A Prospective Comparative Study of Concurrent Chemoradiation with Accelerated Fractionated Radiotherapy versus Concurrent Chemoradiation with Conventional Fractionation in Locally Advanced Squamous Cell Carcinoma of Head and Neck

Joydeep Basu[1], Tanmoy Ghosh[2]

ABSTRACT

Introduction: Concurrent chemo-radiation is the standard of care for locally advanced head and neck carcinoma. During later part of radiation treatment schedule, there is accelerated repopulation of surviving tumour cells. So the treatment should be completed as early as possible. Study aimed to compare the loco-regional control rates between the accelerated fractionated and conventional fractionated radiotherapy and to compare the rate of acute and late toxicities between the two arms.

Material and Methods: Thirty patients with locally advanced head and neck cancer in the study arm (ARM-A) received six fractions of radiotherapy per week and thirty-two patients in the control arm (ARM-B) received five fractions of radiotherapy per week. Total radiation dose was same in both arms. Inj. Cisplatin at a dose of 100mg/m^2 was given to the patients of both the arms every three weeks as a radiosensitizer agent.

Results: Complete response rate (19/30 vs 14/32) rate though higher in the study arm, was not statistically significant. Similarly overall response rate (25/30 vs 21/32) was not statistically significant (*P value – 0.15*). Among acute toxicities only dysphagia was significantly higher in the study arm (*P value-0.024*). Late toxicities were similar in both the arms.

Conclusion: So accelerated fractionation radiotherapy can be used for treating locally advanced head and neck cancer patients to improve loco-regional control rate with acceptable toxicities.

Keywords: Locally Advanced Head and Neck Cancer, Accelerated Fractionated Radiotherapy, Response Rate, Dysphagia.

INTRODUCTION

Head and Neck cancer is one of the most common malignancies. Worldwide nearly five and a half lakh people develop head and neck cancer each year.[1] Around sixty percent of the patients present with loco-regionally advanced but non-metastatic disease.[2] In India also head and neck cancers contribute a major share to the cancer burden. Multiple trials established the superiority of concurrent chemoradiation for the management of locally advanced head and neck cancer.[3] Injection Cisplatin formed the cornerstone of the cytotoxic drug used concurrently with radiation as a radiosensitizing agent. Three weekly schedule of inj. Cisplatin used concurrently with radiation is the most studied and widely accepted regimen.[2,4]

Accelerated repopulation refers to triggering of surviving clonogens to divide more rapidly as tumour starts shrinking after irradiation or chemotherapy.[5] This is one of the reasons for treatment failures in rapidly proliferating cancers such as the head and neck cancer. It starts about four weeks after initiation of radiotherapy. Almost 0.6 Gy/day extra dose of radiation is needed to compensate for this repopulation.[5] Such a dose increment is consistent with a four day clonogen doubling time, as compared to a median of sixty days for unperturbed growth. So the aim should be to complete the treatment as early as possible. In conventional fractionation regimen, radiotherapy is given five days a week, with two days gap. In this study the treatment is accelerated by giving an extra fraction of radiotherapy every week, thereby shortening the overall treatment duration. Thus we can exploit the benefits of shortening the total treatment duration by using the accelerated fractionation regimen to counteract the effect of accelerated repopulation of tumour cells at the expense of acceptable level of toxicities.

Study aimed to compare the loco-regional control rates between the accelerated fractionated and conventional fractionated radiotherapy and to compare the rate of acute and late toxicities between the two arms.

MATERIAL AND METHODS

After receiving ethical committee clearance, this study was conducted between February 2012 and February 2015. A total of sixty-six patients attending the Radiotherapy outpatient department were included in the study after signing of the consent form. Of these sixty-six patients thirty-three were included in the study arm (ARM-A) and the remaining thirty-

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three in the control arm (ARM-B). Patients were allotted alternately in either arm to avoid selection bias.

Patients with 1) locally advanced histologically proven squamous cell carcinoma of oropharynx, hypopharynx and larynx, 2) age between eighteen to seventy years and 3) ECOG (Eastern Cooperative Oncology Group) performance status of ≤ 2 were included in this study. Patients with 1) early stage glottis cancer, 2) history of surgery for the disease apart from biopsy, 3) history of previous chemotherapy or radiotherapy for head and neck cancer, 4) evidence of distant metastasis and 5) evidence of uncontrolled morbidities were excluded from the study.

