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Research Article

Accelerated fractionation radiotherapy: an answer to the financial burden of locally advanced head and neck cancer patients in India seeking treatment at centers far away from home

D.K. Mondal[1], L.M. Aggarwal[2*], U.P Shahi[2]

[1]*Royal Cancer Institute and Research Centre, Kanpur, Uttar Pradesh, India*

[2]*Department of Radiotherapy and Radiation Medicine, IMS, BHU, Varanasi, India*

***Corresponding author. E-mail address:** *lmaggarwal@yahoo.com* (LM Aggarwal)

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Abstract: Radiotherapy with concurrent Chemotherapy is the treatment of choice for locally advanced head & neck cancers as Surgery is often not suitable. Concurrent chemoradiation is associated with higher toxicity and cost. This work was done to study the feasibility and effectiveness of accelerated fractionation radiotherapy in locally advanced head & neck cancers. Total 39 patients of head & neck cancers with Stage: T4, N0 to N2, M0 included. Site wise distribution: oral cavity 21, oropharynx 16, larynx 1 and pyriform fossa 1. External beam radiotherapy given on telecobalt unit with two lateral parallel opposed and lower anterior neck portals. A tumor dose (TD) of 60Gy / 24 #/ 4 weeks was delivered. Spinal cord spared after 40 Gy/16 #. Overall response rate was 100%, 70% and 77% at 0, 3 and 6 months respectively. At 3months, CR in oral cavity 82%, in oropharynx 33%, in N0 patients 100%, in node positive patients 30%. In 85% cases treatment completed within 5 weeks. Grade 3 acute skin reactions in 96% and grade 3 mucosal reactions in 24% cases. The accelerated fractionated radiotherapy (AFRT-4W) in 4 weeks is feasible in locally advanced HNSCC. The overall response seems to be quite good. AFRT-4W seemed to be most effective in oral cavity and N0 cases. Acute toxicities were severe but manageable conservatively. As total treatment time was reduced by 2 weeks (compared to conventional fractionation) duration of hospital stay and expenditure reduced.

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INTRODUCTION

More than 5,50,000 head and neck squamous cell carcinomas (HNSCC) are diagnosed worldwide each year, majority of them in locally advanced stage at presentation (1). Head and neck cancer in India accounted for almost 30% of all cancers in males and 11 to 16% of all cancers in females (2). Early stage HNSCC is treated with surgery or radiotherapy as single modality resulting locoregional control rate of 70 – 80 % but it is markedly reduced in locally advanced cases. Therefore, in locally advanced cases, multimodality treatment with surgery, radiotherapy and chemotherapy are used in different schedules and varying combinations. As surgery amounts to loss of function and cosmetic disfigurement, radiotherapy is preferred in treatment of locally advanced HNSCC. As radiotherapy plays the key role, several approaches tried to improve its efficacy while maintaining acceptable toxicities. Among them, addition of chemotherapy concurrently is shown to improve survival, compared to radiotherapy alone (4-9). The benefit achieved with concurrent chemotherapy evaluated from more than 10000 patients entered in 63 randomized controlled trials (meta-analysis of chemotherapy in head and neck cancers MACH-NC database) was 4% and with use of concomitant boost radiotherapy it was 8% at 5 years (9).

The benefit of concurrent chemoradiation comes at the cost of increased toxicities, hospitalization and increased cost of therapy. Therefore, altered fractionated radiotherapy is tried and studied with considerable interest in last two decades for possibilities of improving the efficacy of radiotherapy and omitting the toxicities related to chemotherapy. Altered fractionation radiotherapy aims to increase the dose intensity of radiotherapy by delivering a total dose as high as possible in an overall time as short as possible. This increased dose intensity can be achieved either by increasing the total dose and/or by decreasing the overall treatment time compared to the dose and schedule of conventional fractionation maintaining a similar biologically equivalent dose (BED).

