.	%
Duration of treatment		7 weeks	-9.4	5-6.4 weeks	
Dermatitis	I	27	87.1	20	71.4
	II	3	9.7	5	17.9
	III	1	3.2	3	10.7
Mucositis	I	16	51.6	6	64.3
	II	14	45.2	18	14.3
	III	1	3.2	4	14.3

Table 4. Response of the treatment

	Arm A (n=31)		Arm B (n=28)	
	No.	%	No.	%
Complete response (CR)	15	48.4	14	50
Partial response (PR)	8	25.8	6	21.4
Stable disease (SD)	4	12.9	6	21.4
Progressive disease (PD)	4	12.9	2	7.1
Total	31	100	28	100

Our study showed the response of the treatment in Arm A 15 (48.4%) showed complete response, 8 (25.8%) showed partial response, 4 (12.9%) showed progressive disease and 4 (12.9%) showed stable disease in comparison to Arm B 14 (50%) showed complete response, 6 (21.4%) showed partial response, 6 (21.4%) showed stable disease and 2 (7.1%) showed progressive disease. Chi-square = 1.238, df = 3, P value = 0.7440 ,not significant.(Table 4).

In our study ,the most common post treatment complication in arm A was dryness of mouth 38.7%, followed by

Table 5. Post treatment complications

	Arm A		Arm B	
	No.	%	No.	%
Pain	8	25.8	5	17.9
Dryness of mouth	12	38.7	9	32.1
Loss of taste	5	16.1	5	17.9
Trismus	4	12.9	5	17.9
Dysphagia	0	0	2	7.1
Neck fibrosis	2	6.5	2	7.1

pain 25.8%,loss of taste 16.1%,trismus 12.9% and neck fibrosis 6.5%. In arm B ,most common was dryness of mouth 32.1% followed by pain,loss of taste ,trismus each 17.9% ,dysphagia and neck fibrosis is seen in 7.1% patients.(Table 5).

Table 6. Disease free survival,duration of follow up and status on last follow up

		Arm A	Arm B
Disease free survival		2-20 months (average-11)	3-21 months (average-9)
Duration of last follow up		6-22 months (average-13)	6-21 months (average-7)
Status on last follow up	NAD	16	15
	Salvage chemo	11	10
	Supportive care	4	3

In our study,disease free survival in arm A was 2-20 months (average 11months) and in arm B was 3-21months(average 9months). Duration of follow up in arm A was 6-22 months (average 13 months) and in arm B was 6-21 months (average 7 months). Status on last follow up in arm A –NAD 16,salvage chemotherapy 11 and best supportive care 4 and in arm B –NAD 15,salvage chemotherapy 10 and supportive care 3.(Table 6).

4 DISCUSSION

Concomitant boost radiotherapy has shown a better response than conventionally fractionated radiotherapy in various studies done till date. [13,14,15] 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. Concomitant boost radiotherapy has been tried keeping in mind the radiobiological aspects of accelerated fractionation RT [16], which gives beneficial results by decreasing the number of clonogen cells to a considerable extent and without doing much harm to the normal cells [17]. The concomitant boost technique of administering twice daily radiation therapy during only part of the treatment course allows for an aggressive fractionation schedule and limits the volume of normal mucosa exposed to twice daily radiation therapy. The significance of accelerated repopulation in conventionally irradiated head and neck tumors has been reported [18]. The isoeffective dose for tumor control significantly increases after 30 treatment days. Most successful treatment schedules attempt to administer the highest possible doses during the shortest time tolerable to early and late responding normal tissues

Prolonged treatment time, for the purpose of this study was defined as completing treatment with a delay of more than 1 week. Patients who were able to complete their treatment within the stipulated time plus a 1 week allowance for logistical problems and public holidays were considered to have completed on time.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. [19] In a study by K Shrivastava, M Shrivastava et al [20], 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. Because of shorter duration of follow up,overall survival and late toxicities cannot not be assessed in our study.

5 CONCLUSION

The results obtained in our study helped us arrive at a conclusion that concomitant boost radiotherapy with concomitant cisplatin has a response comparable to the conventional chemoradiotherapy regimen and a feasible schedule in patients with locally advanced head and neck cancer, with moderate efficacy and acceptable toxicity particularly in limited-resource settings.. Concomitant boost chemoradiotherapy can be used as an alternative to conventional chemoradiotherapy in oral cavity cancers in the setting of developing country,where the total duration can be minimized and the workload can be reduced. But the need of the hour is that studies with larger sample sizes and longer follow-up should be instituted to get significant r esults so that we are able to consider concomitant boost radiotherapy as a routine practice in treatment of locoregionally advanced oral cavity carcinomas in future.

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