DOI: 10.7860/JCDR/2019/41943.13151

Original Article

Oncology Section

A Prospective Randomised Study of Clinical Outcome and Toxicity Patterns of Head and Neck Squamous Cell Carcinoma Treated with Accelerated Fractionated Radiotherapy versus Concurrent Chemoradiotherapy

MADHUP RASTOGI[1], AJEET K GANDHI[2], BHARAT DUA[3], KUNDAN S CHUFAL[4], MADHU SRIVASTAVA[5], SUDHIR SINGH[6], RAJEEV GUPTA[7], MADANLAL B BHATT[8]

ABSTRACT

Introduction: Locally advanced Head and Neck Squamous Cell Carcinoma (HNSCC) is a diverse group of patients and the treatment needs to be individualised. Although Concurrent Chemoradiotherapy (CTRT) remains the standard of care, not all patients are suitable to receive the same. Accelerated Fractionated Radiotherapy (AFRT) is one of the treatment options in these patients and may achieve equivalent therapeutic ratio.

Aim: To compare outcomes of patients of HNSCC treated with concurrent CTRT versus AFRT in a prospective randomised trial.

Materials and Methods: A total of 322 patients of Stage III-IV (AJCC, 6th Edition), HNSCC of oropharynx, larynx and hypopharynx were randomised to receive either definitive CTRT or AFRT. Radiotherapy (RT) dose was 70 Gray (2 Gray, 5 fractions per week over 7 weeks) to the primary and nodes and 46-60 Gray to the elective neck nodes. RT was delivered 5 fractions per week along with concurrent cisplatin 35-40 mg/m^2 weekly in the CTRT arm. In the AFRT arm, RT was delivered as 6 fractions per week of 2 Gray each over 6 weeks. Acute and late toxicities were graded as per RTOG morbidity scoring. Kaplan Meier method was used for survival analysis.

Results: Patients characteristics were balanced between CTRT arm and AFRT arm (161 patients each). Median overall treatment time for CTRT and AFRT arms were 43 and 49 days respectively. A 5-year actuarial locoregional control, disease-free survival and overall survival was 32% vs. 42%; 28% vs. 35% and 30% vs. 35% respectively for CTRT vs. AFRT arm. Need of Ryle's tube feeding (p=0.001), acute mucositis (p=0.015), late subcutaneous toxicity (p=0.05) and late xerostomia (p=0.042) rates were higher for CTRT arm.

Conclusion: AFRT was associated with comparable clinical outcome as compared to CTRT in patients of HNSCC, albeit with reduced acute and late toxicities.

Keywords: Cause of cancer, Chemotherapeutic agents, Head and neck neoplasm

INTRODUCTION

In India, head and neck cancers are the leading cause of cancer morbidity and mortality with an age adjusted incidence in males of 10.8 to 38.8 per 100,000 males and 6.4 to 14.9 per 100,000 females. One of the standards of care in the management of advanced HNSCC, is radiotherapy and chemotherapy used concurrently [1-3]. Although there is a benefit [3] obtained by these chemotherapeutic agents, the toxicity and cost of the total treatment have increased significantly.

Thus, despite encouraging clinical progress, there is still a clear need for further improvement of the therapeutic outcome in locally advanced HNSCC. Altered fractionation schedules have been one such area of intensive research. A variety of fractionation schedules including standard fractionation, hyper fractionation, accelerated fractionation and their variants have been used in radiotherapy of HNSCC [4-7]. Accelerated fractionation is based on the rationale that a reduction in Overall Treatment Time (OTT) decreases the opportunity for tumour cells to regenerate during treatment [8]. Nguyen LN and Ang KK, in their review article of fractionation for head and neck cancer, reviewed 18 trials of altered fractionations including over 6000 patients and gave a general conclusion which can contribute to improving the standard of care for patients with HNSCC that "a modest acceleration of radiotherapy by one week without total dose reduction or a break in the treatment, by giving six fractions of 2 Gray per week, consistently yields better locoregional control of head and neck carcinomas without much increase in late toxic effects" [9]. However, it was also concluded that the effect on survival remains to be determined from future follow-up data.

A promising report has come from the Danish group in a randomised controlled trial [10]. It has been concluded saying that the shortening of OTT by the increase of the weekly number of fractions is beneficial in patients with HNSCC. After the success of this trial, six-fractions-weekly regimen has become the standard treatment in Denmark. It seems that just by adding one more fraction of radiotherapy, weekly, better locoregional control can be achieved with marginal increase in toxicity.

