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A Comparative Study of Two Split Course Accelerated Hypo-fractionated Radiation Therapy (SCAHRT) Schedules in Locally Advanced Head and Neck Carcinoma

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Abstract

- ***Introduction:***

Head and neck cancers include malignant neoplasms that develop in the oral cavity, nasal cavity, paranasal sinuses, pharynx, larynx and salivary glands. Out of the newly diagnosed patients of head and neck carcinoma in India, most of the patients present in locally advanced stage. Because of extensive local disease and associated co-morbidities and compromised KPS, palliative radiation therapy is preferred treatment for these patients.

- ***Material and methods:***

The study was conducted on 60 previously untreated, histo-pathologically proven patients of locally advanced head and neck cancer who were randomized in two equal groups by draw of lots. Study group received radiation dose of 30 Gy/ 10 fractions / 2 weeks followed by repeat dose of 30 Gy/ 10 fractions / 2 weeks (Total dose 60 Gy in 20 fractions delivered with a gap of 4 weeks). Control group received radiation dose of 20 Gy/ 5 fractions/ 5 days followed by repeat dose of 20 Gy/ 5 fractions/ 5 days followed by repeat dose of 20 Gy/ 5 fractions/ 5 days (Total dose 60 Gy in 3 sessions with a gap of 3 weeks each). Objectives were to compare efficacy of above schedules based on symptomatic relief and overall tumor response and to compare the toxicities of the above schedules.

- ***Results and Conclusion:***

To expedite the treatment time in tertiary care centres, control group (20 Gy / 5 fractions / 1 week; 3 weekly X 3) was better than the study group (30 Gy / 10 fractions / 2 weeks; 4 weekly X 2) as it had comparable local control and toxicity (acute mucosal reactions being slightly higher in the study group) with the added advantage of only 15 total fractions (machine days) in control group rather than 20 total fractions (machine days) in study group. This reduced the patient visits to the hospital by one week (i.e. 5 fractions) with comparable local control and toxicity.

I. INTRODUCTION

Head and neck squamous cell carcinomas are the most diverse class of malignancies grouped together under one diagnostic heading, arising from mucous membrane of upper aero-digestive tract linked by a common squamous histology.[1] There are a proportion of patients with head and neck cancer who at initial diagnosis are not candidates for curative therapy as a result of advanced stage and/or medical co-morbidities. For these patients, palliative care is instrumental in providing pain control, autonomy and dignity for the remainder of their lives. Palliation refers to alleviation of symptoms when life expectancy is limited. The goals of ideal palliation include optimal symptomatic relief, tumor response, low toxicity and minimization of the time spent in a health care facility.

Radiation therapy delivered in a fractionated regime is based on the differing radiobiological properties of cancer and various normal tissues, largely based on better sublethal damage repair of radiation damage in normal cells as compared to cancer cells. Normal cells proliferate relatively more slowly compared to the rapidly proliferating cancer cells and therefore have time to repair damage before replication.[2] One of the reasons of treatment failure in head and neck carcinomas includes the phenomenon of accelerated repopulation. This refers to the triggering of the surviving tumor cells to divide more rapidly as a tumor shrinks after irradiation or chemotherapy which starts after about the 4 weeks of radiation in head and neck cancers. This suggests that treatment should be completed as soon as possible once it has been started. So, accelerated radiation scheme aims to deliver the same total dose over a shorter time.[3,4] Hypo-fractionated regimens deliver radiation with higher dose per fraction in shorter overall treatment time. A shorter overall treatment time will reduce the risk of tumor repopulation at the cost of a theoretical increase in late effects due to the higher dose per fraction.[5] Split-course regimens deliver radiotherapy as a form of periodic treatment and is divided into two or more phases separated by a rest interval. This gives time for normal tissue restoration. In clinical practice the rest interval is extremely welcomed by the patients and gives them a chance of improving their general condition.

ISSN No:-2456-2165

II. MATERIAL AND METHODS

A randomized prospective study was conducted on 60 previously untreated, histo-pathologically proven AJCC stage III/IV patients of head and neck squamous cell carcinoma with the Karnofsky Performance Status ≥70, attending the Department of Radiation Oncology, Pt. B. D. Sharma PGIMS, Rohtak where palliative radiation therapy had been decided as the initial treatment were included in the study.

The current study was first approved by the Institutional Review Board. An informed written consent was taken from patients. These patients were divided randomly in two groups of 30 patients each by computer generated randomization.

