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A comparative and prospective study of two different radiation fractionation schedules with concurrent chemotherapy in locally advanced head-and-neck squamous cell carcinoma

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ABSTRACT

Background: Accelerated fractionation radiotherapy has radiobiological advantage of preventing accelerated tumor repopulation and logistic advantage of treating more patients than conventionally fractionated radiotherapy because of its relatively shorter treatment duration. **Aims and Objectives:** In this study, we compared accelerated fractionation with conventionally fractionated radiotherapy in terms of tumor response and acute toxicities for the treatment of locally advanced head-and-neck carcinomas. **Materials and Methods:** Patients with Stage III and IVA carcinoma of head-and-neck region were randomized into two groups. The study group patients received accelerated radiotherapy to a total dose of 66Gy in 33 fractions, 2Gy/fraction, 6 fractions/week over a time period of 5.5 weeks. Control group received conventionally fractionated radiotherapy to same total dose and fraction size but 5 fractions/week, over a time period of 6.5 weeks. Both groups received concurrent weekly Cisplatin. All patients were followed up weekly for treatment related acute toxicity during the treatment and then at every month for 6 months after completion of treatment.**Results:** About 26.6% patients of study arm achieved complete response in comparison to 25.6% of control arm, but the difference was not statistically significant (P=0.957). Although statistically not significant, higher grade of skin toxicity (60%vs.35%, P=0.179) and xerostomia (46% vs. 29%, P=0.155) was also numerically higher in accelerated fractionation. **Conclusion:** For locally advanced head-and-neck carcinoma, accelerated fractionation radiotherapy with concurrent chemotherapy can be considered as an acceptable and effective alternative of conventionally fractionated concurrent chemoradiotherapy in terms of treatment response and acute toxicity profile.

Key words: Head-and-neck carcinoma; Accelerated fractionation radiotherapy; Conventional fractionation

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INTRODUCTION

World-wide nearly 6.5 lakhs people develop head-and-neckcancer every year and there are 3.5 lakhs deaths from this disease. In India, cancers of lip and oral cavity constitute the second most common cancer (10.3%) according to GLOBOCAN 2020 data.[1,2]

The treatment options for patients presenting with locally advanced head-and-neck cancers are surgery followed by post-operative radiotherapy with/without concurrent chemotherapy or definitive concurrent chemoradiation with surgery reserved as a possible salvage option depending on the sub-site of primary disease.

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In radiation therapy, duration of treatment plays a major role, as it has been clinically and biologically proven that prolonging the overall treatment time will reduce the chances of tumor control as it is associated with the accelerated proliferation of tumor cells during treatment.[3] In conventionally fractionated regimen, cancer cells started to repopulate at about 28 days after the initiation of radiotherapy. For the head-and-neck cancers, the local tumor control is reduced by about 0.4–2.5% for each day of prolongation of the overall treatment time.

At the same time however, some recent clinical studies showed that shortening the overall treatment duration by accelerated fractionation with or without reducing the total dose improved local control and to some extent locoregional control and reduce the distant metastasis also.[4] Accelerated radiotherapy can be delivered by increasing the numbers of fractions per week, either by delivering radiation on 6 days/week instead of 5 days/week or by delivering two fractions more than 6 hours apart on the same day. Delivery of radiotherapy 6 days in a week is not much explored which is used in this study. Biologically effective dose of accelerated fractionation, that is, 66.9 is comparatively more than that of conventional fractionation, that is, 61.5 for tumor and early responding tissues. This regimen has the theoretical advantage that the treatment is completed before accelerated repopulation becomes a significant radiobiologic factor. Apart from the radiobiological advantage, accelerated fractionation has. In our resource limited set-up accelerated fractionation by shortening the overall treatment time, can increase the turnover of the machine leading to treatment of a greater number of patients, and reduce the waiting list of patients for treatment.

Aims and objectives

We conducted this study to compare the accelerated fractionation radiotherapy with conventionally fractionated radiotherapy treatment in terms of disease control and treatment-related acute toxicities.

MATERIALS AND METHODS

It was a double arm**,** single institutional, prospective, and comparative study in patients with Stage III and IVA carcinoma of head-and-neck region aged between18 and 70 years having adequate hepatic, renal, hematological parameters and an ECOG score of 0–2. Patients with recurrent carcinoma, previous history of any other malignancy or chemotherapy or radiotherapy were excluded. The study was conducted between January 2018 and April 2019.

