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RESEARCH ARTICLE

THE EFFICACY AND SAFETY OF FIVE VERSUS SIX FRACTIONATIONS PER WEEK OF EXTERNAL BEAM RADIOTHERAPY IN THE MANAGEMENT OF HEAD AND NECK MALIGNANCIES.

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Abstract

A non-randomized, prospective ,single centre study consisting of 50 patients (25 each in the study arm and control arm) suffering from squamous cell carcinoma of head and neck (stage II-IV) were taken up to study the efficacy and safety of six fractions per week against five fractions per week of conventional external beam radiation therapy. Both the arms received a total tumour dose of 66-70 Gy in 33-35 exposures by shrinking field technique by using telecobalt 60. The early treatment results were analysed as per WHO Miler's criteria.

The study arm showed 80% complete clinical response of the primary site as compared to 52% in the control arm. Partial response of the primary was noted in 20% and 28% in the study arm and control arm respectively.

Complete nodal response was seen clinically in 64% in the study arm as compared to 52% in the control am. Partial response was seen in 28% and 32% in the study arm and control arm respectively.

The disease free survival and survival with disease were comparable in both the arms.

Introduction:-

Loco-regional control is the biggest problem in the management of head and neck cancers. In spite of different multimodality approaches the result is still not encouraging. Many trials have been conducted on altered fractionation and chemoradiation in advanced head and neck cancers.

Accelerated fractionation increase the local control by counteracting the accelerated tumour clonogen populationduring irradiation and uses a shortened overall treatment time. Large randomized trials showed altered fractionation schedules improve the loco-regional control rates. The state of the art regarding radiation dose fractionation has evolved from once daily treatment to hyperfractionation and accelerated fractionation. Accelerated fractionation shortens the overall treatment time and improves outcome by counteracting the hazard of accelerated tumour clonogen repopulation during radiation therapy.[1]

Randomized controlled trials have demonstrated major improvements in loco-regional tumour control from altered fractionation, accelerated fractionation and hyperfractionation as compared with the conventional fractionation.[2]

The study was undertaken in the midst of all these uncertainties, in an attempt to study the role of six fractions per week against the conventional five fractions per week in the management of head and neck cancers.

Materials and Methods:-

Fifty patients of head and neck cancer of squamous cell type in stage II-IV(TNM Stage) were enrolled in the study. 25 patients each were grouped in the control arm and study arms respectively.
The approval from the institutional ethical committee was obtained before the study was started.

Inclusion criteria:-
New cases with confirmed squamous cell carcinoma.
No previous surgery, chemotherapy or radiation therapy.
Karnofsky performance status ≥70%
Normal hematological and biochemical parameters.
Age >30-70years
Stage II-IVA
No co-morbid conditions.

The treatment was carried out by telecobalt 60 at a source to skin distance of 80cms by two lateral parallel opposed portals with shrinking field technique, giving a daily tumour dose of 200cGy per exposure upto a total tumour dose of 6600-7000 cGy in 33-35 exposures. The patients were evaluated at weekly intervals during the treatment period and then followed up monthly upto one year.

The patients in the control arm were given 200cGy per exposure, five days in a week.
The patients in the study arm were given 200cGy per exposure, six days in a week.

Study variables:-
Tumour
Regional Lymph Nodes
Radiation reactions

Results:-

The patients in the study arm had a median follow-up of 13months, the shortest being 6 month and longest 19 month. The patients in the control arm had a median follow-up of 13 month, minimum being 7 month and longest 20 month.

Table I:- Patients characteristics

Characteristics	**Study-Arm (n=25)**	**Control-Arm (n=25)**
Sex		
Male	20 (80%)	21 (84%)
Female	5 (20%)	4 (16%)
Age(years)		
30-39	3 (12%)	2 (8%)
40-49	4 (16%)	5 (20%)
50-59	8 (32%)	6 (24%)
60-69	10 (40%)	12 (48%)
TNM-Staging		
Stage-II	3 (12%)	7 (28%)
Stage-III	10 (40%)	9 (36%)
Stage-IV	12 (48%)	9 (36%)
Karnofsky perfomance Score		
90%	4.0 (16%)	3.0 (12%)
80%	18.0 (72%)	17.0 (68%)
70%	3.0 (12%)	5.0 (20%)

Majority of the patients were male in both arm and of the age 40-69years with Karnofsky performance score > 80%.