At the time of conception of this trial no randomised trial had been reported comparing six fractions a week radiotherapy regimen with concurrent chemoradiotherapy in HNSCC. The hypothesis was that if the magnitude of benefit is equivocal between both these treatment regimens then six fractions a week regimen would be more cost-effective. Reducing treatment time by one week would not only have radiobiological impact on tumour control but also would be of great help to those poor patients who had to come from long distances and had to manage their stay during the period of radiotherapy treatment.

This was a non-inferiority study that aimed to compare six fractions a week radiotherapy regimen with concurrent chemoradiotherapy and to determine if accelerated fractionation can serve as an

acceptable substitute for the current standard; that is CTRT in locally advanced HNSCC.

MATERIALS AND METHODS

This is a prospective randomised controlled trial conducted at the Department of Radiation Oncology, King George's Medical University, Lucknow. 328 eligible patients were randomly assigned to five fractions per week of 2 Gray along with concurrent chemotherapy (CTRT Arm) or to six fractions per week of 2 Gray each (AFRT Arm) between March 2006 and March 2008. Randomization was done by computer generated random numbers after the patients met eligibility criteria. Eligible patients were biopsy proven HNSCC with sub-sites including glottic, supraglottic, oropharynx and hypopharynx (excluding nasopharynx and oral cavity), stage III to IV (AJCC 2002, 6th edition), age: 20-70 years, Karnofsky performance score more than or equal to 70, adequate bone marrow, hepatic, and renal functions, white blood cell count >3500/mm^3, hemoglobin >10g/dL, platelet count >100,000/mm^3, total bilirubin <1.5 mg/dL, liver transaminase <2 times upper limit of normal, serum creatinine <1.5 mg/dL. Criteria for ineligibility included severe concomitant illness such as uncontrolled cardiovascular disease, uncontrolled diabetes mellitus, uncontrolled psychological disorders, active infection, active synchronous cancer, prior radiotherapy or chemotherapy, history of other malignancies within the past 5 years except basal cell carcinoma and squamous cell carcinoma in-situ of the skin and cervical cancer in-situ and patients who are pregnant or lactating. Patients underwent a full clinical examination before treatment, together with recording of histopathology and differentiation of the primary tumour, Tumour, Node, Metastasis (TNM) classification; assessment of the localization and the size of the primary tumour and regional lymph-node metastases by either clinical examination, endoscopy, radiography, CT scan, assessment of performance status according to WHO criteria; and chest radiograph.

Of 328 recruited patients, six patients were found to be ineligible and were excluded from the study.

The trial was done in accordance with the Declaration of Helsinki and approved by Institutional Ethical Committee [Ref No. 13 (8127-A)/2006]. Informed consent was obtained from all participants.

Radiotherapy Procedures

Patients were treated with external radiotherapy given with either a linear accelerator or Cobalt-60 Machine (Theratron, 780-C) The treatment principles and dose specifications agreed with the guidelines given in the ICRU-50/62 report. The radiotherapy protocol was as described in the [Table/Fig-1]. The dose to primary tumour and neck nodes for both arms was as follows: primary tumour 70 Gray, neck nodes if N0: 46-60 Gray, node positive neck: 66-70 Gray, spinal cord Dmax <45-50 Gray. No planned neck dissection was done before or after radiation. CTRT arm received chemotherapy as Cisplatin 35-40 mg/m^2/week for a total of 7 cycles along with radiotherapy. In cases of residual tumour, recurrence, or progression of the disease, salvage surgery was done, or palliative treatment given, depending on the status of the individual patient, symptoms, and previous treatment.

STATISTICAL ANALYSIS AND END POINTS

Assuming a hazard ratio of 0.652 in favour of control group and assuming alpha=0.05, power of the study (probability of correctly detecting the real effect) as 80%, 286 patients had to be recruited (assuming equal allocation, 143 in each arm). Also, with the assumption of attrition rate of 10-15%, the sample size to be recruited had to be between 315-328. Hence, 322 patients were recruited 161 in each arm.