Study technique

Patients were selected using above mentioned inclusion and exclusion criteria and randomized into two groups

Control arm

Patients in this group received conventionally fractionated radiotherapy to a total dose of 66 Gy in 33 fractions, single fraction per day, 2 Gy per fraction, 5 fractions/week, over a time period of 6.5 weeks (44days) with concurrent chemotherapy with weekly Cisplatin at a dose of 40 mg/m^2.

Study arm

Patients in this group received accelerated radiotherapy to a total dose of 66 Gy in 33 fractions, 2 Gy/fraction, 6 fractions/week over a time period of 5.5 weeks (37days) with concurrent weekly cisplatin at a dose of 40 mg/m^2.

Radiotherapy Technique

Patient position

Patients were positioned supine with neck extended and immobilized with the help of head rest.

Radiation portals

Bilateral parallel opposed fields with or without low anterior neck field were used for all patients and dose was prescribed at centre of interfield distance.

For lesions involving skin or tracheostomy tube stoma, bolus was used to increase the skin dose.

Radiotherapy was delivered by means of conventional 2D planning using "Theratron 780E" telecobalt machine.

Two-phase planning

Phase I: Total 44 Gy in 22 fractions.

Two lateral parallel opposed facio-cervical fields including the primary and draining lymph node groups were used to deliver EBRT in Phase I. A matched anterior neck field to treat the lower neck nodes with midline shielding to reduce dose to the larynx, pharynx, and spinal cord was used for some patients.

Phase II: Dose of 22 Gy in 11 fractions over 2 weeks in conventional fractionation given.

Two parallel opposed facio-cervical fields were used here also. However, here, the posterior border of the lateral facio-cervical fields was shifted from tip of mastoid process to tragus to spare the spinal cord (off cord) depending on clinical situation.

The conventional field borders were followed based on the standard surface markings and by landmarks as described

in Fletcher's text book of radiotherapy and Gunderson and tepper text book of clinical radiation oncology.[5,6]

Follow-up

Response assessment was done using RECIST1.1 after completion of treatment. All patients were followed up weekly for treatment related acute toxicity during the entire course of treatment and then at every month for 6 months for each patient after completion of treatment. Follow-up included proper history of complaints, clinical examination, CBC, LFT, and KFT parameters, and other necessary investigations as indicated including imaging.Treatment-related toxicities were assessed as per toxicity assessment tools-(Common terminology criteria for adverse events scale version 5.0) and with radiation therapy oncology group (RTOG) scoring. Patients developing Grade III or above toxicity were given treatment interruption and were managed as required.Patients with progressive disease were managed with chemotherapy or surgery as per requirement.

Approval for study was taken from the Institutional Ethics Committee.

There is no source of financial grant or other funding.

Statistical analysis

Data were analyzed and compared according to appropriate statistical tests using SPSS version 20 software and Microsoft word-excel. Data were summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Unpaired proportions were compared by Chi-square test or Fisher's exact test, as appropriate. Any $P<0.05$ will be considered statistically significant.

RESULTS

Demographic Characters

Both the arms of the study were comparable in terms of mean age of the patients, gender, primary site of disease, stage of disease at presentation, and performance status of the patients at the initiation of the study.

Tumor Response

About 26.6% patients of study arm achieved complete response in comparison to 25.6% of control arm. Overall treatment response (complete response+partial response) was numerically slightly higher in control arm (68% vs. 66%). However, results of both the arms were comparable statistically (P=0.970).

Assessment of treatment related toxicity

Skin toxicity of Grade 3 and above was numerically higher in accelerated fractionation schedule (study arm) than conventional fractionation (60%vs.35%). However, this difference was not statistically significant(P=0.179).

Incidence of high-grade acute mucositis (Grade 3 and Grade 4) was almost similar between the arms of study (20% vs.19.3%). In terms of acute mucosal toxicity, both the arms were comparable (P=0.999).

Although Grade 2 xerostomia was numerically higher in study arm (46%vs.29%), the difference was not statistically significant(P=0.155).

Grade1 hematological toxicity was higher in control arm (64% vs.50%). However, the proportion of patients with higher grade of toxicity was little higher in study group than that of control group (50% vs.35%).