Table II:- Distribution of the primary sites.

Primary Tumor sites	**Study-Arm (n=25)**	**Control-Arm (n=25)**
Pyriform fossa	7(28%)	7(28%)
Larynx	2(8%)	4(16%)
Oropharynx	3(12%)	5(20%)
Nasopharynx	8(32%)	6(24%)
Oral-cavity	5(20%)	3(12%)

The most common primary sites were the Nasopharynx and pyriform fossa.

Table III:- Primary tumor status.

T-stage	**Study-Arm (n=25)**	**Control-Arm (n=25)**
T1	1(4%)	2(8%)
T2	11(44%)	14(56%)
T3	9(36%)	5(20%)
T4	4(16%)	4(16%)

Maximum primary were of T2 stage in both arms.

Table IV:- Neck Node status

N-Staging	**Study-Arm (n=25)**	**Control-Arm (n=25)**
N0	3(12%)	9(36%)
N1	12(48%)	9(36%)
N2	10(40%)	7(28%)
N3	0	0

Table V:- TNM-staging

Stage	**Study-Arm (n=25)**	**Control-Arm (n=25)**
I	0	0
II	3(12%)	7(28%)
III	10(40%)	9(36%)
IVA	12(48%)	9(36%)

Table VI:- Early side effects-oral mucositis

Study-Arm (n=25)									
Grade	**Week**							**4th week post-RT**	**8th week post-RT**
	1	**2**	**3**	**4**	**5**	**6**	**7**		
	12Gy	**24Gy**	**36Gy**	**48Gy**	**60Gy**	**70Gy**	**-**		
Gr-I	**0**	**14**	**12**	**5**	**1**	**0**	**2**	**16**	**0**
Gr-II	**0**	**1**	**10**	**16**	**9**	**4**	**12**	**5**	**0**
Gr-III	**0**	**0**	**0**	**4**	**14**	**13**	**10**	**0**	**0**
Gr-IV	**0**	**0**	**0**	**0**	**1**	**8**	**1**	**0**	**0**
Control-Arm (n=25)									
Grade	**Week**							**4th week post-RT**	**8th week post-RT**
	1	**2**	**3**	**4**	**5**	**6**	**7**		
	10Gy	**20Gy**	**30Gy**	**40Gy**	**50Gy**	**60Gy**	**70Gy**		
Gr-I	**0**	**0**	**4**	**14**	**19**	**9**	**6**	**5**	**0**
Gr-II	**0**	**0**	**0**	**0**	**6**	**16**	**12**	**0**	**0**
Gr-III	**0**	**0**	**0**	**0**	**0**	**0**	**7**	**0**	**0**
Gr-IV	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

The onset of oral mucositis is early at 2nd week and 3rd week of starting of radiation treatment in the study arm. Grade-III and Grade-IV reaction were seen mainly in 6th week of radiation treatment at a tumor dose of 70 Gy. There is no mucositis at the end of 2nd month post radiation treatment. All the mucosal reaction had healed up completely without any sequlae by the end of second month of Radiation Therapy. The oral mucositis in the

control arm noticed 3rd and 4th week onward but severity/grade were less than study arm. Grade II reaction in the study arm was noticed at 36Gy of tumor dose, Grade III and IV reaction at 60Gy and 70Gy respectively. In the control arm Grade II reaction started at 50-60Gy and Grade III reaction seen at 70Gy. No Grade IV reaction seen in the study arm.

Table VII:- Early side effects-skin reaction in relation to tumor dose.

Study-Arm (n=25)						
Grade	**Week**					**4th week post-RT**
	3	**4**	**5**	**6**	**7**	
	36Gy	**48Gy**	**60Gy**	**70Gy**	**-**	
Gr-I	**10**	**19**	**9**	**4**	**11**	**6**
Gr-II	**0**	**2**	**13**	**14**	**9**	**0**
Gr-III	**0**	**0**	**3**	**4**	**3**	**0**
Gr-IV	**0**	**0**	**0**	**3**	**1**	**0**
Control-Arm (n=25)						
Grade	**Week**					**4th week post-RT**
	3	**4**	**5**	**6**	**7**	
	30Gy	**40Gy**	**50Gy**	**60Gy**	**70Gy**	
Gr-I	**0**	**12**	**20**	**15**	**7**	**4**
Gr-II	**0**	**0**	**2**	**10**	**14**	**0**
Gr-III	**0**	**0**	**0**	**0**	**4**	**0**
Gr-IV	**0**	**0**	**0**	**0**	**0**	**0**

The onset of early skin reaction which starts at around 3rd week of radiation treatment in the study-arm at a tumor dose of 36 Gy. Grade-III and Grade-IV reaction were observed in a few patients after a tumor dose of 70 Gy. No acute radiation dermatitis was seen one month post radiation treatment in the study-arm. Above table also shows the onset of early skin reaction in the control-arm which had started around 4th week of radiation treatment.