Pretreatment evaluation included 1) physical examination, 2) indirect laryngoscopy, 3) direct laryngoscopy with biopsy for histopathological examination, 4) contrast enhanced computerised tomography scan of head and neck region and 5) chest X – Ray (Antero posterior and lateral view). Three patients complained of cough and contrast enhanced computerised tomography scan of thorax was done in those patients. But none had evidence of lung metastasis. Pretreatment dental, nutritional and swallowing evaluations were done in each patient. Apart from these, each patient was subjected to complete blood count, liver function test, kidney function test and thyroid profile. During treatment complete blood count, liver function test and kidney function test were repeated before each cycle of concurrent chemotherapy. Patients in the control arm (ARM-B) were treated by External Beam Radiotherapy with conventional 2 Gy/Fraction, five days a week for seven weeks upto a total dose of 66 – 70 Gy. Patients in the study arm (ARM-A) were treated with accelerated fractionated radiotherapy, 2 Gy/Fraction, six days a week for six weeks upto a same total dose of 66 – 70 Gy. Radiation treatment planning for each patient was done by Philips CT – Simulator (Brilliiance 16 slice) and ASHA Treatment Planning System. Radiation was delivered by Theratron 780C telecobalt unit. Inj. Cisplatin was concurrently administered at a dose of 100 mg/m^2 of body surface area every 3 weeks during radiation to all the patients. Radiation technique consisted of two parallel opposed radiation fields for the primary tumour and upper neck nodes. These two fields were matched with the low anterior neck field.

Patients in both the arms were followed up after six weeks of completion of treatment with physical examination, fiberoptic laryngoscopy and contrast enhanced computerised tomography scan of head and neck region to assess treatment response. Subsequently follow up was done every three months for the first year and then every four months during the second year. Fiberoptic evaluation was done during every visit. Contrast enhanced computerised tomography scan of head and neck region was done based on worrisome or equivocal signs and symptoms. Thyroid Stimulating Hormone (TSH) level was assessed every six months.

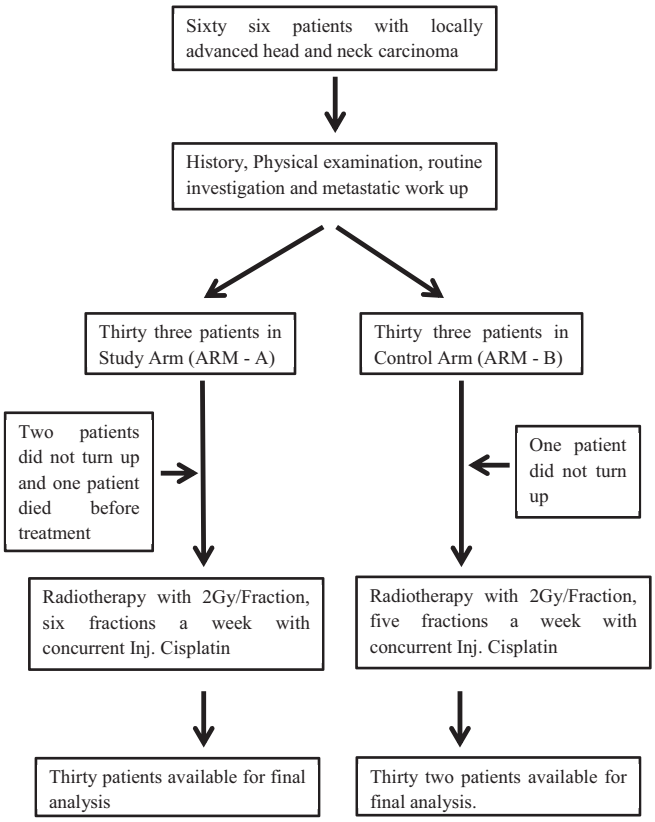
Statistical Analysis: Data analyses were done by SPSS software version 20.0. Response Rate and toxicity rates were compared by Chi-squared test. P-value < 0.05 were considered significant.

RESULTS

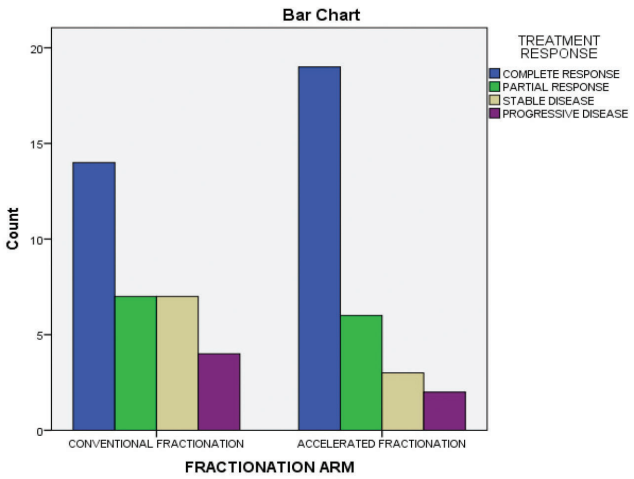
Two patients in the study arm (ARM-A) and one patient in the control arm (ARM-B) did not turn up for treatment. One patient in the study arm died at home before initiation of treatment due to food aspiration. So a total of thirty patients in the study arm (ARM-A) and thirty-two in the control arm (ARM-B) were available for final analysis. Pre-treatment patient profile is given in Table 1.

