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A study on conventional fractionation vs accelerated fractionation radiotherapy with concurrent chemotherapy in Head and Neck squamous cell carcinomas .

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Abstract:
Background*: Head-neck cancer refers to cancers of the upper aero-digestive tract, which arise from the epithelial lining of the oral cavity, pharynx and larynx.Most common histology in head and neck cancer is squamous cell cancers. With the recent lifestyle changes and addiction to tobacco chewing , smoking , alcohol consumption , these cancers are at a rise worldwide.The curative treatment modalities for head and neck squamous cell carcinomas are surgery and radiotherapy, with chemotherapy being used to enhance the effects of radiotherapy.Over the years, many studies have shown that prolongation of overall treatment time (OTT) had detrimental effects on tumor control in head and neck squamous cell cancers.The main aim of this study is to test if accelerated chemoradiotherapy is a potential alternative to concurrent chemo-radiotherapy in head and neck cancers by comparing the tumor responses and treatment related toxicities of both the modalities.*
Materials and Methods*: In this prospective randomised controlled study, pre-treatment evaluation was done with physical examination including height, weight, body surface area and Performance Status. Investigations like Histopathologic proof of squamous cell carcinoma, Complete blood count with differential counts, platelets, blood urea, serum creatinine and liver function tests, CT/MRI scan of the neck, Chest X-ray as a routine workup, Oral care & Pre radiation therapy Dental evaluation was done. Patients were treated on a 6MV linear accelerator in 2D technique to a total dose of 66Gy in 33 fractions, one fraction/day, 6 fraction/week in accelerated arm and 5 fractions/week in conventional arm with weekly cisplatin 40mg/m2 given in both arms. Toxicity grading is done according to the CTCAE criteria. Toxicity assessed are mucositis dysphagia dermatitis local pain xerostomia.Onset, progression, severity, of the side effects have been documented every week for every patient in both the arms of the study.Patients disease assessment was done according the RECIST criteria version 1.1.*
Results*: In the study 65% patients had grade 2,29%had grade 3 and 4%grade 4 skin reaction. In accelerated group 37% had grade 54% had grade 3 and 5% had grade 4 skin reaction.in conventional arm 92% had grade 2 reactions and 4% each grade 3 and 4 reactions with significant p value of 0.00025.In study in accelerated arm 27% had grade 2,55% had grade 3 and 18% had grade 4 mucositis while in conventional arm 55% had grade 2,36% had grade 3 and 9% had grade 4 reactions , though grade 3 and grade 4 mucositis were more in accelerated arm but that was not statistically significant(p value=0.42035).In accelerated arm 4% had grade 2,70 had grade 3 and 26% had grade 4 dysphagia in conventional arm 44% each had grade 2 and grade 3,12% had grade 4 dysphagia patients in both arms with p=0.0061.In accelerated arm 91% had complete primary tumor response and 9% had partial response and in conventional arm 92% had complete primary tumor response and 8% had partial tumor response.In the study 81% had complete nodal response and 19 % had partial response. In accelerated arm 83% patients had complete nodal response and 17% had partial response and in conventional arm 80% had complete response and 20% had partial response and the difference between two arms were not found to be significant (p=0.817)*
Conclusion: *Accelerated arm radiotherapy had more acute side effects than conventional arm. On comparing the primary and nodal tumour response to radiotherapy between accelerated fractionated radiotherapy and conventional fractionated radiotherapy there was no statistically significant difference between both arms.A study with longer follow up and larger sample size is required to comment about the local response of tumor.*
Key Word*: Head and neck squamous cell carcinomas, Accelerated fractionation , Altered fractionation , Decreased overall treatment time.*