Grade 2 and above pharyngeal and esophageal toxicity was higher in accelerated fractionated schedule than conventional fractionation arm (60% vs.41%) although the difference was statistically not significant (P=0.143).

DISCUSSION

In our resource-limited set-up with huge patient burden if accelerated fractionation provides same or better disease control with acceptable toxicities as that of conventional fractionation, then a greater number of patients can be treated in a short span of time leading to judicious use of available resources. In this study, we did a comparative analysis

Table 1: Comparison of baseline characteristics between two arms of study

Characteristics	Arm of the study		P-value
	Study arm (n=30)	Control arm (n=31)	
Mean age of patients (in years)	58.15	56.38	0.440
Gender			
Male	27	29	0.614
Female	03	02	
Total	30	31	
Primary site of disease			
Oropharynx	11	10	0.916
Hypopharynx	04	05	
Larynx	15	16	
Total	30	31	
Stage of disease at presentation			
III	13	13	0.912
IVA	17	18	
Total	30	31	
Performance status (ECOG score)			
1	17	20	0.530
2	13	11	
Total	30	31	

Table 2: Comparison of treatment response

Arm	Treatment response				Total	P-value
	Complete response	Partial response	Stable disease	Progressive disease		
Study	08	12	03	07	30	0.970
Control	08	13	04	06	31	
Total	16	25	07	13	61	

Table 3: Comparison of acute skin toxicity

Arm	Acute skin toxicity				Total	P-value
	Grade 1	Grade 2	Grade 3	Grade 4		
Study	05	07	13	05	30	0.179
Control	05	15	09	02	31	
Total	10	22	22	07	61	

between accelerated fractionation with concurrent cisplatin and conventional fractionation with concurrent cisplatin.

Newlin et al.,[7] conducted a study between 2000 and 2006 to know the outcome of altered fractionation radiotherapy with weekly Cisplatin (30mg/m^2/wk) in patients with head-and-neck squamous cell carcinoma. He found that it was safe and effective.[8]

The majority of our patients were in the range of 40–70 years age group with mean age of 54.5 years and 55.90 years in study and control arms, respectively. About 92% of study population was male which was in accordance with the gender-based incidence and prevalence of head-and-neck cancers.[1,2] Patients of both the arms were comparable in terms of stage at presentation, performance status (ECOG score), and primary site of disease (Table 1).

In our study, there was slightly better locoregional control seen in accelerated fractionation (study arm).Complete response for study and control arm was 26.6% and 25.6%, respectively. The partial response was 40% for study arm and 41.9% for control arm. Stable disease was 23.3% for study arm and 12.9% for control arm (Table 2).

RTOG0129 trial, DAHANCA 6 and 7 trial also showed improved locoregional control in accelerated fractionation arm when compared to conventional fractionation arm.[8-17] The study by Choudhury et al, showed no difference in the overall response rate between altered fractionation and conventional fractionation arms with manageable toxicity. Overall response was 75% in hyper-fractionation, 80% in accelerated fractionation, and 76% in conventional fractionation.[17]

In our study, the incidence of Grade 3 skin reactions was observed more in accelerated fractionation arm compared to conventional fractionation (43.3% vs.29.03% at week 6 of RT). There was a slight prolongation of time taken for repair among the patients of accelerated fractionation arm compared to conventional fractionation arm (Table 3).

Table 4: Comparison of xerostomia between two arms

Arm	Xerostomia		Total	P-value
	Grade 1	Grade 2		
Study	16	14	30	0.155
Control	22	09	31	
Total	38	23	61	

Incidence of Grade 3 or 4 oral mucositis was numerically higher in study arm (20%) compared to control arm (19%). Hematological toxicity of higher grade was also slightly higher in accelerated fractionation arm than conventional fractionation, but the difference was not statistically significant (P=0.154). Incidences of acute xerostomia and acute pharyngeal and esophageal toxicity were numerically higher in study arm although these differences were not statistically significant (Tables 4 and 5).