Post-treatment evaluation was done at six weeks after completion of treatment. Response assessment was done according to RECIST (Response Evaluation Criteria in Solid Tumors) Criteria version 1.1.

Although the complete response rate was numerically



Consort Diagram for the study



Bar Diagram-1: Response Rate

Serial no.	Characteristics	Study arm (ARM-A)	Control Arm (ARM-B)
1	Sex		
i	Male	27/30 (90%)	27/32 (84.38%)
ii	Female	3/30 (10%)	5/32 (15.62%)
2	Age Group		
i	≤ 50	6/30 (20%)	7/32 (21.88%)
ii	51 – 60	10/30 (33.33%)	11/32 (34.37%)
iii	61 – 70	14/30 (46.67%)	14/32 (43.75%)
	Median (in years)	53	57
3	ECOG Performance status		
i	2	7/30 (23.33%)	8/32 (25%)
ii	1	12/30 (40%)	11/32 (34.37%)
iii	0	11/30 (36.67%)	13/32 (40.63%)
4	Primary Site		
i	Oropharynx	10/30 (33.33%)	9/32 (28.13%)
ii	Hypopharynx	6/30 (20%)	8/32 (25%)
iii	Larynx	14/30 (46.67%)	15/32 (46.87%)
5	Stage		
i	III	16/30 (53.33%)	16/32 (50%)
ii	IVA	8/30 (26.67%)	9/32 (28.12%)
iii	IVB	6/30 (20%)	7/32 (21.88%)
6	Histological Grade		
i	Well Differentiated	10/30 (33.33%)	13/32 (40.62%)
ii	Moderately Differentiated	17/30 (56.67%)	15/32 (46.88%)
iii	Poorly Differentiated	3/30 (10%)	4/32 (12.5%)

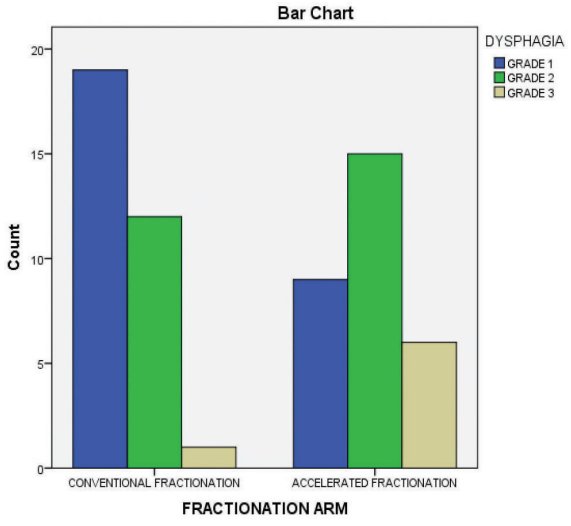
Table-1: Pretreatment Patient Profile

Response	Conventional Fractionation (Total no.= 32)	Accelerated Fractionation (Total no.= 30)	P value (Pearson Chi-square; asymp. Sig. 2 sided)
Complete response	14	19	0.386
Partial response	7	6	
Stable disease	7	3	
Progressive disease	4	2	

Table-2: Response Rate

	Conventional Fractionation (Total no.= 32)	Accelerated Fractionation (Total no.= 30)	P value (Pearson Chi-square; Exact Sig. 2 sided)
Response	21	25	0.15
No response	11	5	

Table-3: Overall Response rate



Bar Diagram-2: Dysphagia Rate

superior in the study arm (ARM-A), the difference did not reach the level of statistical significance. Response rate is given in Table 2 and Bar Diagram 1. Similar is the case with overall response rate (Complete Response + Partial Response). Overall response rate is given in Table 3.