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I. Introduction

Head-neck cancer is a broad term referring to the heterogeneous group of malignant neoplasms arising in the head-neck region. Commonly however, the term head-neck cancer refers to cancers of the upper aero-digestive tract, which arise from the epithelial lining of the oral cavity, pharynx and larynx. In India Oral cavity and pharynx incidence in males is 139,018 and in females is 49,951[1]. Lifestyle factors such as tobacco (either smoking or chewing) and alcohol consumption are the major risk factors associated with head and neck cancers and they have synergistic effects. Most common head and neck carcinomas histology is squamous cell carcinomas (95%)[2,3]. Other histologies such as verrucous carcinoma, adenocarcinoma, sarcoma, melanoma, lymphoma and ameloblastoma are found in relatively lesser numbers. Recently an increasing number of head and neck cancers associated with viral infections such as Human papilloma virus and Epstein-Barr virus are being diagnosed particularly in the younger age groups[4].The curative treatment modalities for HNSCC are surgery and radiotherapy, with chemotherapy being used to enhance the effects of radiotherapy[5,6].Benefits of radiotherapy over surgery include organ and functional preservation and no postoperative complications.Benefits of surgery over radiotherapy include lesser treatment duration and no problems of acute and chronic radiation toxicities.Over the years, many studies have shown that prolongation of overall treatment time (OTT) had detrimental effects on tumor control in head and neck squamous cell cancers[7-9].The main focus of this study is to test if accelerated chemoradiotherapy is a potential alternative to concurrent chemo-radiotherapy in head and neck cancers by comparing the tumor responses and treatment related toxicities of both the modalities, banking on the proven radiobiological benefit of reducing the OTT. Accelerated regimen has the radio biologic advantage as the treatment is completed early when compared with conventional fractionation and thus decreasing the additional tumor load due re-population. The cost of a treatment course is also reduced and the long waiting times can be avoided as the total numbers of days required are less compared to conventional fractionation .This accelerated regimen seems to be an attractive method in improving the loco regional control and maximizing the service productivity when combined with chemotherapy in loco regionally advanced carcinomas of head and neck.

II. Material And Methods

This prospective comparative study was carried out on patients of the Department of radiation oncology at M.N.J.I.O & R.C.C , Hyderabad from . A total of 300 adult subjects (both male and females) of aged ≥ 18 years were in this study.

Study Design: Prospective two arm comparative study

Study Location: M.N.J.I.O&R.C.C , LAKDIKAPUL , HYDERABAD

Study Duration: July 2017 to May 2019.

Sample size: 51 PATIENTS

Sample size calculation: The sample size was estimated on the basis of a single proportion design. We assumed a confidence interval of 10% and a confidence level of 95%. The sample size actually obtained for this study was 25 patients for each group.

Subjects & selection method: The study population was drawn from patients with proven head and neck squamous cell cancers attending the radiation oncology outpatient department for radical radiation therapy.

Inclusion criteria:

1. Proven head and neck malignancy (squamous cell carcinoma)
2. Either sex
3. Previously non - irradiated patients .
4. ECOG: - 0-2
5. Age :->20 yrs & <60yrs.
6. Weight: - >40 kgs.
7. Non - metastatic.

Exclusion criteria:

1. Pregnant women
2. Distant metastases.
3. Prior surgical intervention of tumour
4. The existence of synchronous malignancies or previous history of head and neck cancer
5. Prior radiotherapy
6. Patient with renal disorders

Methodology:

Study was conducted after receiving the approval from the institutional ethics committee. Pre-treatment evaluation was done with physical examination including height, weight, body surface area and Performance Status. Investigations like Histopathologic proof of squamous cell carcinoma, Complete blood count with differential counts, platelets, blood urea, serum creatinine and liver function tests, CT/MRI scan of the neck, Chest X-ray as a routine workup, Oral care & Pre-radiation therapy dental evaluation by Dentist was done. Patients were treated on a 6MV linear accelerator in 2D technique to a total dose of 66Gy in 33 fractions,1 fraction/day, 6 fraction/week in accelerated arm and 5 fractions/week in conventional arm with weekly cisplatin.

Treatment delivery :

Patients were immobilized using a head and neck five point thermoplastic mass in supine position with head in slight extension using appropriate neck rest. Patients were simulated using a dedicated big bore Phillips CT simulator.After simulation the CT series are exported to Varian planning system via PACS.Target delineation was done using contouring application of Varian eclipse planning system. Appropriate GTV CTV and OAR'S are contoured according the ICRU 52.After target and OAR delineation radiation is planned with eclipse TPS in 2D technique in two phases - 44Gy in 22 fractions with field encompassing whole neck posteriorly up to tip of second cervical spine. Second phase is the cord off phase to spare the spinal cord, 22 Gy in 11 fractions delivered to a total dose of 66Gy in 33 fractions. Weekly chemotherapy cisplatin 40mg/m2 given weekly once in both arms. Toxicity grading is done according to the CTCAE criteria. Toxicity assessed are mucositis dysphagia dermatitis local pain xerostomia.Onset, progression, severity, of the side effects have been documented every week for every patient in both the arms of the study.

