Original Article

Hyperfractionated concurrent chemoradiation against conventional concurrent chemoradiation in locally advanced head and neck carcinoma: a prospective randomised trial

Zarmina Alam, Mohsin Khan, Shahid Ali Siddiqui, Mohd Akram, Mohd Shadab Alam, M. A. Bilal Hussain

Department of Radiotherapy, JN Medical College, Aligarh, India

Contributions: (I) Conception and design: M Khan, SA Siddiqui, M Akram; (II) Administrative support: SA Siddiqui, M Akram; (III) Provision of study materials or patients: M Khan, Z Alam, MS Alam; (IV) Collection and assembly of data: Z Alam; (V) Data analysis and interpretation: Z Alam, M Khan, MAB Hussain; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Mohsin Khan. Department of Radiotherapy, JN Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh-202002, India. Email: mohsinkhan793@gmail.com.

Background: Concurrent chemoradiotherapy is the mainstay of treatment in locally advanced head and neck cancer (LAHNC). Several studies have shown better outcome with altered fractionation radiation schedules, especially with hyperfractionation (HF-RT). For the last few decades attempts are being done to combine altered fractionation regimens with concurrent chemotherapy to achieve higher therapeutic gain. This study was done to evaluate the efficacy and toxicity of hyperfractionated concurrent chemoradiation (HF-CRT) in comparison to conventional concurrent chemoradiotherapy (CF-CRT).

Methods: This was a prospective trial registered with Clinical Trials Registry-India (REF/2022/01/050552), randomizing LAHNC patients into control group (CF-CRT) (70 Gy/35 fractions/5 fractions per week, 2 Gy/fraction/day) or study group (HF-CRT) (81.6 Gy/68 fractions/10 fractions per week, 1.2 Gy/fraction, twice daily at 6 hours interval). Concurrent chemotherapy consisted of weekly cisplatin (40 mg/m^2). The primary and secondary endpoints were response to therapy and treatment-induced toxicities respectively.

Results: A total of 214 eligible patients were recruited: 106 patients in control group & 108 patients in study group. Median follow-up was 7 months. Median overall treatment time was 59 & 63 days in control & study groups respectively. Complete response rates at primary and nodal sites were statistically similar (64% *vs.* 74%; P=0.1 and 54% *vs.* 61%; P=0.3 for CF-CRT & HF-CRT respectively). For objective response rate (ORR) and late toxicity rate, again there was no significant difference between the two radiation protocols. However, HF-CRT was associated with significantly higher rate of severe acute mucositis.

Conclusions: Combining HF-RT with concurrent chemotherapy did not provide any significant gain in response rate, rather it was associated with higher acute toxicity, inconvenience and logistic issues giving CF-CRT a practical advantage over this protocol especially in resource-restrained settings.

Keywords: Cancer; concurrent; head and neck; hyperfractionation; radiation

Received: 11 September 2021; Accepted: 04 March 2022; Published: 30 March 2022.
doi: 10.21037/jxym-21-34
View this article at: https://dx.doi.org/10.21037/jxym-21-34

Introduction

Head & neck cancer (HNC) is a major oncologic burden in developing countries including India. About two-third of cases are diagnosed at a loco-regionally advanced stage (1). The prognosis of such patients is dismal and locoregional control (LRC) poses a major therapeutic challenge.

For unresectable tumors, radiotherapy (RT) is the mainstay of treatment, given in standard fractionation of 1.8–2 Gy/fraction for 5 days a week to a total of 70 Gy/35 fractions for 7 weeks (2). Historically, with standard radiation

these patients have a 5-year survival rate of 30–35% (3). The two possible ways which have been attempted in the last few years to improve the LRC and survival figures in locally advanced head and neck cancer (LAHNC) are firstly, combining conventional radiation with another modality of treatment i.e., chemotherapy and secondly, altered fractionation radiotherapy.

Numerous trials that combined chemotherapy and standard radiation showed significantly better loco-regional response and survival rates (4). Thereafter, a landmark meta-analysis with 63 trials and >10,000 patients compared locoregional radiation &chemotherapy (induction/concurrent/adjuvant) versus locoregional therapy alone. The study concluded that the addition of chemotherapy provided an absolute survival benefit of 4% at 5 years (P<0.0001) and concomitant chemotherapy was the one giving the highest benefit (5). Subsequently, for advanced tumors conventional concurrent chemoradiation (CF-CRT) became the standard of care.

With the better understanding of radiobiology in succeeding decades, altered fractionation came into practice. Fractionation schedules different from conventional regimen were developed thereby, modifying total dose and overall treatment time to achieve better therapeutic ratio. The two most 'tried and tested' altered fractionation regimens are hyperfractionation and accelerated fractionation.