Treatment related acute toxicities include radiation induced skin toxicity, oral mucositis and dysphagia. Grading was done by CTCAE (Common Terminology Criteria for Adverse Events) version 4.03. Grade wise distribution of acute toxicities is given in Table 4. Though the incidence rate of higher grades of skin toxicities and oral mucositis were more in the study arm, their differences were not statistically significant. Cases of skin toxicities and oral mucositis were treated conservatively and there was no treatment delay. Incidence of higher grades of dysphagia was more in the study arm and the difference was statistically significant *(P-value: – 0.024)* (Table 4, Bar Diagram 2). Patients with

Toxicities	Conventional Fractionation (Total no. = 32)	Accelerated Fractionation (Total no.= 30)	P value (Pearson Chi-square; asymp. Sig. 2 sided)
Mucositis			
Grade 1	18	8	0.064
Grade 2	8	12	
Grade 3	5	10	
Grade 4	1	0	
Grade 5	0	0	
Skin Toxicity			
Grade 1	18	12	0.406
Grade 2	11	13	
Grade 3	3	5	
Grade 4	0	0	
Grade 5	0	0	
Dysphagia			
Grade 1	19	9	0.024
Grade 2	12	15	
Grade 3	1	6	
Grade 4	0	0	
Grade 5	0	0	

Table-4: Acute Toxicities

Toxicities	Conventional Fractionation (Total no.= 32)	Accelerated Fractionation (Total no.= 30)	P value (Pearson Chi-square; asymp. Sig. 2 sided)
Xerostomia			
Grade 0	7	7	0.636
Grade 1	12	13	
Grade 2	13	9	
Grade 3	0	1	
Grade 4	0	0	
Grade 5	0	0	
Subcutaneous Fibrosis			
Grade 0	8	10	0.703
Grade 1	12	12	
Grade 2	9	7	
Grade 3	3	1	
Grade 4	0	0	
Grade 5	0	0	

Table-5: Late Toxicities

Grade 3 dysphagia were admitted in hospital for Ryle's Tube feeding and other supportive care. But there was no treatment breaks.

Late toxicities include xerostomia and subcutaneous fibrosis. Late toxicities were assessed by RTOG (Radiation Therapy Oncology Group) toxicity criteria. Incidence of xerostomia and subcutaneous fibrosis in both arms are given in Table 5. In case of both the toxicities there was no statistical difference between the two arms.

DISCUSSION

Several studies had been conducted for evaluating various radiotherapy fractionation schedules in Head and Neck cancer. MARCH meta-analysis published in 2006 by Bourhis et al.[6] analyzed fifteen trials with 6515 patients with locally advanced head and neck cancer. Patients treated with altered fractionation radiotherapy schedules showed significantly better overall survival and loco-regional control rates. Benefit was particularly more in the hyperfractionated arm (two fractions of radiotherapy per day) in comparison to accelerated fractionation with or without total radiotherapy dose reduction. Update of MARCH meta-analysis by Benjamin Lacas et al.[7] published in 2017 analysed thirty three trials with 11,423 patients with head and neck carcinoma. It showed significant benefit in overall survival in altered fractionation radiotherapy, particularly hyperfractionation radiotherapy as compared to conventional fractionation radiotherapy. Meta-analysis also analysed five trials with 986 patients. It showed significantly better overall survival in concurrent chemoradiation as compared to altered fractionation radiotherapy. Trial by Overgard et

al.[8] published in 2003 compared six fractions of radiotherapy per week versus five fractions of radiotherapy per week with total dose remaining the same. Of the 1476 patients with locally advanced Head and Neck cancer studied, 5 year loco regional control rate and disease specific survival rate were significantly better in the six fractions per week arm. Acute toxicities were more in the accelerated fractionation arm but they were transient. There was no difference in overall survival. Another study by Phuc Felix Nguyen-Tan et al.[9] analysed 743 patients with locally advanced head and neck cancer. They compared standard fractionation radiotherapy with accelerated fractionation radiotherapy (giving a second dose of radiotherapy for last twelve treatment days). Inj. Cisplatin was used in both arms as a radiosenstizer agent. There was no significant difference in overall survival, progression free survival and acute toxicities.

Similarly in this study the complete response rate was higher in the accelerated fractionation arm (19/30 vs 14/32). Overall response rate was also higher in the study arm (25/30 vs 21/32). But none of the difference reached statistical significance. Higher grades of acute toxicities were more in the study arm. But only dysphagia rate was significantly more in study arm as compared to the control arm (*P-value – 0.024*). Late toxicities were similar in both arms.

Drawbacks of the study

The sample size was small and that is why probably the response rate in the study arm though numerically superior to the control arm, was not statistically significant. Moreover telecobalt machine was used and not linear accelerators. This might be responsible for higher rates of some of the acute toxicities in the study arm.

CONCLUSION

Loco-regional control rates with accelerated fractionated radiotherapy in locally advanced head and neck cancers are encouraging. Larger studies with more modern technologies and longer follow up are required to assess the loco-regional control and survival as well as acute and late toxicities in patients treated with altered fractionation radiotherapy as compared with conventional fractionation radiotherapy

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