Follow up and response assessment: After completion of radiotherapy patients are put on regular follow up with regular work up including CT scan of head and neck after 1 month 3 month and 6 months and 1year of radiotherapy completion. Any residual lesion or recurrence lesion is duly noted and appropriate management of the lesion was done based on the current treatment standards of the institute. Patients disease assessment was done according to the RECIST criteria version 1.1.

Statistical analysis:

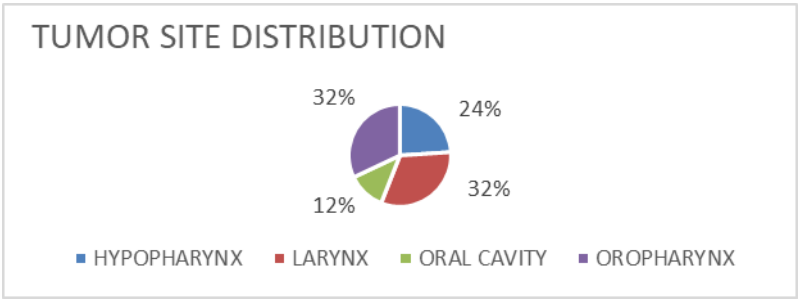
Data was analyzed using SPSS version 20 (SPSS Inc., Chicago, IL). The data are reported as the mean +/- standard deviation or the median, depending on their distribution. The differences in quantitative variables between groups were assessed by means of the unpaired t test. Comparison between groups was made by the Non parametric Mann - Whitney test. A chi - square test was used to assess differences in categorical variables between groups. A p value of <0.05 using a two-tailed test was taken as being of significance for all statistical tests. All data were analyzed with a statistical software package.

III. Result

A total number of 51 patients were randomized. One patient in each of the arm defaulted for treatment. So only the baseline characteristics could be analyzed for all the 51 patients. One patient in the accelerated arm died during treatment due tracheoesophageal fistula. These three patients couldn't be included in the response assessment criteria. Hence the final response assessment was possible for only 49 patients.

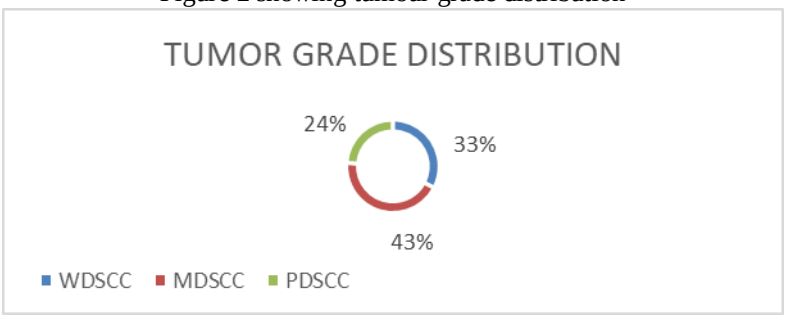
About 61% of patients were below 45 years of age . Age of the patients ranged from 21 to 57 years, with the mean being 42.5 years. The median age was 45 years. One patient in each arm had ECOG performance status of 2 , rest all others had ECOG performance status 1. 20% of patients in the study had some kind of co-morbidities like HTN, DM, OR BOTH. All patients in both arms received weekly chemo with cisplatin at a dose of 40 mg/m2. In the study 20% patients had RT interruptions due treatment related toxicities.About 28% in accelerated group had interruptions and 12% in conventional arm had interruptions.24%of the patients in the study were hypopharynx primary,33% laryngeal primaries,31% oropharyngeal primaries and 12% had oral cavity primaries, with almost equal distribution among both arms (p-value is .997958) and statistically insignificant.

Figure 1 showing tumour site distribution.