Overall, our study showed slightly improved complete response in study arm but, there was an increase in manageable acute toxicities without any significant increase in treatment interruption. Similar results were seen in study conducted by Bourhisetal.[18] In their study, LRC at 2 years was increased by 24% in accelerated arm and also the increase in toxicities by 55% in accelerated arm when compared to conventional arm. The results of DAHANCA 6 and 7 randomized and controlled trial and RTOG 0522 trial were similar with respect to acute toxicities.[9,19-21] Recently published study by Kumar et al., also reflected the similar outcome of improved local control but increased radiation induced acute toxicities for treatment with accelerated fractionation.[22] On the contrary,a recent meta-analysis of six trials evaluating 988 patients showed that accelerated fractionation has no significant benefit in terms of locoregional control but increased acute toxicities.[23]

Table 5: Comparison of acute pharyngeal and esophageal toxicity

Arm	Acute Pharyngeal and Esophageal Toxicity			Total	P-value
	Grade 1	Grade 2	Grade 3		
Study	12	13	05	30	0.143
Control	18	12	01	31	
Total	30	25	06	61	

Rades et al., also showed accelerated radiotherapy plus chemotherapy provided no significant benefit but increased toxicity compared to conventional radiochemotherapy.[24] Hence, at present, it is not clear whether to or not to consider accelerated fractionation as a better substitute of conventionally fractionated radiochemotherapy based on the disease control and toxicity profile. However, in terms of logistic reasons, it is always a preferable option than conventional regime. Thus, findings of these studies should be further explored by large randomized controlled trials with large sample size and long-term follow-up.

Limitations of the study

This study had its limitations also our sample size was small, so any statistical data have to be interpreted with caution. It was a single institutional study; hence, result derived can not be extrapolated on entire population. Entire study duration was about 15 months including patient accrual, intervention, and assessment. Hence, the late toxicity and the locoregional control and survival could not be assessed.

CONCLUSION

For locally advanced head-and-neck cancer patients, treated with radical intent, concurrent chemoradiation in the form of accelerated fractionation with weekly cisplatin can be considered as an acceptable alternative to conventionally fractionated concommitant chemoradiotherapy in terms of efficacy and toxicity. Treatment with accelerated fractionation will reduce the overall treatment time and the treatment cost leading to judicious and optimum use of limited resources in delivering treatment to maximum possible number of patients.

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REFERENCES

1. Dar MA and Sharma KK. Burden of cancer in India: GLOBOCAN 2018 estimates incidence, mortality, prevalence and future projections of cancer in India.2019;6(6):505-514. https://doi.org/10.1729/Journal.22750
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90. https://doi.org/10.3322/caac.20107n
3. Withers HR, Taylor JM and Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol. 1988;27(2):131-146. https://doi.org/10.3109/02841868809090333m
4. Nguyen LN and Ang KK. Radiotherapy for cancer of the head and neck: Altered fractionation regimens. Lancet Oncol. 2002;3: 693-701. https://doi.org/10.1016/s1470-2045(02)00906-3
5. Fletcher GH. Textbook of Radiotherapy. 3rd ed. London: Lea & Febiger 1991.
6. Gunderson LL and Tepper JE. Clinical Radiation Oncology. 4thed. Philadelphia: Elsevier; 2016.
7. Newlin HE, Amdur RJ, Riggs CE, Morris CG, Kirwan JM and Mendenhall WM. Concomitant weekly cisplatin and altered fractionation radiotherapy in locally advanced head and neck cancer. Cancer. 2010;116(19):4533-4540. https://doi.org/10.1002/cncr.25189
8. Nguyen-Tan PF, Zhang Q, Ang KK, Weber RS, Rosenthal DI, Soulieres D, et al. Randomized Phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the radiation therapy oncology group 0129 trial: Long-term report of efficacy and toxicity. J Clin Oncol. 2014;32(34):3858-3866. https://doi.org/10.1200/JCO.2014.55.3925
9. Overgaard J, Hansen HS, Grau C. The DAHANCA6 and 7 trial: A randomized multicenter study of 5 versus 6 fractions per week of conventional radiotherapy of squamous cell carcinoma (scc) of the head and neck. Radiother Oncol. 2000;56(S1):S4.
10. Wendt TG, Grabenbauer GG, Rodel CM, Thiel HJ, Aydin H, Rohloff R, et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: A randomized multicenter study. J Clin Oncol.1998;16(4):1318-1324. https://doi.org/10.1200/JCO.1998.16.4.1318
11. Brizel DM, Albers ME, Fisher SR, Scher RL, Richtsmeier WJ, Hars V, et al.Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med. 1998;338(25):1798-1804. https://doi.org/10.1056/NEJM199806183382503
12. Dobrowsky W and Naude J. Continuous hyper fractionated accelerated radiotherapy with/without mitomycin C in head and neck cancers. Radiother Oncol. 2000;57(2):119-124. https://doi.org/10.1016/s0167-8140(00)00233-4
13. Staar S, Rudat V, Stuetzer H, Dietz A, Volling P, Schroeder M, et al. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy--results of a multicentric randomized German trial in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys.2001;50(5): 1161-1171. https://doi.org/10.1016/s0360-3016(01)01544-9
14. Budach W, Hehr T, Budach V, Belka C and Dietz K. A meta-analysis of hyperfractionated and accelerated radiotherapy

and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer. 2006;6:28.