Accelerated fractionation tackles the problem of tumor repopulation by delivering the same total dose in same dose fraction as conventional radiation in a shorter duration of 5–6 weeks instead of 7 weeks. On the other hand, hyperfractionation is the use of smaller than standard doses per fraction with two or three fractions delivered per day to achieve a higher biological effective dose to the tumor. Hyperfractionation regimen allows an increase in total dose to about 80 Gy without increase in long-term complications.

Altered fractionation radiotherapy has consistently been associated with an improvement in tumor response and/or survival rates (6,7). MARCH meta-analysis of 2006 which dealt with optimization of radiation fractionation showed a significant survival benefit with altered radiation therapy (3.4% at 5 years) (8). The benefit was greater with hyperfractionation (8% at 5 years) than accelerated fractionation (2% at 5 years). In GORTEC 99-02 three arm prospective randomised trial, patients were randomised to standard chemoradiation, accelerated chemoradiation or very accelerated radiation alone. Conventional chemoradiation was found to improve PFS compared with very accelerated radiation This study concluded that acceleration alone cannot completely compensate for the absence of chemotherapy (9). RTOG 90-03 trial updated report came in 2014 by Beitler *et al.* comparing altered fractionation schemes (accelerated fractionation, continuous and accelerated fractionation with split and hyperfractionation) with standard fractionation. The authors noted that at 5 years only hyperfractionated radiation was associated with an increase in locoregional control and OS without increase in late toxicity (10).

With these interesting results of concomitant chemotherapy and hyperfractionated RT (HF-RT) individually, combining the two appears promising and logical to us. This was also evaluated by Budach *et al.* who concluded that the addition of simultaneous chemotherapy to all radiation schedules resulted in an overall survival (OS) benefit of 12 months (P<0.0001) (11). The recent update of MACH-NC also confirms the benefit and superiority of the addition of concomitant CT for non-metastatic head and neck cancer (12).

With this background we conducted the present study with the aim to evaluate the efficacy and safety of combining HF-RT with concomitant chemotherapy and to compare it with the CF-CRT to address the question whether the addition of chemotherapy to the more biologically-sound HF-RT can provide some advantage over the present standard of care.

We present the following article in accordance with the CONSORT reporting checklist (available at https://jxym.amegroups.com/article/view/10.21037/jxym-21-34/rc).

Methods

Study design

It was a prospective randomized study conducted between November 2017 and October 2019 at a tertiary hospital in North India. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Ethical Committee (EC/NEW/INST/2020/904) and written informed consent was taken from all the patients.

Patient selection

Inclusion and exclusion criteria

Patients aged ≥18 years with histologically confirmed

squamous cell carcinoma (SqCC) of HNC region having unresectable and non-metastatic disease were included. Other inclusion criteria were Karnofsky performance status (KPS) of >70, adequate hematologic (Hb >10%, WBC >4,000/μL and platelets >100,000/μL), renal (serum creatinine <1.4 mg/dL) and hepatic (serum bilirubin <1 mg/dL) functions and no previous chemotherapy or radiation treatment. Patients with primary tumor in nasal cavity, paranasal sinuses, salivary gland and nasopharynx were excluded. Other exclusion criteria were history of any prior or concurrent cancer in the last 5 years, serious comorbidities and pregnant or lactating females.

Pre-treatment evaluation

After thorough history and complete physical examination (including indirect and direct laryngoscopy) all the patients underwent CT scan of face and neck (contrast enhanced), chest X-ray, routine blood investigations and dental examination.

Clinical staging was performed using AJCC 7th edition TNM classification.

Randomization

All the recruited patients were randomized in 1:1 ratio into the two treatment groups-control group (CF-CRT) and study group [hyperfractionated concurrent chemoradiation (HF-CRT)] by computer generated random table number. Treating doctors as well as patients were not masked to the treatment-group assignment.

Treatment

Radiotherapy protocol

Patients in the control group received conventional fractionation (CFRT) at 2 Gy/fraction/day, 5 days/week to 70 Gy/35 fractions/7 weeks and patients in the study group received hyperfractionation (HFRT) at 1.2 Gy/fraction, twice daily with a 6-hour interfraction interval, 5 days/week to 81.6 Gy/68 fractions/7 weeks. Radiation was given Monday to Friday, Saturday & Sunday being the rest days. All the patients were treated with 2D-RT technique on Cobalt-60 teletherapy unit (Theratron 780C).