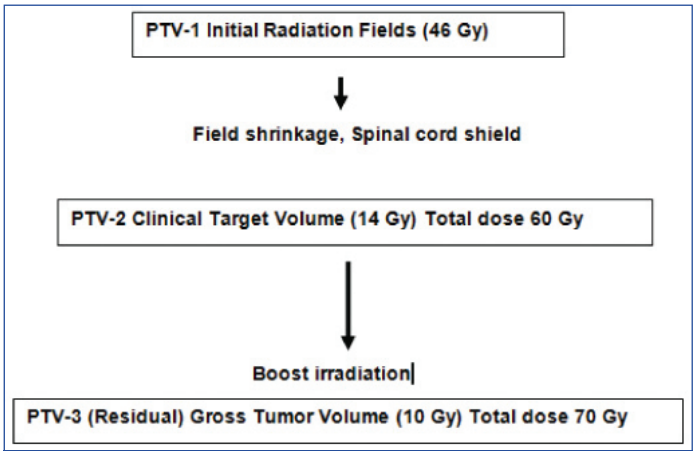
The primary end point was five-year Loco Regional Control (LRC) defined as complete and persistent disappearance of the disease in the primary tumour and regional lymph nodes after radiotherapy, not including salvage procedures. Secondary endpoints included disease specific survival (DFS), Overall Survival (OS), and early and late treatment-related morbidity and compliance rate. Acute and late radiation morbidities were graded as per Radiation Therapy Oncology Group (RTOG) morbidity scoring criteria [11-13]. Failure was recorded in the event of recurrence, or if the primary tumour never completely disappeared, in which case the tumour was then assumed to have failed at the time of randomization. All time estimates were calculated using the date of randomization as the initial value. We planned to follow-up patients for at least 5 years or until death.

The actuarial values of the endpoints were assessed by the Kaplan-Meier product-limit method using the SPSS (version 17.0). The p-values estimated were for a two-tailed test, and the significance level was set at 5%.

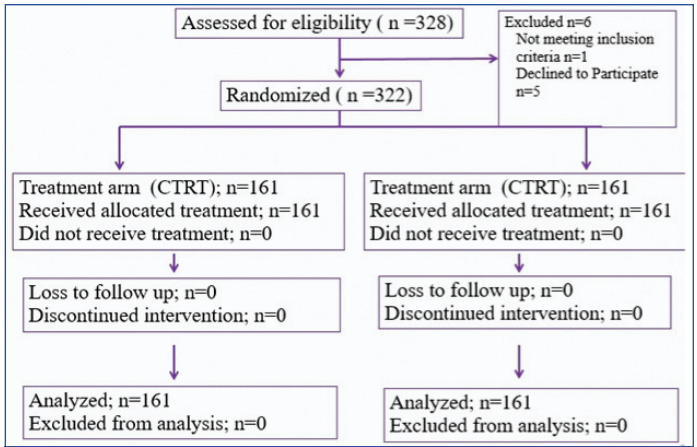
RESULTS

Between March 2006 and March 2008, 328 patients were recruited and randomly assigned to treatment. Out of these, six patients were found to be ineligible and were excluded from the study [Table/Fig-2]. The baseline characteristics of the 322 evaluable patients are shown in [Table/Fig-3]. There were 292 men and 30 women, with a median age at Randomisation of 52 years (range 30-77 years); there were no significant differences in terms of tumour characteristics between the groups. Compliance with radiotherapy was good in both treatment groups, with (90%) patients assigned to receive CTRT and (95%) of those assigned to receive AFRT completing planned radiotherapy as per protocol.

Median OTT was 43 days for the AFRT arm and 49 days for the CTRT arm. At the time of final assessment, after a mean follow-up since



[Table/Fig-1]: Radiotherapy protocol of the study.



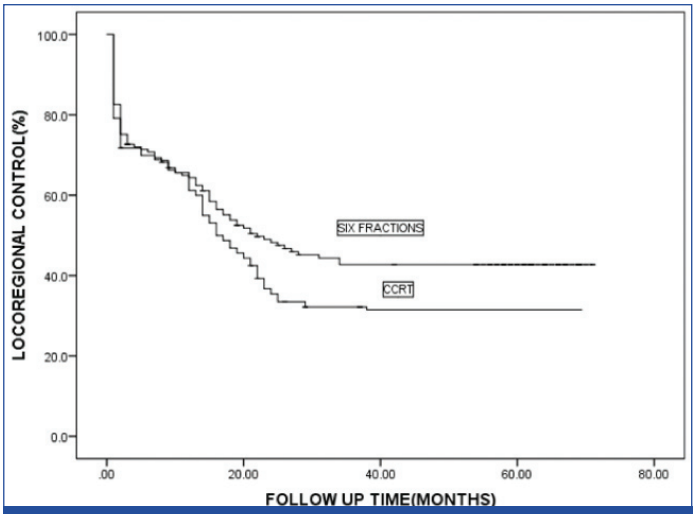
[Table/Fig-2]: Trial profile according to CONSORT recommendations.