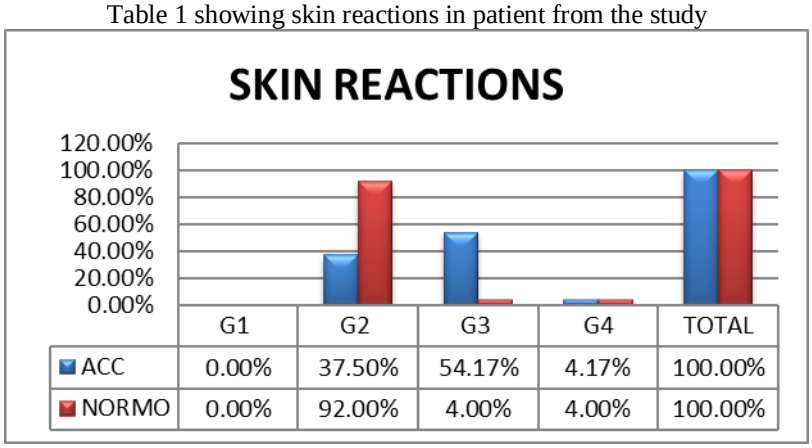
In the study 33% were well differentiated squamous cell carcinoma (WDSCC), 43% were moderately differentiated squamous cell carcinoma (MDSCC) and 24% were poorly differentiated squamous cell carcinoma (PDSCC).

Figure 2 showing tumour grade distribution



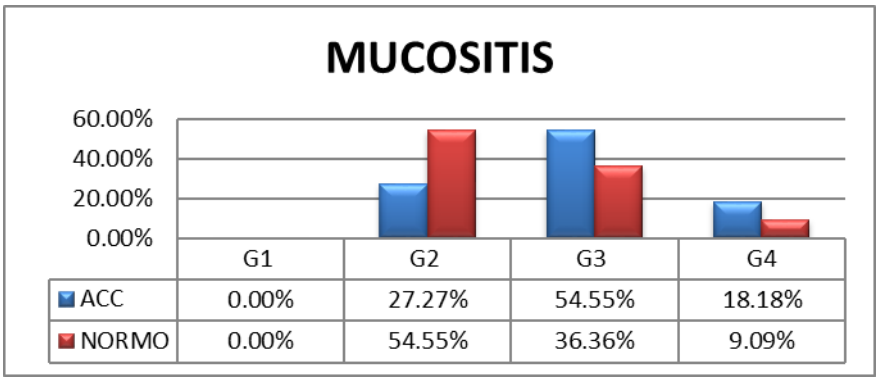
On follow-up assessment of the patients for skin reactions ,in the accelerated group 37% had grade 54% had grade 3 and 5% had grade 4 skin reaction , when it came to conventional arm 92% had grade 2 reactions and 4% each grade 3 and 4 reactions.

Table 1 showing skin reactions in patient from the study



	G1	G2	G3	G4	TOTAL
ACC	0.00%	37.50%	54.17%	4.17%	100.00%
NORMO	0.00%	92.00%	4.00%	4.00%	100.00%

In accelerated arm patients - 27% had grade 2 reactions 55% had grade 3 and 18% had grade 4 mucositis reactions and in conventional arm, 55% patients had grade 2 reaction, 36% had grade 3 and 9% had grade 4 reactions



	G1	G2	G3	G4
ACC	0.00%	27.27%	54.55%	18.18%
NORMO	0.00%	54.55%	36.36%	9.09%

Table 2 showing mucositis reactions recorded among patients

When assessment regarding dysphagia was done , in accelerated arm 4% had grade 2,70% had grade 3 and 26% had grade 4 dysphagia and in conventional arm 44% each had grade 2 and grade 3,12% had grade 4 dysphagia.