https://doi.org/10.1186/1471-2407-6-28

15. Bernier J. Alteration of radiotherapy fractionation and concurrent chemotherapy: A new frontier in head and neck oncology? Nat Clin Pract Oncol.2005;2(6):305-314.

https://doi.org/10.1038/ncponc0201

16. Lyhne NM, Primdahl H, Kristensen CA, Andersen E, Johansen J, Andersen LJ, et al. The DAHANCA 6 randomized trial: Effect of 6 vs 5 weekly fractions of radiotherapy in patients with glottic squamous cell carcinoma. Radiother Oncol.2015;117(1):91-98.

https://doi.org/10.1016/j.radonc.2015.07.004

17. Choudhury KB, Sharma S, Maiti S, Roy C and Mallick C. A comparison of outcomes with Christie Regimen and pure accelerated radiotherapy versus conventional radiation in locally advanced squamous cell carcinoma of head and neck: A randomized controlled study. Clin Cancer Investig J. 2012;1(3):118-126.

https://doi.org/10.4103/2278-0513.102878

18. Bourhis J, Lapeyre M, Tortochaux J, Etessami A, Wibault P, Geoffrois L, et al. Preliminary results of the GORTEC 96-01 randomized trial, comparing very accelerated radiotherapy versus concomitant radio-chemotherapy for locally inoperable HNSCC. Int J Radiat Oncol Biol Phys. 2001;51(3):39.

https://doi.org/10.1016/S0360-3016(01)01893-4

19. Ang KK, Zhang Q, Rosenthal DI, Nguyen-Tan PF, Sherman EJ, Weber RS, et al. Randomized Phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for Stage III to IV head and neck carcinoma: RTOG 0522. J Clin Oncol. 2014;32(27):2940-2950.

https://doi.org/10.1200/JCO.2013.53.5633

20. Bourhis J, Sire C, Graff P, Grégoire V, Maingon P, Calais G, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): An open-label Phase3 randomised trial. Lancet Oncol. 2012;13(2):145-153.

https://doi.org/10.1016/S1470-2045(11)70346-1

21. Hliniak A, Gwiazdowska B and Szutkowski Z. Radiotherapy of the laryngeal cancer: The estimation of the therapeutic gain and the enhancement of toxicity by the one-week shortening of the treatment time. Results of the randomized Phase III multicenter trial. Radiother Oncol. 2000;56(S1):S5.

22. Suman MK, Pradeep G, Prabhat KS, Velmurugan K and Abhishek S. Comparison of conventional versus accelerated fractions of radiotherapy per week for squamous cell carcinoma of the head and neck. Canc Therapy Oncol Int J. 2020;17(4):555968.

23. Matuschek C, Haussmann J, Bölke E, Gripp S, Schuler PJ, Tamaskovics B, et al. Accelerated vs. conventionally fractionated adjuvant radiotherapy in high-risk head and neck cancer: A meta-analysis. Radiat Oncol. 2018;13(1):195.

https://doi.org/10.1186/s13014-018-1133-8

24. Rades D, Narvaez CA, Janssen S, Schröder U, Bruchhage KL, Hakim SG, et al. Accelerated fractionation plus chemotherapy versus conventionally fractionated radiochemotherapy for unresectable head-and-neck cancer. Anticancer Res. 2021;41(2):877-884.

https://doi.org/10.21873/anticanres.14840

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CR- Concept and design of the study and preparation of the first draft of manuscript; **LB**- Data collection and statistical analysis and reviewed the manuscript; **AR-**Concept and coordination and prepared the manuscript; **SS**-Literature review, interpretation of results, and reviewed the manuscript; **FK**- data collection and preparation of manuscript; and **SM**- did the literature review, intellectual contribution, and final editing of the manuscript.

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