There was no Grade-IV reaction in the control-arm till the end of treatment. No radiation induced dermatitis was seen one month post radiation treatment. Maximum radiation induced dermatitis were of Grade-II variety in the control-arm.

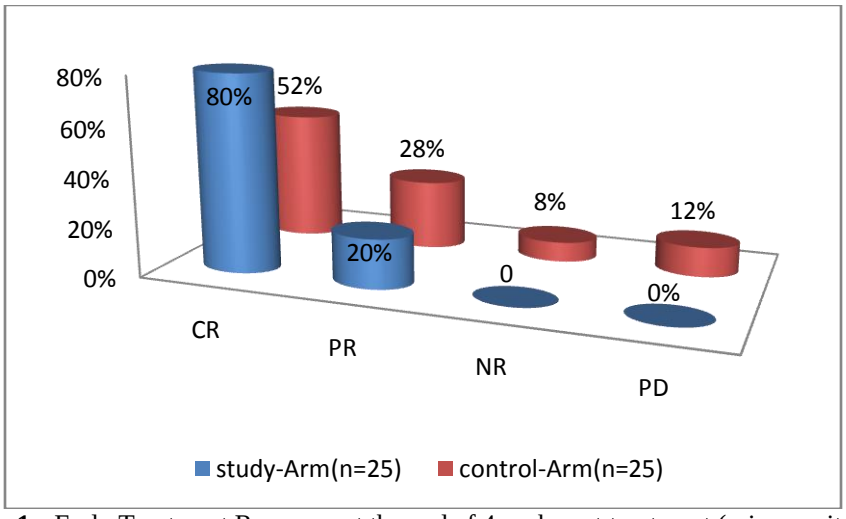

Fig 1:- Early Treatment Response at the end of 4week post treatment (primary sites)

Fig-1 shows early treatment results. The early treatment results are analysed as per WHO Miller's criteria and assessment were done at the end of one months after completion of treatment. 20 patients (80%) had clinical complete response (CR) in the study arm, as compared to 13 (52%) patients in the control arm which is statistically significant (P<0.05). Partial response (PR) was noted in 5 patients (20%) in the study arm and in 7 patients (28%) in the control arm (P>0.05). 2 patients (8%) in the control arm did not show any response to treatment whereas 3

(12%) patients developed progressive disease in the control arm. The achieval of CR in the study arm was significantly higher compared to that of the control arm.

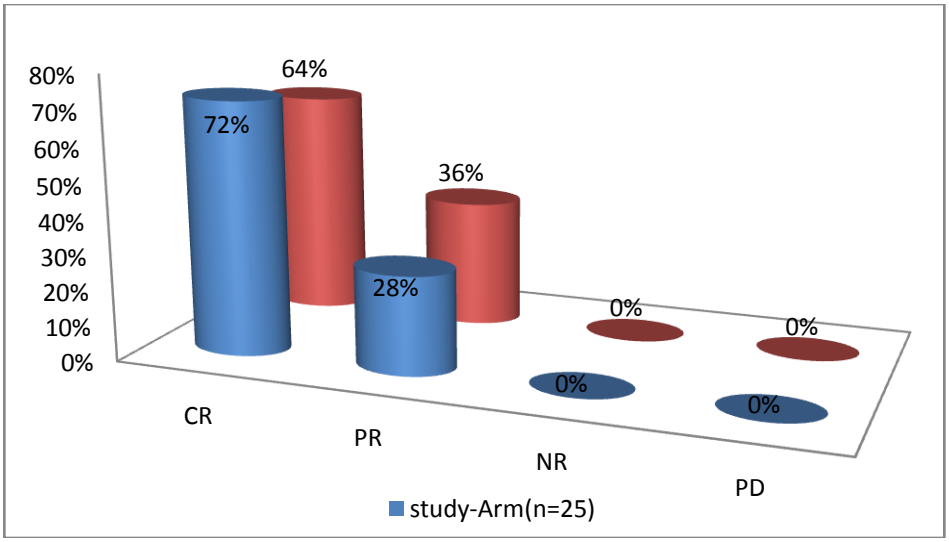

Fig 2:- Nodal response 4week post treatment.