Variables	Five fractions per week and concurrent chemotheraphy (N=161)	Six fractions per week (N=161)
Age (years)		
<55	119	88
55-56	33	49
>65	9	24
Sex		
Male	145	147
Female	16	14
WHO PS		
<70	21	12
70-80	79	115
>80	61	34
Site		
Oropharynx	74	75
Larynxor hypopharynx	87	86
T stage		
T1-T2	11	12
T3-T4	150	149
Nodal status		
Negative	48	47
positive	113	114
Stage		
Stage 3	38	21
Stage 4	123	140
Differentition		
Well	55	56
Moderate	46	44
Poor	60	61

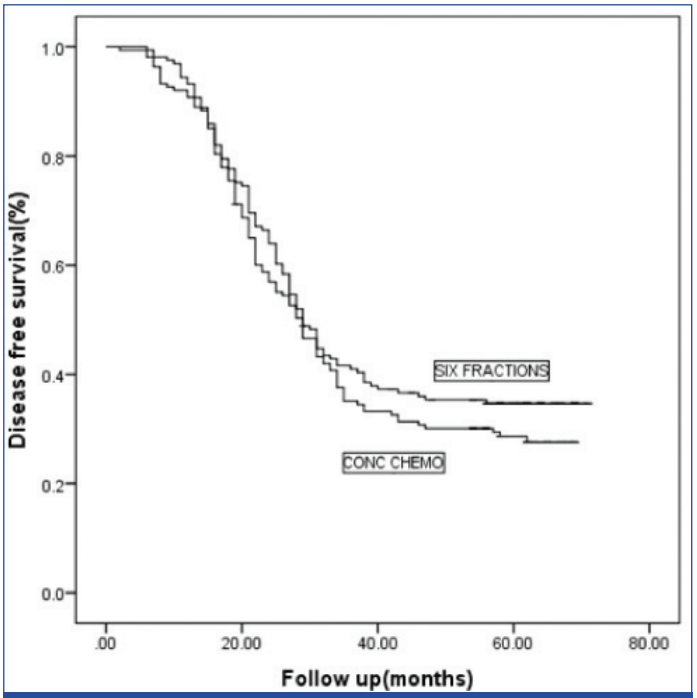
[Table/Fig-3]: Baseline characteristics of patients according to treatment group.

Randomisation of 35 months (range 6-71 months), 198 patients had failed to achieve persistent locoregional control after primary irradiation. 169 patients died from HNSCC, with 171 deaths overall. At 5 years, the actuarial rate of locoregional control [Table/Fig-4] was slightly worse for patients in the CTRT group than for those in the AFRT group (32% vs. 42% at 5 years), this difference was of borderline statistically significant; (p=0.071). At 5 years, the actuarial rate of DFS [Table/Fig-5] was 28% for those patients in the CTRT group versus 35% for those in the AFRT group with this difference not statistically significant (p=0.282). The OS [Table/Fig-6] was 30% for those in the CTRT group versus 35% for those in the accelerated group (p=0.388).

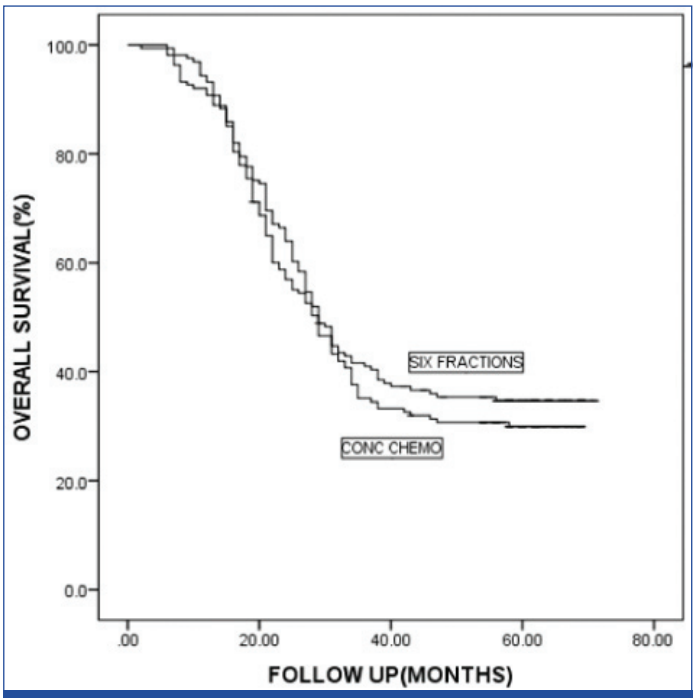
Regarding the acute toxicity analysis, while Grade II mucositis was more common in the AFRT arm, confluent mucositis was more common in the CTRT arm and these differences were statistically significant. The more frequent severe mucosal reactions in the CTRT group resulted in a significantly increased incidence of Ryle's tube placement during treatment compared with the AFRT group with a longer median duration of placement. Acute severe skin reactions were not significantly different in the AFRT arm than in the CTRT arm [Table/Fig-7]. However, with regards to the late reactions, there was a trend to significance for both Grade 3 skin as well as subcutaneous toxicity in the AFRT arm whereas the increased incidence of Grade 3 reactions in the CTRT arm did not translate into more severe late mucosal sequelae. The present authors also found that the incidence of late Grade 2-3 xerostomia was more in the CTRT arm [Table/Fig-8].