After proper positioning and immobilisation field markings were done as per the clinical assessment of target volume. The target volume included the primary tumor and the draining cervical lymph nodes. The primary tumor and neck nodes were treated with two parallel opposed lateral fields to 44 Gy in CF-CRT and 50.4 Gy in HF-CRT, after which shrinking field technique was used to save the spinal cord up to the dose of 60 Gy in CF-CRT and 72 Gy in HF-CRT. Boost of 10 Gy in 5 fractions to the primary tumor and involved nodes was given after 60 Gy to a total dose of 70 Gy in 35 fractions in conventional RT group. Similarly, in hyperfractionated RT group a boost of 9.6 Gy in 8 fractions was given reaching to a total dose of 81.6 Gy in 68 fractions.

Chemotherapy

Patients in both the treatment groups received concomitant chemotherapy in the form of weekly cisplatin 40 mg/m^2 of body surface area.

Endpoints

The primary endpoint of the study was response to therapy and the secondary endpoints were acute and late treatment-induced toxicities.

Assessment

Response

Patients were evaluated for response to treatment 8 weeks after the completion of therapy by clinical and radiological examination using Response Evaluation Criteria In Solid Tumors (RECIST) criteria (13). Both the primary and nodal responses were evaluated separately.

Acute & late toxicities

During RT patients were evaluated weekly for acute radiation toxicities. Complete blood count and Renal function test were done on weekly basis prior to chemotherapy for hematological toxicities. Post treatment patients were followed monthly for 3 months, then two monthly for next 6 months, then 3–4 monthly after wards. Acute toxicities (within 90 days of start of radiation) were assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Late radiation toxicities (after 90 days from the start of treatment) were graded as per the Radiation Therapy Oncology Group (RTOG) scale (14).

Statistical analysis

The treatment-induced response was analyzed and compared in both the radiation groups. The frequency of acute and late toxicities was also compared. Data was

analyzed using Pearson's chi square test and Fisher's exact test. All the tests were performed using computer program SPSS, version 16.0. A P value of <0.05 was considered as statistically significant.

Results

A total of 214 patients were recruited in this study, control group having 106 patients and study group having 108 patients. Fourteen patients did not undergo complete treatment: 8 patients in control group [reasons: death (n=2), defaults for alternative treatment (n=2), unknown (n=4)] and 6 patients in study group [reasons: death (n=2), defaults due to treatment toxicity (n=2), unknown (n=2)]. One patient in each group died of treatment related complications while the other two deaths were because of non-tumor/treatment related causes. So, at the end of the treatment we had 98 patients in the CF-CRT group and 102 patients in the HF-CRT group who were evaluable for acute toxicities. A total of 178 patients out of these total 200 (89%) underwent response evaluation. The rest 22 patients had a small follow up period and were not assessed for response to treatment. For late toxicity assessment we had 162 patients with a follow up period of 3 months or more (80 patients in CF-CRT group and 82 patients in HF-CRT group) (*Figure 1*).

Patient, tumor and treatment characteristics (Table 1)

Age of the patients ranged between 28–75 years in the control group and 30–70 years in the study group. Majority of the patients (57%) were in the age group of 41–60 yrs and the median age was 54 years in both the groups. Most of the patients (>90%) were male in both the radiation groups. Most common anatomic site was oropharynx (>40%) followed by oral cavity (>30%) in each group. Base of tongue was the most frequent subsite involved in oropharynx. In both the RT groups the most frequent tumor and nodal stages were T_4 (>40%) and N_2 (>50%) respectively. Stage IV was the most common overall clinical stage (74% & 68% in control and study groups respectively). There was no significant difference between the two groups in terms of pre-treatment patient and tumor characteristics.

Treatment compliance

Around 60% of the patients in each group completed their radiation schedule without any delay. The mean overall treatment time was 59 days in the control group and 63 days in the study group. The most common reasons for radiation interruption were treatment toxicity and family/personal issues. Regarding concurrent chemotherapy, majority of the patients (64% in conventional RT group *vs.* 68% in HF-CRT group) received ≥6 cycles. Interruptions in the chemotherapy cycles were mainly due to hematological toxicity, infection, RT toxicity and poor compliance.

Response to treatment (Table 2)

Response to the two treatment schedules were the primary end-point of this study. The objective response rates (ORR) for CF-CRT versus HF-CRT were 93% versus 95% (P=0.6). There was no statistically significant difference between the two groups with regard to complete response (CR) at primary site (P=0.1) or nodal site (P=0.3) or combined local and regional sites (P=0.8) though an absolute gain of 10% & 7% in CR rate was achieved with HF-CRT at primary and nodal sites respectively.