Fig-2 shows early treatment response of involved lymph nodes at the end of one month after completion of treatment. Here also results were analysed as per WHO Miller's criteria. 16(sixteen) patients (64%) had clinical complete response (CR) in the study arm, as compared to 13(thirteen) patients (52%) in the control arm ($p>0.05$). Partial response (PR) was noted in 7(seven) patients (28%) in the study arm and in 8(eight) patients (32%) in the control arm ($P>0.05$). One patient in the study arm (4%) and two patients in the control arm (8%) showed no response (NR) with p value >0.05. whereas one patient in the study arm (4%) and two patients in the control arm (8%) developed progressive disease (PD) with p value >0.05. No statistically significant difference was seen in the nodal response between the study and control arm .

Table VIII:- Subset analysis of radiation treatment response in primary tumor(T) and nodal(N) area

		Study-Arm(n=25)		Control-Arm(n=25)	
Disease		**Primary (T)**	**Node (N)**	**Primary (T)**	**Node (N)**
PFS	**CR**	**5**	**6**	**3**	**2**
	PR	**2**	**1**	**2**	**5**
	NR	**0**	**0**	**1**	**0**
	PD	**0**	**0**	**1**	**0**
L_X	**CR**	**2**	**1**	**4**	**3**
	PR	**0**	**1**	**0**	**1**
	NR	**0**	**0**	**0**	**0**
	PD	**0**	**0**	**0**	**0**
OP	**CR**	**3**	**3**	**2**	**3**
	PR	**0**	**0**	**1**	**2**
	NR	**0**	**0**	**1**	**0**
	PD	**0**	**0**	**1**	**0**
NPX	**CR**	**7**	**5**	**3**	**6**
	PR	**1**	**3**	**2**	**0**
	NR	**0**	**0**	**0**	**0**
	PD	**0**	**0**	**1**	**0**
OC	**CR**	**3**	**3**	**1**	**2**
	PR	**2**	**2**	**2**	**1**
	NR	**0**	**0**	**0**	**0**
	PD	**0**	**0**	**0**	**0**

Abbreviations : PFS = pyriform sinus, L_X = larynx, OP = oropharynx, NPX = nasopharynx, OC = oral cavity

Table shows responses of primary (T) and nodal (N) areas of different anatomical sites. In the pyriform fossa, out of 7 patients in the study-arm 5 patients had clinical complete response (CR) and 2 patients had partial response (PR) in the primary sites to accelerated radiation treatment whereas in the control-arm 3 patients had clinical CR, 2 patients had PR, 1 patient had no response (NR) and 1 patient had progressive disease (PD). Incase of nodal area in carcinoma pyriform fossa, in the study-arm 5 patients had CR, 1 patient had PR whereas in the control-arm 1 patient had CR, 5 patients had PR and 1 patient had NR. In the laryngeal site, in the study-arm out of 2 patients 2 had CR in the primary site whereas in the control-arm out of 4 patients 4 had CR. In nodal area of carcinoma larynx, the study-arm had 1 CR and 1 PR whereas in the control-arm 3 had CR and 1 had PR. In case of oropharynx (OP) out of 3 primary sites 3 had CR in the study-arm but in the control-arm out of 5 primary sites 2 had CR,1 had PR, 1 had NR and 1 had NR. In the nodal area of carcinoma oropharynx 3 patients had CR whereas in the control-arm 2 patients had CR, 1 had PR, 1 had NR and 1 had PD. In the study-arm of nasopharynx (NPX) in the primary sites out of 8 patients 7 had CR, 1 had PR whereas in the control-arm out of 6 patients 3 had CR, 2 had PR and 1 had PD. In the nodes in carcinoma nasopharynx, the study-arm had 4 CR, 3 PR, 1 NR whereas the control-arm had 5 CR, 1 PD out of 6 patients. In case of oral cavity (OC) in the primary site, study-arm had 3 CR, 2 PR out of 5 patients whereas control-arm had 1CR, 2 PR out of 3 patients. In the nodes the study-arm had 3 CR, 2 PR and control-arm had 2 CR, 1 PR.