[Table/Fig-4]: Kaplan Meier analysis of locoregional control for two arms.



[Table/Fig-5]: Kaplan Meier analysis of disease-free survival for two arms.



[Table/Fig-6]: Kaplan Meier analysis of overall survival for two arms.

Variables	AFRT arm	CCRT arm	p-value
Ryle's tube			
Required	17	62	0.001
Not required	124	80	
Required but			
Refused	20	19	
Skin toxicity			
Grade 1	26	15	0.315
Grade 2	99	108	
Grade 3	35	39	
Grade 4	1	1	
Mucositis			
Grade 1	4	8	0.015
Grade 2	122	100	
Grade 3	34	55	
Duration of Ryle's tube (days)	45	50	0.001

[Table/Fig-7]: Acute radiation morbidity between treatment arms.

Variable	CCRT	Six fractions	p-value
Skin toxicity			
Grade 1	41	41	0.053
Grade 2	112	96	
Grade 3	5	16	
Grade 4	5	8	
Mucositis			
Grade 1	92	90	0.968
Grade 2	60	61	
Grade 3	11	10	
Subcutaneous toxicity			
Grade 1	38	34	0.051
Grade 2	115	102	
Grade 3	10	24	
Grade 4	0	1	
Salivary			
Grade 1	5	16	0.042
Grade 2	94	88	
Grade 3	64	57	

[Table/Fig-8]: Late radiation-related morbidity by fractionation schedule.

DISCUSSION

The benefit for CTRT vis-à-vis radiotherapy alone has been demonstrated in several meta-analyses [14]. Altered fractionation is another treatment approach that has improved the poor results of conventional radiotherapy in this group of patients especially hyper-fractionation and accelerated radiotherapy. The Meta-analysis of Radiotherapy in Carcinoma of Head and Neck (MARCH), of more than 6500 HNSCC patients, has confirmed a survival benefit of altered fractionation [15]. In the MARCH analysis, altered fractionated demonstrated a 23% reduction in local failure, at five years, as well as a benefit in LRC (13% reduction in the risk at five years). The present study was a randomised comparison of the efficacy and toxicity of the two regimens; the DAHANCA protocol [10] of AFRT given as 6 fractions a week and the current standard in head and neck cancer of CTRT.

The 5-year OS and LRC of present patient cohort was 32% and 37% respectively. This agrees with international data which puts the OS of locally advanced HNSCC between 30-50% [16-24]. The predominance of T4 patients (73%) and Stage 4 patients in the study (82%) might explain the present survival results being at the lower end of this spectrum.

The predominant pattern of failure in patients in the present study was locoregional with nearly 40% of the patients developing a local or a regional recurrence or both with only 8% developing distant metastasis. This is in accordance with published data which show locoregional as being the predominant mechanism of failure in these patients [14-24]. The rate of distant metastasis is also within the range of 5-10% cited by most studies. Owing to this, there was a strong correlation between the locoregional control and disease specific survival and as such both were similar for the two trial arms. Of note, while the number of local or regional recurrences were similar in the two arms (34 vs. 33), the number of distant metastasis were three times in the accelerated arm than in the concurrent chemoradiation arm (20 vs. 6) and this difference was statistically significant (p=0.004). This, however, did not impact the overall survival and there are perhaps certain implications of this observation. It is debated whether weekly concurrent chemotherapy impacts distant metastasis at all [14,25,26], and if so, is it by impacting locoregional failure or by acting on micro-metastatic disease or both. The available data is controversial regarding equivalent efficacy even if provided a certain cumulative dose of weekly cisplatin is given with varying toxicity results [27,28], However, weekly cisplatin continues to be used in most Indian institutions as the preferred regimen [29]. Based on the present study results, while the locoregional control was similar for the two arms, the rate of distant metastasis was not, implying that the latter mechanism may be the reason for these findings. However, it must be noted that the nodal failures were slightly higher in the altered fractionation arm and although not statistically significant, nodal metastasis is often a harbinger of distant metastasis.