Acute toxicity (Table 3)

Acute toxicities were comparable between the two groups except for mucositis. Severe mucosal toxicity (grade 3 & 4) rate was significantly higher in HF-CRT group (33%) than CF-CRT (16%) (P=0.005). Among hematological toxicities, leucopenia was the most frequent, largely of grades 1 & 2. Only a small fraction of population presented with grade 3 leucopenia.

Late toxicity (Table 4)

Majority of the patients had grade 1 or 2 late toxicities of mucosa, skin, subcutaneous tissue, salivary gland, pharynx and larynx. None of the patients presented with grade 4 toxicity. No significant difference was found between the two RT schedules for late adverse events.

Discussion

Cure of LAHNC is challenging. Radiation therapy is the mainstay of treatment in advanced stage, providing both eradication of disease as well as organ preservation. But with conventional radiotherapy only, the rate of locoregional control is low (15). Repopulation of tumor cells during treatment, tumor hypoxia and resistance to radiotherapy have all been implicated as causes of treatment failure after

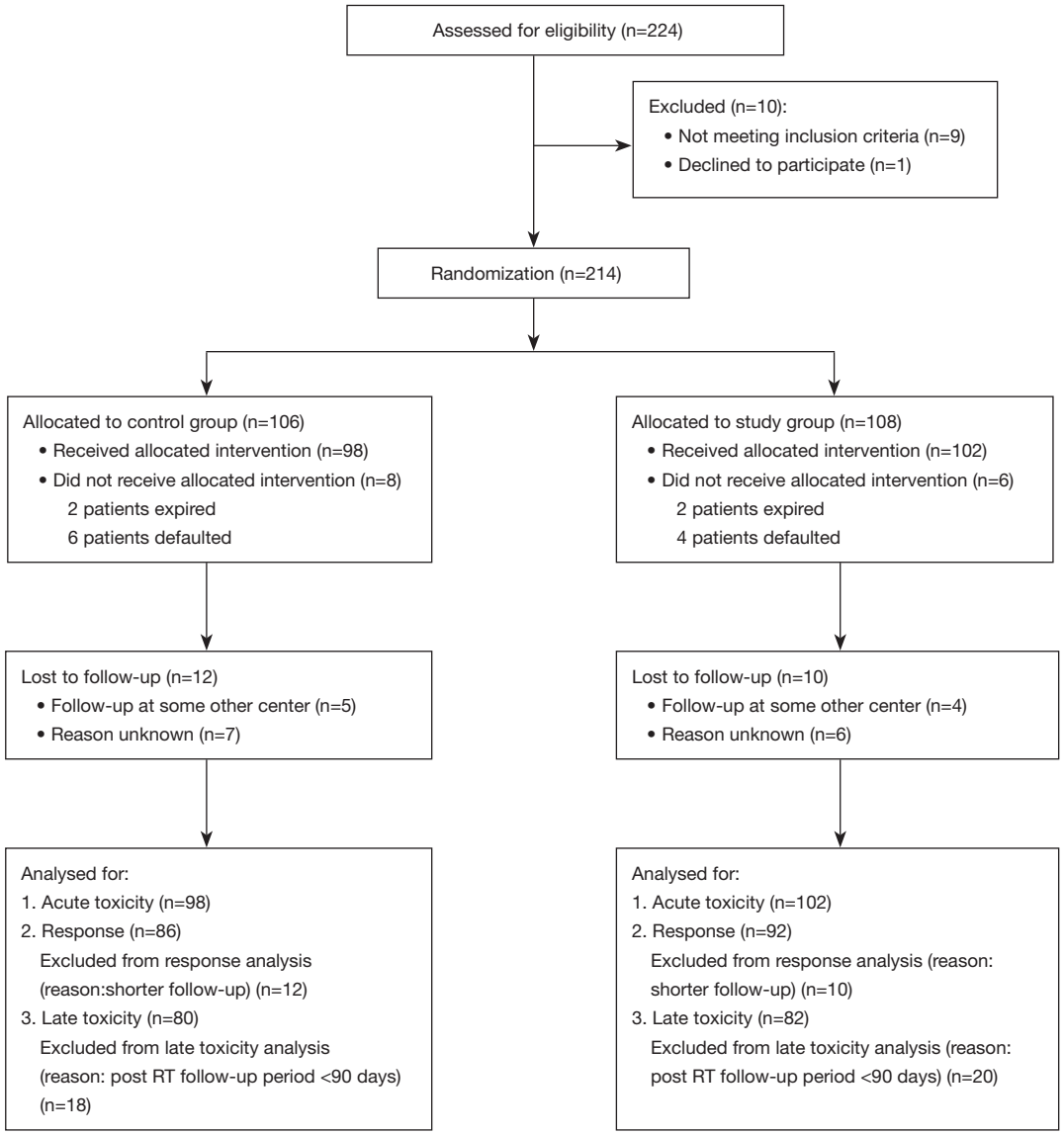

Figure 1 Consort flow diagram.

primary radiotherapy (16-18).