Group I (Study Group) comprised of 30 randomly selected patients, having histopathologically proven carcinoma of head and neck. All these patients received split-course accelerated hypo-fractionated radiation therapy (SCAHRT) regimen of 30 Gy / 10 fractions / 2 weeks followed by repeat dose of 30 Gy / 10 fractions / 2weeks (total dose 60 Gy in 20 fractions delivered in two halves with a gap in between with interval of 4 weeks). In this schedule the per fraction dose was 3 Gy per fraction.

Group II (Control Group) also comprised of 30 randomly selected patients, having histopathologically proven carcinoma of head and neck. All these patients received split-course accelerated hypo-fractionated radiation therapy (SCAHRT) regimen of 20 Gy / 5 fractions / 1 week repeated three weekly, three times (total dose 60 Gy in 15 fractions delivered in three phases with a gap in between with interval of 3 weeks). In this schedule the per fraction dose was 4 Gy per fraction.

All the patients were treated in supine position on teletherapy machine by bilateral parallel opposing fields or anterior-posterior/posterior-anterior fields. The dose was prescribed to the mid plane at the central axis. In both groups the spinal cord was excluded from the radiation field after the tolerance dose reached.

Overall tumor response was assessed by WHO response criteria (one month post-treatment completion; by two consecutive assessments 1 month apart by thorough clinical examination). Symptomatic relief was assessed by subjective regression of disease. Radiation reactions were assessed by using the Radiation Therapy Oncology Group (RTOG) criteria. The patients were followed up regularly for a minimum period of three months after completion of treatment, weekly during radiation treatment and then every month.

The data obtained was entered in MS-Excel 2010 and percentage proportion was calculated. The statistical analysis was carried out by Chi-square test, unpaired t test and paired t test to compare the significance of the results using SPSS (Statistical Package for Social Sciences) software version 20.

III. RESULTS

The patient parameters were closely matched in both the arms. The age wise distribution in study group and control group was: 41-50 years age group – 11 each, 51-60 years age group – 11 versus 7 and 61-70 years age group – 8 versus 12, respectively. The mean age in study group and control group was: 54 versus 55.7 years. The gender wise distribution in study group and control group was: males – 28 versus 29 and females – 2 versus 1, respectively. The area wise distribution in study group and control group was: rural – 27 versus 23 and urban – 3 versus 7, respectively. Smoker / non-smoker status in study group and control group was: smokers – 30 versus 29 and non-smoker – 0 versus 1. Alcoholic / non-alcoholic status in study group and control group was: alcoholic – 20 versus 19 and non-alcoholic – 10 versus 11. The chief complaints in study group and control group were as follows: difficulty in swallowing – 16 versus 15, neck mass – 5 versus 9, pain in throat – 6 versus 3, ulcer – 2 versus 0 and hoarseness of voice – 1 versus 3. The Karnofsky Performance Status in study group and control group was: KPS 70 – 21 versus 23, KPS 80 – 9 versus 7. The histopathological distribution in study group and control group was: MDSCC – 28 each and PDSCC – 2 each. The tumor morphological distribution in study group and control group was: ulcerative – 2 versus 0, proliferative – 1 versus 0 and ulceroproliferative – 27 versus 30. The site wise distribution in study group and control group was: oral cavity – 3 versus 1, oropharynx – 24 each, hypopharynx – 0 versus 1 and larynx – 3 versus 4. The TNM stage wise distribution in study group and control group was: stage III – 2 versus 0 and stage IV – 28 versus 30. Patient and tumor characteristics are described in Tables 1 and 2. The mean dose received by the patients was 60 Gy in both the groups. One patient in study group left the treatment after receiving one cycle of 30 Gy/ 10 #/ 10 days, due to non-compliance. Two patients in control group left the treatment after receiving 20 Gy/ 5 #/ 5 days once and twice respectively, due to non-compliance. Treatment fall-out in non-compliant patients was comparable in both the groups without any significant P value($P \geq 0.05$).