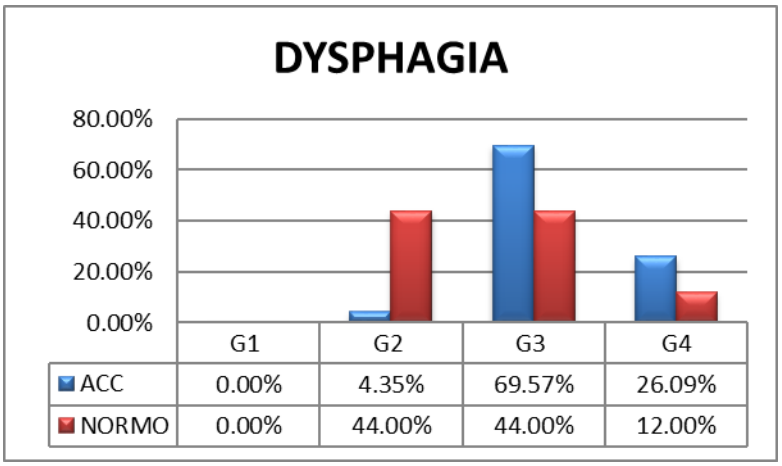


Table 3 showing dysphagia reactions in patients of both arms

Disease response assessment at the end of 6 weeks to 8 weeks of radiation therapy was done for all the patients in both the arms . Primary disease and nodal disease status was assessed in both the arms.
In the accelerated arm 91% had complete primary tumor response and 9% had partial response and in conventional arm 92% had complete primary tumor response and 8% had partial tumor response.

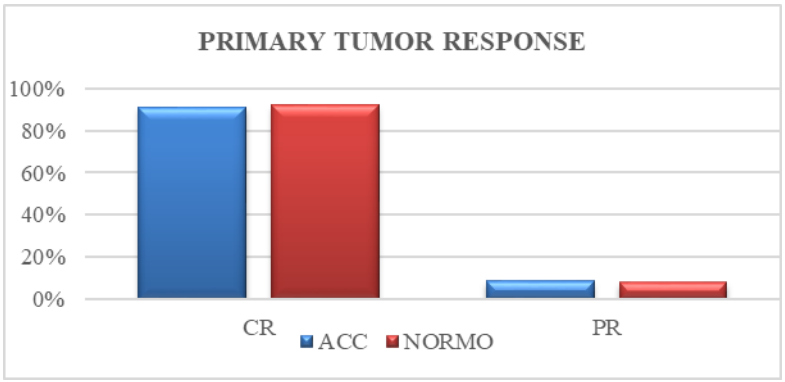


Table 4 showing primary tumour respose in both arms

When it comes to nodal disease response in accelerated arm 83% patients had complete nodal response and 17% had partial response and in conventional arm 80% had complete response and 20% had partial response.

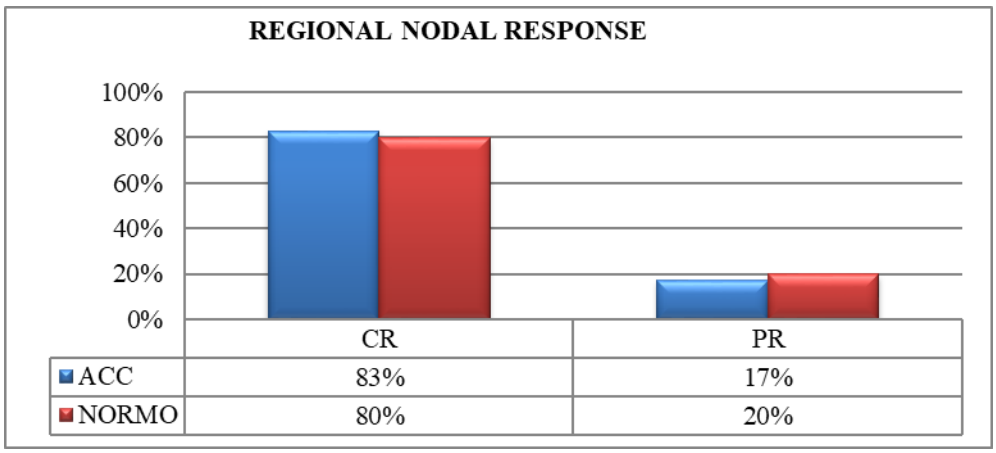


Table 5 showing regional nodal response in both arms.