Accelerated radiotherapy schedules aim to overcome accelerated repopulation during the course of radiotherapy which usually starts after 21-28 days of starting radiotherapy. Several randomized controlled trials have compared

conventional fractionation radiotherapy to accelerated radiotherapy in HNSCC. In some of these trials, a significant improvement in local control was evident in accelerated arm, without a significant gain in overall survival (10). In some studies, accelerated hyperfractionation is used to shorten the treatment time while some studies used increased number of fractions per week with once daily fraction to accelerate the treatment. These schedules which used six or seven fractions per week had dose per fraction 1.8-2 Gyand the total treatment time was decreased by 1-2 weeks. In this present study, we have studied accelerated fractionation radiotherapy in 4 weeks with six fractions per week and 2.5 Gy per farction. So, in our study the total treatment time is decreased by 3 weeks while increasing the dose per fraction.
The objectives of this study are to determine the feasibility of AFRT-4W in advanced HNSCC and its efficacy in terms of locoregional control of disease and normal tissue toxicity.

MATERIAL AND METHODS

Inclusion criteria

Patients were eligible if they had no previous history of cancer or radiotherapy or chemotherapy and if they had an ECOG performance score of 0-2. T4 and N0, N1 and N2 cases of histologically confirmed HNSCC (oral cavity, oropharynx, larynx and laryngopharynx) were included with no metastasis and no liver or kidney damage detected in work up.

Treatment

After informed consent patients were treated with External beam radiotherapy on cobalt teletherapy unit (Theratron 780E and Phoenix) with two lateral parallel opposed portals. Proper immobilsation of the head and neck region done with the help of head rests and thermoplastic casts. Conventional simulation done. A tumour dose (TD) of 60Gy / 24 #/ 4 weeks, 2.5 Gy/ #, 6 #/ week was delivered. Spinal cord sparing was done after 40 Gy in 16 #. Shrinking fields used.
Patients were evaluated weekly for treatment response and toxicities. After treatment completion, patients were followed up weekly or more frequently for 1 month and then monthly for 6 months.

RESULTS

Patient profile

Between March 2013 to April 2014, 39 patients were enrolled in this study from radiotherapy OPD of Dept. of Radiotherapy and Radiation medicine, Institute of Medical Sciences, Banaras Hindu University. The analysis was performed in 34 patients as 5 patients did not turn up for treatment after registration to this study. Out of these 34 patients 27 completed radiotherapy as 4 patients defaulted at 1st week of radiotherapy and 3 patients died during the course of radiotherapy. One died after 1 fraction due to progressive disease, one patient died of renal failure due to chronic kidney disease after 21 fractions and the 3rd one died of treatment related acute toxicities after 18 fractions.

The median age of presentation of patients in the study was 55 years. All were male patients. Commonest sites were oral cavity (54%) and oropharynx (41%). All patients had T4 disease. Out of which 92% had T4A and rest 8% had T4B disease. Fourteen out of 34 patients (36%) had N0 disease, 15% had N1 and 49% had N2 disease. Thirty seven out of 39 patients (95%) had history of tobacco intake either in the form of smoke or chewable. Surprisingly no patient had history of alcoholism. Table 1 shows different aspects of patient profile.

Table 1: patient profile (N=39)

Characteristics		**No. of patients (%)**
Age group(years)		
41-50		15 (38)
51-60		11 (28)
61-70		12 (31)
71-80		1 (3)
Religion		
Hindu		36 (92)
Muslim		3 (8)
Occupation		
Agriculture		22 (56)
Office job		8 (21)
Business		3 (8)
Skilled labor		3 (8)
Unskilled labor		2 (5)
Unemployed		1 (2)
Habituation		
Tobacco chewing		31 (80)
Tobacco smoking		15 (39)
Both		9 (23)
nil		2 (5)
ECOG performance status		
0		27 (69)
1		10 (26)
2		2 (5)
Primery site		
Oral cavity		21 (54)
	Tongue	6 (29)
	Buccal mucosa	8 (38)
	Lip	4 (19)
	Alveolus	3 (14)
Oropharynx		16 (41)
	Base of tongue	15 (94)
	Soft palate	1 (6)
Larynx		1 (3)
Laryngopharynx		1 (2)
WHO grade of squamous cell carcinoma		
I well differentiated		19 (49)
II moderately differentiated		12 (31)
III poorly differentiated		8 (20)
T stage		
T4A		36 (92)
T4B		3 (8)
N stage		
N0		14 (36)
N1		6 (15)
N2		19 (49)
	N2A	1 (5)
	N2B	8 (42)
	N2C	10 (53)