Compliance with radiotherapy was good overall but was different in both treatment groups, with 95% (153/161) patients assigned to receive six fractions and 147/163 (91%) of those assigned to receive five fractions receiving their planned radiotherapy dose. Although this difference was not statistically significant, the present authors do acknowledge that it could have impacted our results and led to inferior outcomes for the CTRT arm. The compliance rates were much better than the TMH trial [18] (82%) and almost as good as the DAHANCA trial [10] (98%). This might be the reason for the positive results of the DAHANCA trial vis a vis the negative results of the TMH trial.

The median OTT in accelerated RT arm was 43 days (37-78) and in the chemoradiation arm was 49 days (41-65). The treatment time in the accelerated arm compares well with the RTOG trial [22], the IAEA-ACC trial [23] and is slightly higher vis a vis the DAHANCA trial [10]. The reduction in OTT by 1-week improved LRC (70 vs. 60%), DFS (73% vs. 66%) but not OS in the DAHANCA-7 trial. The lack of improvement in overall survival is not a sine qua non of efficacy as the poor general condition of these patients often leads to them having competing causes of mortality [24].

Looking at the present toxicity results, while acute grade II mucositis was more common in the accelerated arm, confluent mucositis was more common in the CTRT arm and these differences were statistically significant. The overall rate of Grade 3 mucosal reactions in the six fractions arm (21%) and CTRT arm (35%) were well within the rates of 28-77% reported by most investigators [10,16-23]. The increased incidence of Grade 3 mucosal reactions in our chemoradiation cohort is in accordance with other studies that have used the same accelerated schedule [18,19]. There was an increased incidence of Grade 2-3 xerostomia in the chemoradiation arm in our trial as well as the above-mentioned studies and while these differences were not statistically significant, they concur with the meta-analysis [22] that suggests that AFRT reduces late xerostomia vis a vis CTRT. Interestingly, while the acute skin toxicity was not significantly different between the two arms there was a trend for worse late skin Grade 3 toxicity in the altered fractionation arm. One possible reason for this could be that the acute reactions

in this arm showed delayed healing vis a vis the CTRT arm. Although such reactions have not been seen in other recent trials of AFRT [10,18,23], the incidence of such reactions is multifactorial [30-32] and will be investigated further.

We did not do HPV testing for our oropharyngeal cancer patients as this was not standard at the time the trial was conceived. The incidence rates of HPV in Indian patients is not known at present although single institutional studies exist and estimate the rate at about 22% in a predominantly north Indian population [33].

This is less than our western counterparts and although ours was a predominantly north Indian population, considering the present patient demographic with only 8% patients less than 40 and mostly heavy smokers and alcoholics we assume that the number would have been lower. HPV as a prognostic factor in the Indian context is still debatable [34]. Lastly, the impact of altered fractionation is not influenced by HPV positivity or negativity as has been shown by the RTOG 0129 trial [35].

Thus, while incorporation of altered fractionation in head and neck management paradigms as a substitute for CTRT is perhaps premature, is there perhaps a subgroup of patients that can be managed with altered fractionation alone at present? This is not a new concept and has been suggested by earlier authors [36,37] but is not widely followed in the oncology community. It is recommended that patients of unfavourable T2 or exophytic T3 with N0- N1 disease constitute an intermediate risk subgroup and should be considered for altered fractionation alone given that in these patients, it achieves a good balance of improving locoregional control and at the same time maintaining an acceptable toxicity profile. Even a stage based indirect comparison of the effects of chemoradiation reveals a greater benefit of CTRT in Stage 4 versus Stage 3 in the MACH NC metanalysis [14]. Finally, even the MARCH metanalysis [15] suggests that altered fractionation should be considered for N0-N1 disease with chemoradiation reserved for more advanced nodal disease. Thus, altered fractionation could be considered a good option for these patients particularly in the Indian subcontinent based on available evidence and our study.

The strengths of the present study were that it had a prospective randomised design, achieved its planned accrual, had a good sample size and had a median follow-up of 30 months.

LIMITATION

The limitations include non-usage of intensity modulated radiotherapy, lack of routine HPV testing and lack of quality of life assessment which would have allowed us to further define the magnitude or lack of benefit of AFRT over CTRT.

CONCLUSION

Accelerated Fractionated Radiotherapy yields comparable and descent clinical outcomes as compared to concurrent chemoradiotherapy in head and neck squamous cell carcinoma. This also has better tolerability and safety profile and would be particularly valuable in intermediate risk group (T2-T3, N0-1) patients.