IV. Discussion

The rationale for accelerated fractionation is that reduction in overall treatment time decreases tumor cell repopulation and increases the probability of tumor control. Because overall treatment time has little influence on the probability of late normal tissue injury if the dose per fraction is the same, a therapeutic gain is

expected with acceleration with slightly increased acute normal tissue injury. This hypothesis has been used by many investigators in the past to evaluate accelerated fractionation schedules with or without concurrent chemotherapy with mixed results. Based on radiobiological data many altered fractionated regimens have been tried in head and neck cancers to improve local tumor response and decrease normal tissue toxicity. It has been shown in several randomized trials that accelerated fractionated radiotherapy has improved locoregional tumor control when compared with conventional fractionated radiotherapy in locally advanced HNSCC. Bourhis et al[10] had done a meta- analysis which showed a significant 5 – year survival benefit with altered fractionated radiotherapy, corresponding to an absolute benefit of 3.4% at 5 years. Hyper-fractionated RT showed a better survival benefit of 8% at 5 years than with accelerated radiotherapy (2% without total dose reduction and 1.7% with total dose reduction).

All the patients in this study had comparable baseline characteristics. About 61% of patients were below 45 years of age. Age of the patients ranged from 21 to 57 years, with the mean being 42.5 years. 86% of the patients were male and 14% of them were females (P value equals 0.7030), age and sex differences between the both arms were not statistically significant (p-value is .907354). In the study all patients were having performance status ECOG 1 except two patients one in each arm had (p-value is .977427). 20% of patients in the study had some kind of co-morbidities like HTN, DM, OR BOTH. Difference between both arms is not significant(p-value is .9156).

Mean difference of pre and post treatment in accelerated arm was 9.7% whereas in conventional arm it was 7.3%(=0.003).patients losing wt. < 10 kgs in accelerated arm are 43% and >10 was 57%,in conventional arm 84% lost <10 kgs and 16% lost >10 kgs of weight, the weight loss in accelerated was found to be significant compared to conventional arm.

In accelerated arm weight loss was more and likely reasons for this significant weight loss are

1.most patients in the study were oropharyngeal, hypo pharyngeal and laryngeal primaries presenting with early grade of dysphagia in both the arms but due to increased dose per week and less time for mucosal repair patients had higher rates of grade 4 dysphagia.

2.patients having oropharyngeal; and oral cavity primaries also had significant weight loss due to combined effects of mucositis and dysphagia caused by accelerating the radiotherapy leading to less time for mucosal recovery.

24%of the patients in the study were hypopharynx primary,33% laryngeal primaries,31% oropharyngeal primaries and 12% had oral cavity primaries, with almost equal distribution among both arms (p-value is .997958) and statistically insignificant. In the accelerated group there was a death due to development of tracheo-esophageal fistula and one patient absconded and other interruptions (5 patients) were due to grade 4 toxicities, in conventional arm one patient absconded and others (2 patients) had grade 4 reactions.

In the study 65% patients had grade 2,29%had grade 3 and 4%grade 4 skin reaction. In the accelerated group 37% had grade 54% had grade 3 and 5% had grade 4 skin reaction.in conventional arm 92% had grade 2 reactions and 4% each grade 3 and 4 reactions with significant p value of 0.00025.

In the conventional arm most patients had grade 2 skin reactions whereas in the accelerated arm patients had more grade 3 reactions due to less time for cell repair and leading to severe skin reactions compared to the conventional group.

In the study oral mucositis was assessed in patients with oropharyngeal and oral cavity primaries where a significant dose will be delivered to the oral mucosa. Mucositis was assessed in 22 patients , 11 patients in each arm. In study in accelerated arm 27% had grade 2,55% had grade 3 and 18% had grade 4 mucositis while in conventional arm 55% had grade 2,36% had grade 3 and 9% had grade 4 reactions , though grade 3 and grade 4 mucositis were more in accelerated arm but that was not statistically significant(p value=0.42035).

In the accelerated arm 4% had grade 2,70 had grade 3 and 26% had grade 4 dysphagia in the conventional arm 44% each had grade 2 and grade 3,12% had grade 4 dysphagia patients in both arms with p=0.0061.