Radiotherapy

Twenty five out of 34 patients (74%) received total dose of 60 Gy, 1 patient received 57.5 Gy and 1 patient received 55 Gy (Table 2). Twenty four out of 34 patients (82%) achieved BED_{10} of 71-75 Gy_{10} (Table 3). Twenty three out of 27 patients (85%) who completed treatment, completed in 4-5 weeks' time. The cause of prolongation of total treatment time beyond 4 weeks was treatment related toxicity in 19% cases whereas in 63% cases default of patients due to various factors like personal reasons, generalized weakness, no one to accompany, ignorance etc. were responsible. In 52% cases, treatment time prolonged due to holidays and problem in machine.

Response to radiotherapy

Three months after treatment 20 patients were evaluated. Out of them 12 patients (60%) had complete response, 10% had partial response and 30% had progressive disease. At 6 months, 13 patients were evaluated. Among them 10 patients (77%) had complete response and remaining 3 patients (23%) had progressive disease (Table 6, Fig. 1). At 3 months after treatment complete response rate of carcinoma oral cavity cases was 82% compared to 33% in carcinoma oropharynx cases (Fig. 2). The complete response rate at 3 months after treatment, in N0 case were 100% compared to 30% in node positive cases (Fig. 3). At 3 months after treatment, complete response rate of cabuccal mucosa cases was 100% whereas in ca base of tongue it was 38%.

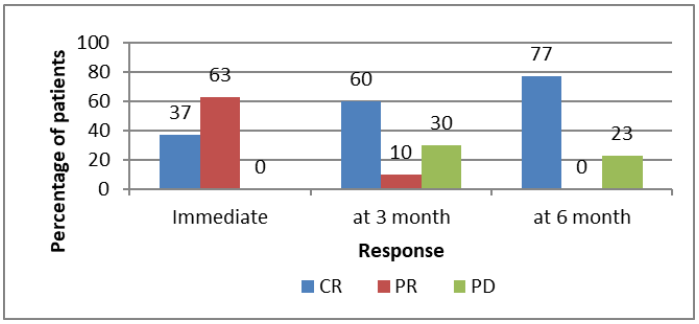

Fig. 1: Responses (CR, PR, PD) at various interval after completion of radiotherapy.

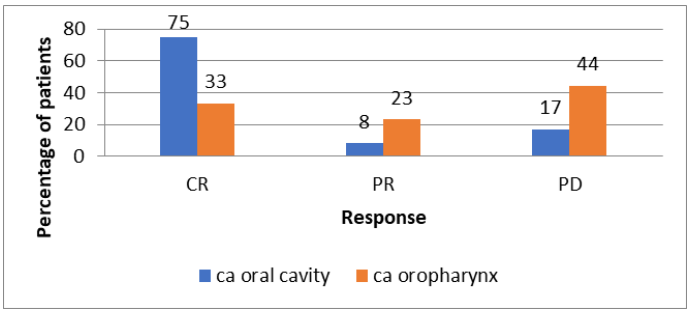

Fig. 2: Comparison of responses in ca oral cavity and ca oropharynx at 3 months after treatment

Toxicities

At 1st week patients had no skin reactions. Grade I reactions appeared in 2nd week and Grade II reactions started showing up in 3rd week. At 4th week Grade III reaction seen in 50% cases and the remaining 50% had grade II skin reactions. At 5th week almost all (96%) patients had Grade III reaction and at 6th week it came down to 69%. No Grade IV reaction seen. At 1st week no mucosal reaction seen. At 2nd week Grade I reaction appeared. At 3rd week 71% had Grade II reaction. At 4th week all patients had Grade II mucosal reaction. Grade III reactions seen in 24% cases at 5th week and at 6th week it was 19% only.