ISSN No:-2456-2165

Patient characteristics		**Group-I Study Group** [30 Gy/10 #/2 weeks; 4 weekly × 2] **(n=30)** Frequency	(%)	**Group-II Control Group** [20 Gy/5 #/1 week; 3 weekly × 3] **(n=30)** Frequency	(%)	***P*-value**
Age Group (Years)	41-50	11	36.7	11	36.7	
	51-60	11	36.7	7	23.3	
	61-70	8	26.7	12	40	
	Range	42-70		43-70		
	Median	54 years		55.7 years		0.48
Background	Rural	27	90	23	76.7	
	Urban	3	10	7	23.3	0.16
Gender	Male	28	93.3	29	96.7	
	Female	2	6.7	1	3.3	0.55
Chief complaint	Difficulty in swallowing	16	53.3	15	50	
	Neck mass	5	16.7	9	30	
	Pain in throat	6	20	3	10	
	Ulcer	2	6.6	0	0	
	Hoarseness of voice	1	3.3	3	10	0.39
Smoking status	Smoker	30	100	29	96.7	
	Non-smoker	0	0	1	3.3	0.31
Alcoholic status	Alcoholic	20	66.7	19	63.3	
	Non-alcoholic	10	33.3	11	36.7	0.78
Karnofsky Performance Status(KPS)	70	21	70	23	76.7	
	80	9	30	7	23.3	0.56

Table 1:- Patient Characteristics

Tumor characteristics		**Group-I Study Group** [30 Gy/10 #/2 weeks; 4 weekly × 2] **(n=30)** Frequency	(%)	**Group-II Control Group** [20 Gy/5 #/1 week; 3 weekly × 3] **(n=30)** Frequency	(%)	***P*-value**
Histopathology	MDSCC	28	93.3	28	93.3	
	PDSCC	2	6.7	2	6.7	
Morphology	Ulcero-proliferative	27	90	30	100	0.206
	Ulcerative	2	6.7	0	0	
	Proliferative	1	3.3	0	0	
Primary tumor status	T1	2	6.7	0	0	
	T2	1	3.3	7	23.3	0.001
	T3	13	43.3	9	30	
	T4	14	46.7	14	46.7	
Nodal status	N0	2	6.7	2	6.7	
	N1	6	20	3	10	0.01
	N2	17	56.7	15	50	
	N3	5	16.7	10	33.3	
Stage	III	2	6.7	0	0	0.02
	IV	28	93.3	30	100	

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Site of primary tumor	Oral cavity	3	10	1	3.3	0.65
	Oropharynx	24	80	24	80	
	Hypopharynx	0	0	1	3.3	
	Larynx	3	10	4	13.3	
	Negative	27	90	28	93.3	

Table 2:- Tumor Characteristics

Symptomatic relief (subjective regression of disease) was observed in 86.7% (26/30) in study group and 83.3% (25/30) in control group patients but this was not statistically significant (*P*: 0.71). Locoregional control in study group and control group was: Complete Response (CR) - 16.7% versus 23.3%, Partial Response (PR) – 60% each, No Response (NR) – 0% each and Progressive Disease (PD) – 23.3% versus 16.7%, respectively but this was not statistically significant (*P*: 0.7). Symptomatic relief and locoregional control is described in Table 3. The patients were followed for a minimum period of 3 months (range 3-13 months, median follow up of 5.15 months).

Acute radiation toxicity is described in Table 4. Acute skin reactions in study group and control group were grade I – 60% versus 50%, respectively, not statistically significant (*P*: 0.43). Acute mucosal reactions in study group and control group were grade I – 63.3% versus 56.7% and grade II – 36.7% each in both the groups respectively, statistically significant in Group I (*P*: 0.01). Late radiation toxicities (described in Table 5) were not statistically significantly in both the groups ($P \geq 0.05$).

Disease status at last follow up in study group and control group respectively (described in Table 6) was: No evidence of disease (NED) – 13.3% versus 16.7%, Residual disease (RD) – 83.3% versus 76.7% and Recurrent disease (REC) – 3.3% versus 6.7%, but not statistically significant ($P \geq 0.05$).

Groups	**Number of patients (%)**	**Symptomatic Relief**	**Overall Tumor Response**			
			CR	**PR**	**NR**	**PD**
STUDY GROUP 30 Gy/10 #/2 weeks; 4 weekly × 2	Number of patients	26	5	18	0	7
	%	86.7%	16.7%	60%	0%	23.3%
CONTROL GROUP 20 Gy/5 #/1 week; 3 weekly × 3	Number of patients	25	7	18	0	5
	%	83.3%	23.3%	60%	0%	16.7%

Table 3:- Symptomatic Relief and Overall Tumor Response

RTOG Grade	**STUDY GROUP** 30 Gy/10 #/2 weeks; 4 weekly × 2	**CONTROL GROUP** 20 Gy/5 #/1 week; 3 weekly × 3
Acute Skin Radiation Toxicity		
Grade 0	12 (40%)	15 (50%)
Grade 1	18 (60%)	15 (50%)
Acute Mucosal Radiation Toxicity		
Grade 0	0 (0%)	2 (6.7%)
Grade 1	19 (63.3%)	17 (56.7%)
Grade 2	11 (36.7%)	11 (36.7%)