Most patients in both arms are oropharyngeal ,hypo pharyngeal and laryngeal primaries presenting with grade 1 or grade 2 dysphagia but the accelerated arm has got significant dysphagia due to less time for recovery of normal tissues in the field. This clearly shows us that accelerated arms has more acute side effects than conventional arm , similar results were also seen in DAHANCA6&7[11] studies which evaluated tumor response and morbidity after moderate accelerated radiotherapy compared to conventional fractionated radiotherapy in patients treated for glottic squamous cell carcinoma (SCC). Six hundred and ninety-four patients with non-metastatic glottic SCC were randomized between six or five weekly fractions (fx/w) of radiotherapy to the same total dose. The primary endpoint was loco-regional failure. The hazards of disease-specific death, event-free survival, and overall survival were comparable between the two groups. Significantly more patients experienced severe acute mucositis in the 6 fx/w group but no difference in the incidence of late morbidity between the groups.

In another randomized trial conducted by Skladowski et al [12], a 7-day-a-week continuous accelerated irradiation(CAIR) was compared to a 5 day per week conventional treatment in patients with T2-4, N0-1, M0 HNSCC.The dose per fraction (1.8-2Gy) and the total dose(66-72Gy) were similar in both the arms, the only difference being the overall treatment time which was 5 weeks in the CAIR arm and 7 weeks in the control arm.

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There was a significant difference in the 3 year local tumor control (82% vs 37%) and 3 year overall survival (78% vs 32%), which favored the CAIR arm. The acute and late toxicities were higher in the CAIR arm.

The (IAEA) ACC[13] trial was done to find out whether accelerated fractionation could be applied in developing countries, where there are fewer therapeutic resources and where tumor burdens can be heavier. About 908 patients of HNSCC were randomly assigned to receive either a 6 fractions per week accelerated regimen or 5 fractions per week conventional regimen, to a total dose of 66–70 Gy. The results of the trial showed that the 5-year locoregional control was 42% in the accelerated group and 30% in the conventional group. Confluent mucositis and severe skin reactions were more in the accelerated group than in the conventional group. The late radiation side-effects were similar in both the arms. This trial concluded that accelerated schedule is more effective than conventional schedule and that it might be a suitable new international standard of treatment as no additional resources are required.

MANOJ GUPTA et.al[14] showed at a median follow up of 12 months, 62.1% of patients in the accelerated radiotherapy arm and 70.1% of patients in the CCRT arm were disease free Local disease control was comparable in both the arms. Acute toxicities were significantly higher in the CCRT arm as compared with accelerated radiotherapy arm. There was no difference in late toxicities between the two arms.

In the accelerated arm 91% had complete primary tumor response and 9% had partial response and in the conventional arm 92% had complete primary tumor response and 8% had partial tumor response (p=0.93) with no statistically significant difference between two arms. Possible reason for partial responses in most patients in both groups had partial responses had very advanced primaries with chronic tobacco, alcohol abuse which may have confounded treatment resistance.In the study 81% had complete nodal response and 19 % had partial response. In the accelerated arm 83% patients had complete nodal response and 17% had partial response and in the conventional arm 80% had complete response and 20% had partial response and the difference between two arms were not found to be significant (p=0.817). All the patients with nodal failure either had very large tumor volume or had clinical extra nodal extension i.e. fixed nodes. On overall response assessment 73% had complete response and 27 % had partial response.

The incidence of acute reactions in this study is high and similar to other studies like DAHANCA 6 & 7, IAEA (ACC) and manoj gupta et.al. local control in this study is more than the similar studies but local control needs long term follow up.

LIMITATIONS OF THE STUDY: -

1.HPV status was not assessed.
2. Late effects were not assessed.
3.Short term follow-up.
4. small sample size.
5. Most patients in both arms had logistical delays in treatment.

V. Conclusion

The primary objective of this study is to compare the acute normal tissue toxicity between conventional radiotherapy and accelerated radiotherapy. The acute skin reactions, dysphagia and weight loss have shown statistically significant differences between both the arms. Accelerated arms had more acute side effects than conventional arms with significant grade 3 and grade 4 reactions leading to treatment delays but were managed conservatively. Comparing the response to radiotherapy an accelerated fractionated radiotherapy versus conventional fractionated radiotherapy is the secondary aim of this study. There was no statistically significant difference between both arms in local response with p=0.881.However, in view of the drawbacks mentioned above a study with longer follow up and larger sample size is required to comment about the local response of tumor.

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