Out of 27 patients who completed treatment only 22 patients could be followed up till all the reactions subsided. In 20 out of these 22 patients (91%) skin reactions subsided by 8th week and the remaining by 9 -10th week. In 19 out of 22 patients (86%) mucosal reactions subsided by 9thweek and the remaining by 10th week (Fig. 4).

Table 2: No. of patients as per radiation dose received: (N=34)

Total dose (Gy)	N (%)
60	25 (74)
45 to 57.5	4 (11)
<30	5 (15)

Nasogastric tube insertion

Fourteen out of 34 patients (41%) needed nasogastric tube insertion during radiotherapy to maintain nutrition, mostly in the 3rd week of radiotherapy. Nine out of these 14 patients needed nasogastric tube feeding for more than a month.

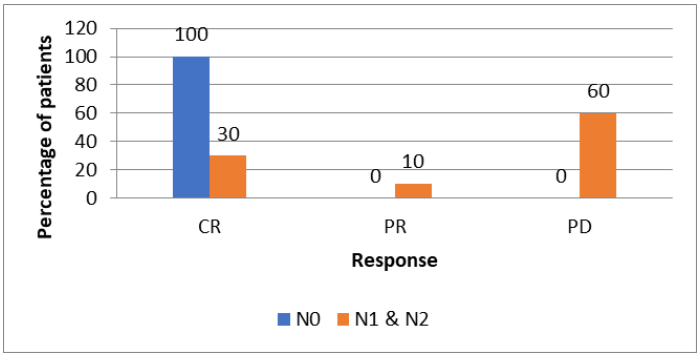

Fig. 3: Comparison of responses in N0 and node positive cases at 3 months after treatment.

Table 3: No. of patients and response as per Biological effective dose (BED_{10}) for acute effect: (N=34)

BED_{10} (Gy_{10})	N (%)	Response at 3 months after treatment or at last FU whichever is greater		
		CR	PR	PD
71–75 Gy_{10} equivalent to 66 to 70 Gy in 33 to 35 fractions	24 (82)	12 (50%)	6 (27%)	6 (11%)
45–68 Gy_{10} equivalent to less than 60 Gy in 30 fractions	5 (9)	1 (20%)	3 (60%)	1(20%)
3–37 Gy_{10} equivalent to less than 30 Gy in 15 fractions	5 (9)	-	-	-

Hospitalization
Eleven out of 34 patients (32%) who received RT needed hospitalization during or after treatment for management of toxicities.

Surgical assistance
Three out of 34 patients who received RT needed surgical intervention. One patient needed facial artery ligation for lip bleeding after 2 fractions of radiotherapy. Another patient underwent external carotid artery ligation for tongue bleeding at 1 month after completion of treatment and the third patient had tracheostomy done before starting treatment.

Follow up
Twenty patients came at follow up after 3 months of treatment. Thirteen patients came for follow up till 6 months after treatment. 2 patients out of 27 who completed radiotherapy developed lung metastasis in follow up period. 6 out of 27 patients who completed radiotherapy received palliative chemotherapy in follow up period for progressive disease.