REFERENCES

[1] Bachaud JM, Cohen-Honathan E, Alzieu C, David JM, Serrano E, Daly-Schveitzer N. Combined postoperative radiotherapy and weekly Cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. Int J Radiat Oncol Biol Phys. 1996;36:999-1004.

[2] Wendt TG, Grabenbauer GG, Rodel CM, Thiel HJ, Aydin H, Rohloff R, et al. Simultaneous radio chemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized multi center study. J Clin Oncol. 1988;16:1318-24.

[3] Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to loco regional treatment for head and neck squamous-cell carcinoma: Three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet. 2000;355:949-55.

[4] Withers HR. Biological basis for altered fractionation schemes. Cancer. 1985;55:2086-95.

[5] Ang KK. Altered fractionation trials in head and neck cancer. Semin Radiat Oncol. 1998;8:230-36.

[6] Horiot JC, Le Fur R, N'Guyen T, Chenal C, Schraub S, Alfonsi S, et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother Oncol. 1992;25:231-41.

[7] Horiot JC, Bontemps P, van den Bogaert W, Le Fur R, van den Weijngaert D, Bolla M, et al. Accelerated fractionation (AF) compared with conventional fractionation (CT) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. Radiother Oncol. 1997;44:11-121.

[8] Withers HR, Taylor JMG, Maciejewski B. The hazard of accelerated tumour clonogen repopulation during radiotherapy. Acta Oncol. 1988;27:131-46.

[9] Nguyen LN, Ang KK. Radiotherapy for cancer of the head and neck: altered fractionation regimens. Lancet Oncol. 2002;3:693-701.

[10] Overgaard J, Hansen HS, Specht L, Overgaard M, Grau C, Andersen E, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet. 2003;362:933-40.

[11] Trotti A, Byhardt R, Stetz J, Gwede C, Corn B, Fu K, et al. Common toxicity criteria: version 2.0. an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. Int J Radiat Oncol Biol Phys. 2000;47:13-47.

[12] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31:1341-46.

[13] WHO handbook for reporting results of cancer treatment. Geneva (Switzerland): World Health Organization Offset Publication No. 48;1979.

[14] Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACHNC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009;92:04-14.

[15] Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet. 2006;368:843-54.

[16] Fallai C, Bolner A, Signor M, Gava A, Franchin G, Ponticelli P, et al. Long-term results of conventional radiotherapy versus accelerated hyperfractionated radiotherapy versus concomitant radiotherapy and chemotherapy in locoregionally advanced carcinoma of the oropharynx. Tumouri. 2006;92:41e54.

[17] 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 phase 3 randomised trial. Lancet Oncol. 2012;13:145-53.

[18] Ghosh-Laskar S, Kalyani N, Gupta T, Budrukkar A, Murthy V, Sengar M, et al. Conventional radiotherapy versus concurrent chemoradiotherapy versus accelerated radiotherapy in locoregionally advanced carcinoma of head and neck: Results of a prospective randomized trial. Head Neck. 2016;38:202-07.

[19] Gupta M, Mahajan R, Kaushal V, Seem RK, Gupta M, Bhattacharyya T. Prospective randomized trial to compare accelerated (six fractions a week) radiotherapy against concurrent chemoradiotherapy (using conventional fractionation) in locally advanced head and neck cancers. J Cancer Res Ther. 2015;11:723-29.

[20] Chitapanarux I, Tharavichitkul E, Kamnerdsupaphon P, Pukanhapan N, Vongtama R, et al. Randomized phase III trial of concurrent chemoradiotherapy vs accelerated hyperfractionation radiotherapy in locally advanced head and neck cancer. J Radiat Res. 2013;54:1110-17.

[21] Rishi A, Ghoshal S, Verma R, Oinam AS, Patil VM, Mohinder R, et al. Comparison of concomitant boost radiotherapy against concurrent chemoradiation in locally advanced oropharyngeal cancers: a phase III randomized trial. Radiother Oncol. 2013;107:317-24.

[22] Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. J Clin Oncol. 2013;31:845-52.

[23] Beitler JJ, Zhang Q, Fu KK, Trotti A, Spencer SA, Jones CU, et al. Final results of local-regional control and late toxicity of RTOG 9003: a randomized trial of altered fractionation radiation for locally advanced head and neck cancer. Int J Radiat Oncol Biol Phys. 2014;89:13-20.

[24] Overgaard J, Mohanti BK, Begum N, Ali R, Agarwal JP, Kuddu M, et al. Five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study): a randomised, multicentre trial. Lancet Oncol. 2010;11:553-60.