1. **Table IX:-** Survival rate (Median follow-up: study-Arm = 13 months Control-Arm =13 months).

Types of response	**Study-Arm (n =25)**	**Control-Arm (n=25)**	**P-value**
DFS	**18(72%)**	**13(52%)**	**0.550**
SWD	**7(28%)**	**12(48%)**	**0.223**
OS	**25(100%)**	**25(100%)**	**-**

DFS =Disease Free Survival
WD = Survival With Disease
OS = Overall Survival

The Disease Free Survival (DFS) and the Survival With Disease (SWD) are comparable in both arms. The differance is not significant statistically (P>0.05). The median follow-up in the study-arm and in the control arm were 13 months in each arm.

Discussion:-

The study was a non-randomized prospective study. The study was designed to include 50 patients of which 25 were in the study-arm and 25 were in the control-arm. Male & female ratio was 5:1 in the study-arm and 5.25:1 in the control-arm. ICMR – PBCR project report also shows the same pattern of incidence. Majority of the patients were in the 5^{th} & 6^{th} decades with advanced stage at presentation. Major sites of involvement were nasopharynx, pyriform fossa, oropharynx and oral cavity. Almost all the patients belonged to poor socio-economic status, illiterate and ignorant about the disease. Majority of them were having habit of smoking, chewing pan and other form of tobacco consumption. Most of the patients had history of consumption of smoked meat and fish as a tradition. Difficult geographic location also added to this burden of late diagnosis. Histopathologically confirmed cases of head and neck squamous cell carcinoma (stage II to IVA), previously untreated and fulfilling the inclusion criteria, already included in material and method were recruited consecutively. Pre-treatment detailed work-up was done for all patients. Staging was done by the UICC TNM classification. During the staging procedures along with physical examination CT scan, MRI of head and neck was taken into account. Plain x-ray chest & abdominal ultrasonography was done to exclude distant metastasis.

The study-arm received external beam radiation therapy six fractions per week (Monday to Saturday) while the control-arm received five fractions per week (Monday to Friday) by telecobalt 60 according to standard shrinking field technique after simulation.

The most common primary sites were nasopharynx, pyriform fossa and oral cavity in the study-arm whereas in the control-arm the pyriform fossa, nasopharynx and oropharynx were the most commonly involved site. The distribution was statistically comparable (p>0.05).

Table-III shows the distribution of primary tumor stage which were comparable in both arms. Maximum primaries were of T2 stage in both the arms. Table-IV shows the nodal status of the patients in both arm which were comparable. In the study-arm 3 (12%) patients were in N0 category, of the 3 patients one patient of ca. buccal mucosa had T2N0, another patient was of ca. base of tongue (T2N0) and other patient was ca. hard palate (T2N0). In the control-arm 9 (36%) patients were in N0 category but no one had T1N0 status as per Table-IV. TNM staging distribution of patients in the study-arm were stage-I: 0,stage-II: 3(12%), stage-III: 10(40%), stage-IV: 12(48%) and in the control-arm were stage-I: 0, stage-II: 7(28%), stage-III: 9(36%) and stage-IVA: 9(36%). The types of primary tumors in the study were mainly of moderately-differentiated and well-differentiated squamous cell variety.

According to ICMR project report of population based cancer registry of RIMS, Imphal, Manipur 2008-2009, the prevalence of HNSCC in male is 14.7% and in female it is 4.7% of all cancers.[3] Population based cancer registry shows Kohima and Imphal West has maximum incidence rate of AAR (19.4 per 100,000 and 7.4 per 100,000 respectively) on district wise comparision for nasopharyngeal cancer.[4] Since NPC is common in this place, the number of NPC was more in the accrual of the cases.

The statistical analysis was done using statistical package for social science (SPSS) programe version 17. In our study, primary tumor response 1 month post treatment as per analysis of Table IX showed, 20 (80%) patients had clinical complete response (CR) in the study-arm, whereas in the control-arm 13 (52%) patients had clinical CR which is statistically significant ($p<0.05$). Five patients (20%) in the study-arm and seven (28%) patients in the contro-arm had PR. No patients in the study-arm had NR and PD whereas in the control-arm, two patients (8%) had NR and three patients (12%) had progressive disease. T-site control of 80% vs 52% in our study (gain of 28%) is comparable to the other studies.