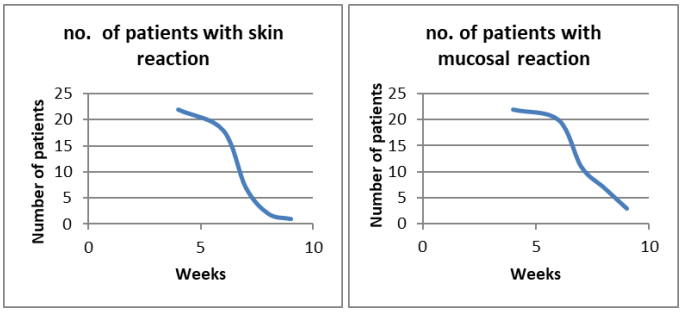

Fig. 4: showing trend of subsidence of skin and mucosal reactions against time in weeks in X axis.

DISCUSSION

Conventional fractionation radiotherapy in HNSCC (66-70 Gy/33-35 fractions/6.5-7 weeks, 2 Gy/fraction, 5 fractions/week) is widely accepted and practiced out of empiricism and convenience. Locoregional control of disease is hampered in this schedule due to accelerated repopulation. Therefore, continuous search is on to increase the therapeutic ratio by altering the fractionation schedule.

In this present study we have tried to complete the treatment in 4 weeks as accelerated repopulation starts after 3-4 weeks of starting treatment. BED_{10} and BED_3 of the present study schedule was 75 Gy_{10} and 109.99 Gy_3 respectively. In conventional fractionation radiotherapy schedule the BED_{10} and BED_3 is 73 Gy_{10} and 116.66 Gy_3 respectively. So, with the present schedule though we are giving 2.5 Gy per fraction the late effect is less than that of conventional fractionation radiotherapy.

Researchers at the M Sklodowska-Curie Institute, Gliwice, Poland gave trial participants in the experimental group continuous daily irradiations (1·8–2·0 Gy, 7 days per week) to total doses ranging from 66 Gy to 72 Gy, reducing the overall treatment time by 2 weeks (Skladowski K et al., 2000). An acceleration of 2 weeks resulted in a significant improvement in 3-year local control (82% vs37%, p<0·0001) and overall survival (78% vs32%, p<0·0001). However, the results in the control group were rather poor, because the study did not include patients with N2 or N3 disease, unlike most other large trials (11). As in our study they have also increased the number fractions per week but dose per fraction was not increased. Locoregional control rate of the accelerated arm in this study is better (82% vs 77%) than ours may be because unlike this study our study included N0 as well as N1 & N2 cases.

Danish Head and Neck Cancer Study Group (DAHANCA) conducted a multicenter, controlled, randomized trial in head and neck cancer patients. Eligible patients were randomly assigned five or six fractions per week at the same total dose and fraction number (66–68 Gy in 33–34 fractions to all tumor sites except well-differentiated T1 glottictumours, which were treated with 62 Gy). All patients, except those with glottis cancers, also received the hypoxic radiosensitizer nimorazole. More than 97% of the patients received the planned total dose. Median overall treatment times were 39 days (six fraction group) and 46 days (five-fraction group). Overall 5-year locoregional control rates were 70% and 60% for the six fraction and five-fraction groups, respectively (p=0·0005). The whole benefit of shortening of treatment time was seen for primary tumor control (76 vs64% for six and five fractions, p=0·0001), but was non-significant for neck-node control. Six compared with five fractions per week improved preservation of the voice among patients with laryngeal cancer (80 vs68%, p=0·007). Disease-specific survival improved (73 vs66% for six and five fractions, p=0·01) but not overall survival. Acute morbidity was significantly more frequent with six than with five fractions but was transient. The shortening of overall treatment time by increase of the weekly number of fractions is beneficial in patients with head and neck cancer (Overgaard J et al. 2003) (12). This study also tried to shorten the treatment time by increasing number of fractions per week as in our study but unlike our study they didn't increased the dose per fraction. This study shortened the total treatment time by 1 week whereas in our study the total treatment time is shortened by 3 weeks. May be because of that we found better locoregional control with accelerated radiotherapy (77% vs 70%) than in this study. However, this study included patients of all stages whereas we took only stage IV cases.