Table 4:- Acute Radiation Toxicity

ISSN No:-2456-2165

RTOG Grade	STUDY GROUP 30 Gy/10 #/2 weeks; 4 weekly × 2	CONTROL GROUP 20 Gy/5 #/1 week; 3 weekly × 3
Late Cutaneous Radiation Toxicity		
Grade 0	19 (63.3%)	20 (66.7%)
Grade 1	11 (36.7%)	10 (33.3%)
Late Subcutaneous Radiation Toxicity		
Grade 0	21 (70.0%)	18 (60.0%)
Grade 1	8 (26.7%)	9 (30%)
Grade 2	1 (3.3%)	3 (10%)
Late Mucosal Radiation Toxicity		
Grade 0	21 (70.0%)	21 (70.0%)
Grade 1	8 (26.7%)	8 (26.7%)
Grade 2	1 (3.3%)	1 (3.3%)
Late Salivary Gland Radiation Toxicity		
Grade 0	14 (46.7%)	10 (33.3%)
Grade 1	8 (26.7%)	13 (43.3%)

Table 5:- Late Radiation Toxicity

Groups	Number of patients (%)	Disease Status at last follow up		
		Residual Disease	Recurrent Disease	No Evidence of Disease
STUDY GROUP 30 Gy/10 #/2 weeks; 4 weekly × 2	Number of patients	25	1	4
	%	83.3%	3.3%	13.3%
CONTROL GROUP 20 Gy/5 #/1 week; 3 weekly × 3	Number of patients	23	2	5
	%	76.7%	6.7%	16.7%