The EORTC 22851 trial reported significant improvement in loco-regional control in the accelerated arm. At 5 years, the loco-regional control gain was 13%.[5]

Skladowski et al in 7-day CAIR reported in 2000 a significant gain in 3-year loco-regional control of AF vs SF (82% vs 37% : $p<0.0001$).[6]

The randomized RTOG 9003 trial showed that accelerated fractionated radiotherapy significantly improved local control rate compared to conventional radiotherapy (54% vs 43%).[7]

Lee AW et al (2001) showed AF group had significantly higher progression-free rate than CF group 74% vs 63% at 3 years.[8]

DAHANCA 6 & 7 trial showed 5 year loco-regional control rates were 70% for AF (6 fractions/week) and 60% for SF ($p=0.005$).[9]

Poulsen MG et al in their randomized trial of accelerated and conventional radiotherapy showed the loco-regional control was 47% for conventional vs 52% for accelerated-arm.[10]

N-site response was not significant statistically (64% vs 52%, $p>0.05$) in our study. According to DAHANCA study group[41], their N-site failure was the cause of loco-regional failure. They also observed the whole benefit of shortening of treatment was in primary tumor control but was not significant for neck node control.

As per International Atomic Energy Agency-ACC study, a randomized, multicentre trial the effect of acceleration on loco-regional control was mainly related to a better response at the primary tumor site; there was no difference in the effect on the lymph nodes between treatment groups.[11]

According to Valentine et al, irrespective of the modality of primary treatment for head and neck squamous cell carcinoma, local or loco-regional residual or recurrent tumors represent the major cause of treatment failure.[1]

When analysed by sub-group (Table-XI) accelerated arm was of greatest benefit in patients with tumors of pyriform fossa, oropharynx and nasopharynx.

In the pyriform fossa, in study-arm out of 7 patients 5 had CR in primary site whereas in control-arm 3 patients had CR. Two patients in the study-arm had PR. In the control-arm 2 patients had PR, 1 had NR and 1 had PD. In the study-arm in case of pyriform fossa 5 patients had CR in nodal areas whereas in the control-arm only one patient had CR. In the control-arm 5 patients had PR in nodal areas, 1 had NR whereas in the study-arm only 1 patient had PR and 1 had PD.

In case of nasopharynx,in the study-arm, out of 8 patients 7 had CR in primary site, 1 had PR whereas in the control-arm 3 patients had CR & 2 had PR, 1 had PD. In nodal areas, in nasopharynx out of 8 patients 4 had CR in the study-arm, and in the control-arm 5 patients out of 6 had CR, 1 had PD.

In case of oropharynx, in study-arm, out of 3 patients 3 had CR, whereas in the control-arm out of 5 patients 2 had CR in primary site. In nodal areas, in the study-arm 3 patients out of 3 had CR, but in control-arm 2 patients had CR, 1 had PR, 1had NR and 1 had PD.

In case of oral cavity, in the study-arm out of 5 patients 3 had CR, 2 had PR whereas in the control-arm 1 patient had CR, 2 had PR out of 3 patients in primary sites. In nodal region in the study-arm out of 5 patients 3 had CR, 2 had PR but in control-arm out of 3 patient 2 had CR, 1 had PR.

The radiation response of primary site of larynx were similar in both arms, but in nodal areas in the study-arm 1 patient out of 2 had CR, 1 had PR whereas in the control-arm out of 4 patients 3 had CR, 1 had PR.

Conventional 2D radiotherapy successfully controlled T1 and T2 tumors in between 75% to 90% of cases, and T3 and T4 tumors in 50% to 75% of cases. Nodal control is achieved in 90% for N0 and N1 cases, but the control rate drops to 70% for N2 and N3 cases.[10]

In the present study we observed more radiation reactions in the study-arm as compared to the control-arm. Onset of oral-mucositis was earlier in the study-arm (2^{nd} and 3^{rd} week of starting of radiation treatment) than the control-arm (around 3^{rd} and 4^{th} week). More severe mucositis was observed in the study-arm (Gr-III & Gr-IV) then in the control-arm (Gr-I & Gr-II). Duration of oral mucositis was slightly longer in the study-arm but no mucositis was observed after 8week of complete treatment.