[25] Bourhis J, Syz N, Overgaard J, Ang KK, Dische S, Horiot J, et al. Conventional vs modified fractionated radiotherapy: meta-analysis of radiotherapy in head and neck squamous cell carcinoma-a meta-analysis based on individual patient data. Int J Radiat Oncol Biol Phys. 2002;54 (suppl 0):71-72.

[26] Fayette J, Molin Y, Lavergne E, Montbarbon X, Racadot S, Poupart M, et al. Radiotherapy potentiation with weekly cisplatin compared to standard every 3 weeks cisplatin chemotherapy for locoregionally advanced head and neck squamous cell carcinoma. Drug Des Devel Ther. 2015;9:6203-10.

[27] Brizel DM, Esclamado R. Concurrent chemoradiotherapy for locally advanced, nonmetastatic, squamous carcinoma of the head and neck: consensus, controversy, and conundrum. J Clin Oncol. 2006;24:2612-17.

[28] Negi P, Kingsley PA, Srivastava H, Sharma SK. Three weekly versus weekly cisplatin as radiosensitizer in head and neck cancer: a decision dilemma. Asian Pac J Cancer Prev. 2016;17:1617-23.

[29] Rawat S, Srivastava H, Ahlawat P, Pal M, Gupta G, Chauhan D, et al. Weekly versus Three-Weekly Cisplatin-based Concurrent Chemoradiotherapy as definitive treatment in Head and Neck Cancer- Where do we stand? Gulf J Oncolog. 2016;1:06-11.
[30] Gupta T, Agarwal JP, Ghosh-Laskar S, Parikh PM, D'Cruz AK, Dinshaw KA. Radical radiotherapy with concurrent weekly cisplatin in loco-regionally advanced squamous cell carcinoma of the head and neck: a single-institution experience. Head Neck Oncol. 2009;1:17.
[31] Denham JW, Peters LJ, Johansen J, Poulsen M, Lamb DS, Hindley A, et al. Do acute mucosal reactions lead to consequential late reactions in patients with head and neck cancer? Radiother Oncol. 1999;52:157-64.
[32] Gupta T, Kannan S, Ghosh-Laskar S, Agarwal JP. Systematic review and meta-analysis of conventionally fractionated concurrent chemoradiotherapy versus altered fractionation radiotherapy alone in the definitive management of locoregionally advanced head and neck squamous cell carcinoma. Clin Oncol (R Coll Radiol). 2016;28:50-61.
[33] Hezel M, von Usslar K, Kurzweg T, Lörincz BB, Knecht R. Endpoints and cutpoints in head and neck oncology trials: methodical background, challenges, current practice and perspectives. Eur Arch Otorhinolaryngol. 2016;273:837-44.
[34] Bahl A, Kumar P, Dar L, Mohanti BK, Sharma A, Thakar A, et al. Prevalence and trends of human papillomavirus in oropharyngeal cancer in a predominantly north Indian population. Head Neck. 2014;36:505-10.
[35] Laskar SG, Swain M. HPV positive oropharyngeal cancer and treatment deintensification: how pertinent is it? J Cancer Res Ther. 2015;11:06-09.
[36] 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;32:3858-66.
[37] Rosenthal DI, Ang KK. Altered radiation therapy fractionation, chemoradiation, and patient selection for the treatment of head and neck squamous carcinoma. Semin Radiat Oncol. 2004;14:153-66.

PARTICULARS OF CONTRIBUTORS:
1. Professor and Head, Department of Radiation Oncology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.
2. Assistant Professor, Department of Radiation Oncology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.
3. Consultant, Department of Radiation Oncology, Max Super Specialty, New Delhi, India.
4. Consultant, Department of Radiation Oncology, Rajeev Gandhi Cancer Institute, New Delhi, India.
5. Consultant (Retired), Department of Radiation Oncology, KGMU, Lucknow, Uttar Pradesh, India.
6. Associate Professor, Department of Radiation Oncology, KGMU, Lucknow, Uttar Pradesh, India.
7. Professor and Head, Department of Radiation Oncology, KGMU, Lucknow, Uttar Pradesh, India.
8. Vice Chancellor, Department of Radiation Oncology, KGMU, Lucknow, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Madhup Rastogi,
Professor and Head, Department of Radiation Oncology, Dr. Ram Manohar Lohia Institute of Medical Sciences,
Vibhuti Khand, Gomti Nagar, Lucknow, Uttar Pradesh, India.
E-mail: drmadhup1@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **May 10, 2019**
Date of Peer Review: **Jun 07, 2019**
Date of Acceptance: **Jul 17, 2019**
Date of Publishing: **Sep 01, 2019**