Table 6:- Disease Status at last follow up

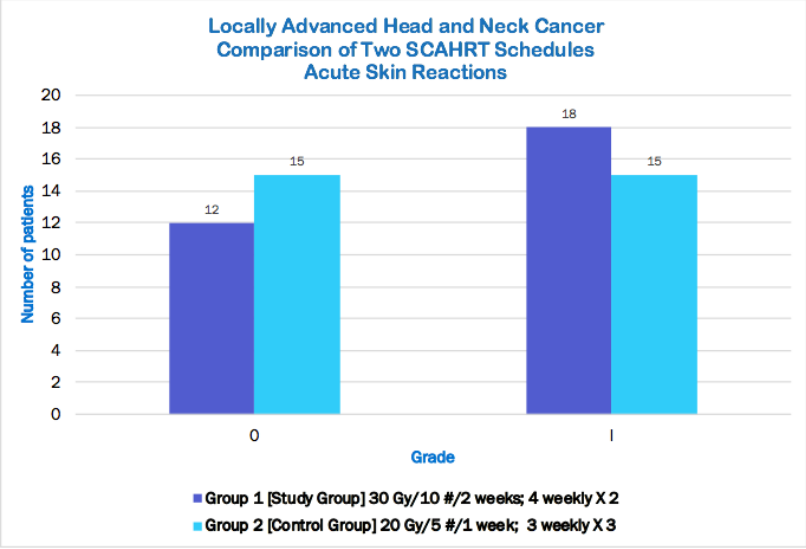

Fig 1

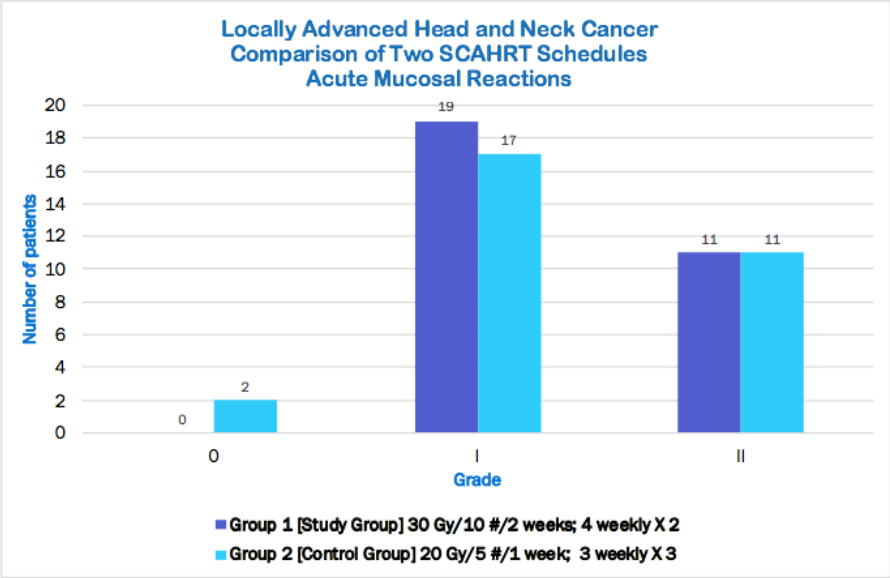

Fig 2

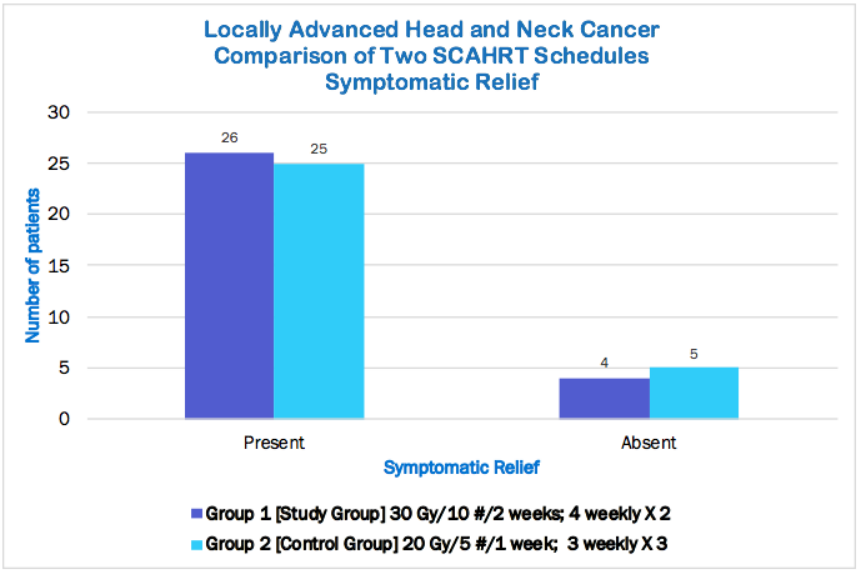

Fig 3

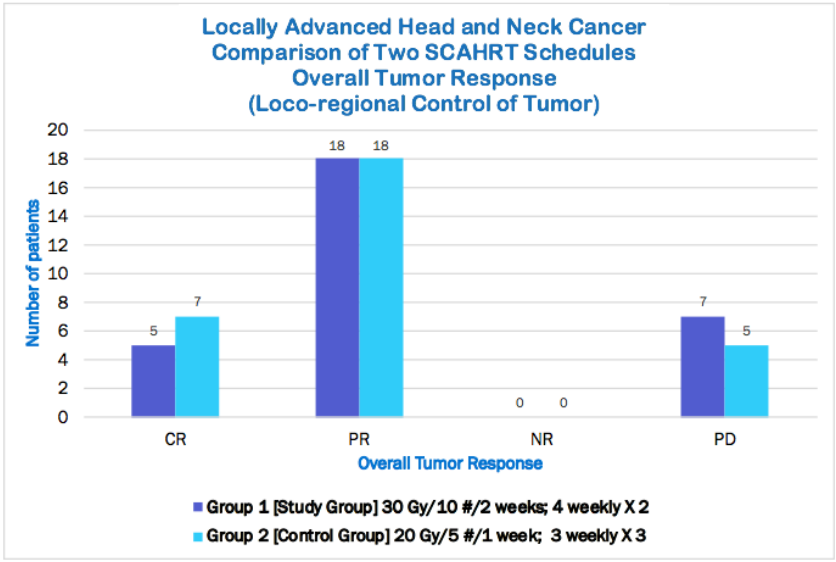

Fig 4

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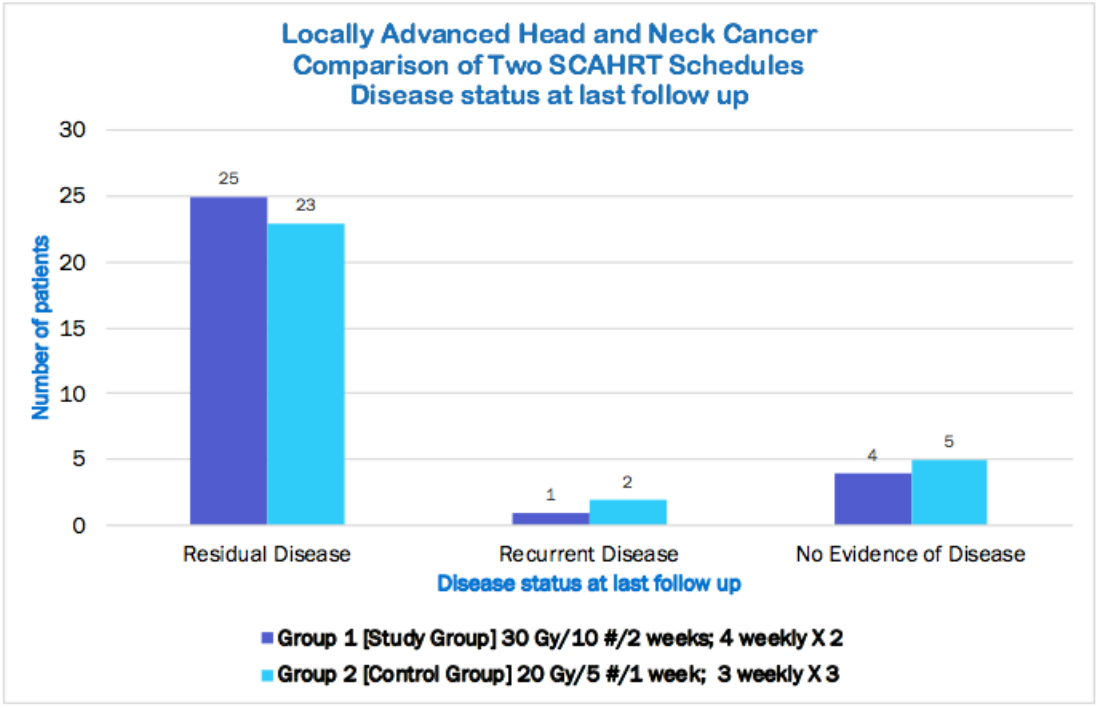

Fig 5

IV. DISCUSSION

Head and neck cancer is the 6th most common cancer globally. The global burden of head and neck cancers in the year 2018 accounted for 887,659 new cases (4.9% of all cancers worldwide) and 453,307 deaths (4.8% of all cancer deaths) in year 2018.[6] Majority of the head and neck cancer patients, i.e., 92.3% present as locally advanced head and neck cancer (LAHNC) Stage III and IV and accounts for 22.9% of cancer-related mortality in India.[7,8] Smoking and alcohol consumption are strong and independent risk factors responsible for increased risk of head and neck cancers.[9,10]

Accelerated radiation scheme aims to deliver the same total dose over a shorter time.[3,4] Hypo-fractionated regimens deliver radiation with higher dose per fraction in shorter overall treatment time. A shorter overall treatment time will reduce the risk of tumor repopulation at the cost of a theoretical increase in late effects due to the higher dose per fraction.[5] Split-course regimens delivers radiotherapy as a form of periodic treatment and is divided into two or more phases separated by a rest interval. This gives time for normal tissue restoration.