DAHANCA study group observed acute radiation-related morbidity significantly higher in the accelerated fractionation group with a 53% frequency of confluent mucositis compared with 33% in the conventional treatment group. The mucositis persisted longer in the accelerated fractionation patients, but all healed within 12week of complete treatment.[9]

Poulsen MG et al in their randomized trial of accelerated and conventional radiotherapy for stage-III and stage-IV squamous cell carcinoma of the head and neck showed that in the accelerated-arm, confluent mucositis was more severe (94% vs 71%; p<o.oo1) and peaked about 3 weeks earlier than the conventional-arm, but healing appeared complete in all cases.[10]

Other important toxic effect was radiation dermatitis. As energy used was megavoltage range by telecobalt machine, due to skin sparing advantage of beam, skin reaction was lesser than the oral mucositis. Table-VIII shows the onset of early skin reaction around 3^{rd} week in the study-arm whereas in the control-arm it was around 4^{th} week of radiation treatment. Study-arm had more severe grade of skin reaction than the control-arm but no acute radiation induced dermatitis was observed in both arm one month post radiation treatment.

Withers HR et al showed that clonogen repopulation in squamous cell carcinomas of the head and neck accelerates only after a lag period of the order of 4 ± 1 weeks after initiation of radiotherapy and that a dose increment of about 0.6 Gy per day is required to compensate for this population. The tumor clonogens accelerates their rate of increase after a lag period. So once treatment completed as quickly as possible.[13]

The six fractions per week schedule, resulting in a one week reduction in treatment time relative to conventional treatment is a better treatment option with improved tumor control and acceptable radiation toxicity.

References:-

1. Valentine K and Simonida C(2006) : Altered and conventional fractionated radiotherapy in locoregional control and survival of patients with squamous cell carcinoma of the larynx,oropharynx and hypopharynx, Croat Med J.,47: 42-52.
2. Bernien J, Bentzen SM.(2003 Mar): Altered fractionation and combined radio-chemotherapy approaches: Pioneering new opportunities in head and neck oncology. Eur J Cancer., 39 (5): 560-71.
3. Nandakumar A and Gupta PC. (2007.):Two-year report of the population based cancer registries,2004-2005 and 2005-2006,NCRP, Bangalore.
4. Nandakumar A and gupta PC.(2004):development of an atlas of cancer in India, co-ordinating unit National Cancer Registry Programme.ICMR, Bangalore.
5. Horiot JC, Bontemps P, Van Den Bogaert W, Le Fur R, Van Den Weijingaert D, Bolla M, et al. (1997):Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. Radiother Oncol ., 44(2): 111-21
6. Skladowski K, Maciejewski AW, Golen M, Pilecki AW, przeorek AW, Tarnawski R(2000): Randomized Clinical trial on 7-day continuous accelerated irradiation (CAIR) of head and neck cancer – report on 3-year tumour control and normal tissue toxicity. Radiother Oncol.,55: 101-10.
7. Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL, et al.(2000): A radiation therapy oncology group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck suqmaous cell carcinoma: First report of RTOG 9003. Int J Radiat Oncol Biol Phys., 48: 7-16.
8. Lee AW, Sze WM, Yau TK, Yeung RM, Chappelt R and Fowler JF.(2001): Retrospective analysis on treating nasopharyngeal carcinoma with accelerated fractionation (6 fraction per week) in comparison with conventional fractionation (5 fraction per week): report on 3-year tumor control and normal tissue toxicity, Radiother Oncol.,58(2): 121-130.
9. Overgaard J, Hansen HS, Specht L, Overgaard M, Grai C, Andersen E et al. (2003):Five compared with six fractions per week of conventional radiotherapy of squamous cell carcinoma of the head and neck. DAHANCA 6 & 7 randomized controlled trial. Lancet., 362: 933-40.
10. Poulsen MG, Denham JW, Peters LJ.(2001): A randomized trial of accelerated and conventional radiotherapy for stage III & IV squamous cell carcinoma of the head and neck: a Trans-Tasman Radiation Oncology Group Study. Radiother Oncol.,60:113-22.
11. Five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study) : a randomized, multicentre trial.www.thelancet.com/oncology. Published(2010.): Vol 11.
12. Lee AW, PoonYF, Foo W, Law SC, Cheng FK, Chan DK, et al.(1992): Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976-1985: overall survival and patterns of failure. Int J Radiat Oncol Biol Phys..,23(2):261-70.
13. Withers HR, Taylor JMG, Maciejewski B.(1988): The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol., 27: 13-46.