A study conducted at Dept. of Radiotherapy Pt. B D S PGIMS Haryana India evaluated the feasibility and efficacy of six fractions per week radiation schedules in terms of loco-regional control of the tumor and radiation induced side effects in locally advanced head and neck cancer patients. Stage III and stage IV, locally advanced squamous cell carcinoma of head and neck patients were included in the study. All the patients were given radical-radiotherapy. The patients were given a dose of 66 Gy over 33 fractions in 5.3 weeks. All the patients were evaluated in terms of treatment response, treatment related toxicity and survival. Skin and mucosal toxicity were most common side effect observed during treatment. Complete response observed in 77% of the patients while 21% showed partial response. It was concluded that six fractions per week radiation schedule showed superior tumor control, but at the same time produced higher but acceptable mucosal toxicity. Supportive care can be used effectively to overcome the toxicities

associated with this treatment (Chauhan A et al., 2010) (13). Like our study they have also used six fractions per week but the dose per fraction was not increased and they took both stage III & IV while we included only stage IV cases. This study had decreased total treatment time by 1.5 weeks while we have decreased the total treatment time by 3 weeks. May be because of that we found similar locoregional control rate even after enrolling only stage IV cases. Therefore, in this present study 77% patient's complete response rate at 6 months after treatment is similar or better than the studies mentioned above. Among ca base of tongue patients 38% complete response rate seen at 3 months after treatment. Lindberg and Fletcher had reported 33% complete response rate in T4 ca base of tongue treated with conventional fractionation radiotherapy. Cabuccal mucosa patients in this study achieved 100% complete response at 3 months after treatment. Lindberg and Fletcher had reported 90% complete response in T4 cabuccal mucosa with conventional fractionation radiotherapy alone (14). In ca oral cavity cases we found 82% complete response at 3 months whereas in ca oropharynx it was 33%. In N0 patients we found 100% complete response at 3 months whereas in node positive patients it was 30%. Therefore, results in this study seem to be quite encouraging and similar to the results reported earlier.

As expected based on the experiences of previous studies (15-17), acute toxicity was a major concern with grade 3 skin reactions and grade 2 mucosal reactions in most patients and prolonged time (8-9 weeks) for healing.

Table 4: Overall response in patients who completed treatment: (N=27)

Response (as per RECIST criteria)	Evaluable patient (N)	Complete response (CR)		Partial response (PR)		Progressive disease (PD)		Lost FU
		No. of patients	Percentage (%)	No. of patients	Percentage (%)	No. of patients	Percentage (%)	No. of patients (%)
Immediately after completion of treatment	27	10	37	17	63	-	-	-
3 months after completion of treatment	20	12	60	2	10	6	30	7(26)
6 months after completion of treatment	13	10	77	-	-	3	23	7(35)

CONCLUSION

In conclusion, it can be said that AFRT-4W seems to be quite feasible. However, treatment duration may be prolonged to 5 weeks due to factors other than treatment related toxicities. Locoregional control of the disease with AFRT-4W is similar to the results of accelerated arm in other reported studies. AFRT-4W seems to be quite effective in ca oral cavity and oropharynx. Clinical outcome was better in patients with ca oral cavity particularly with N0 status. The acute toxicities with AFRT-4W was more severe than conventional radiotherapy alone but it is manageable and tolerable by some measures like N-G tube feeding, hydration and hospitalization if needed. However, these toxicities can be reduced with use of more conformal radiotherapy. AFRT-4W is beneficial in terms of less financial burden to the patient as patient has to stay in hospital for a less duration. It also saves treatment machine slots which can be used for other patients. However, small sample size and short duration of the study may forbid us to make any definite conclusion. A farther large study may be required to reach a definite conclusion.

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CONFLICT OF INTEREST: None

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About Author

Dr. Dulal Kiran Mondal is working as a consultant clinical oncologist in Royal Cancer Institute & Research Centre, Kanpur. He had his postgraduate training in Banaras Hindu University. He is well versed with all the modern radiotherapy techniques. He takes keen interest in head & neck cancers.