In our study, 95% of patients completed the intended treatment. The patient parameters were closely matched in both the arms. Symptomatic relief and loco-regional control were similar in both the groups and was not statistically significant. Acute as well as late radiation reactions were also similar in both the groups. However, acute mucosal reactions in group 1 (30 Gy/10 fractions/2 weeks; 4 weekly × 2) were significantly higher ($P = 0.001$).

V. CONCLUSION

The present study is a randomized prospective study that has assessed two split course accelerated hypofractionated radiation therapy (SCAHRT) schedules [30 Gy / 10 fractions / 2 weeks followed by repeat dose of 30 Gy / 10 fractions / 2weeks after 4 weeks (total dose 60 Gy in 20 fractions delivered in two halves with a gap in between with interval of 4 weeks) versus 20 Gy / 5 fractions / 1 week repeated three weekly to a maximum of three times (total dose 60 Gy in 15 fractions delivered in three parts with a gap in between with interval of 3 weeks)] in terms of symptomatic relief, loco-regional control and toxicity.

Thus, we conclude that to expedite the treatment time in tertiary care centres, control group (20 Gy / 5 fractions / 1 week; 3 weekly X 3) was better than the study group (30 Gy / 10 fractions / 2 weeks; 4 weekly X 2) as it had comparable local control and toxicity (acute mucosal reactions being slightly higher in the study group) with the added advantage of only 15 total fractions (machine days) in control group rather than 20 total fractions (machine days) in study group. This reduced the patient visits to the hospital by one week (i.e. 5 fractions) with comparable local control and toxicity.

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