Several studies and meta-analysis have reported superior locoregional control and survival rates with concurrent chemotherapy along with conventional radiation as compared to radiation alone particularly when chemotherapy includes cisplatin or analogues (12,19). Chemotherapy when given concurrently with radiation, not only eradicates systemic microscopic disease but also simultaneously enhances the cytotoxicity of radiation.

Another novel approach to improve the outcome is intensification of radiation delivery. Repopulation of tumor clonogen starts around the 4th week of radiotherapy and to combat this, 60 cGy of extra dose per day is needed (20). Hyperfractionation is employed to escalate the total dose by giving multiple small fractions each day with no increase in long-term toxicity. Another regimen of altered fractionation RT is accelerated fractionation which was investigated to shorten the overall treatment time for the same total dose to reduce the risk of tumor repopulation. Evidence has shown that these altered fractionation regimens can convincingly improve the outcome in LAHNC and the highest benefit has been seen with hyperfractionation (7).

CF-CRT and altered fractionation radiotherapy strategies independently improve outcomes for patients

Table 1 Patient, tumour and treatment characteristics

Patient characteristics	Subgroup	Control group (n=106)	Study group (n=108)	P value
Age (years)	Median	54	54	
	Range	28–75	30–70	
Sex	Male	96 (91%)	100 (93%)	0.5
	Female	10 (9%)	08 (7%)	
Primary site	Oral cavity	36 (34%)	34 (32%)	0.3
	Oropharynx	44 (41%)	56 (52%)	
	Hypopharynx	4 (4%)	2 (1%)	
	Larynx	22 (21%)	16 (15%)	
T stage	T1	4 (4%)	1 (1%)	0.08
	T2	10 (9%)	22 (20%)	
	T3	42 (40%)	38 (35%)	
	T4	50 (47%)	47 (44%)	
N stage	N0	32 (30%)	28 (26%)	0.3
	N1	14 (13%)	22 (20%)	
	N2	60 (57%)	58 (54%)	
Stage grouping	III	28 (26%)	34 (32%)	0.4
	IV	78 (74%)	74 (68%)	
Total dose of radiation (Gy)		70	81.6	
Biologic effective dose$_{(tumor)}$ (Gy)		70	79.39	
Number of radiation fractions each day		1	2	
Mean overall treatment time		59 days	63 days	

Percentage of patients is shown in the brackets. n, number of patients; T, tumor stage; N, nodal stage; Gy, gray.

with HNSCC. In the last few years attempts have been done to combine altered fractionation with concomitant chemotherapy to have better therapeutic ratio.

In our study we also tried to investigate the efficacy of combination of HF-RT and concurrent chemotherapy along with its toxicity profile and feasibility. The question we proposed to address was whether the combination of these two can improve the therapeutic outcome without undue toxicity. For this we compared the results of HF-CRT against CF-CRT in terms of treatment response and acute & late toxicities.

Our pre-treatment patient and tumor characteristics matched with the reports of other studies like conducted by Karasawa *et al.* In their study 90% of patients were male, most common primary site was oropharynx (36%) and most common stage was stage IV (61%) though median age of patients was higher, 66 years (range, 32–82 years) (21). Similar patient characteristics were also seen in the study by Jeremic *et al.* (22).

In our study majority of the patients completed their planned treatment schedule within the expected time period (70% patients in control group & 68% patients in the study group). In the study by Jeremic *et al.* treatment interruptions occurred in 8% patients of CF-CRT group (range, 5–11 days) & 11% patients of HF-CRT group (range, 7–14 days) (22). In our CF-CRT group, none of the patients had a treatment delay of >3 weeks while 3 patients of HF-CRT completed their therapy with a delay of 4 weeks or more, reasons being, severe acute mucosal toxicity (in 2 patients) and family issues (in 1 patient). So, compared to CF-CRT, HF-CRT had an increased mean overall treatment time (59 *vs.* 63 days respectively). In the RTOG

Table 2 Response assessment

Variable	Clinical response	CF-CRT (n=86)	HF-CRT (n=92)	P value
Primary site	CR	55 (64%)	68 (74%)	0.1
	PR	26 (30%)	22 (24%)	0.3
	SD	5 (6%)	2 (2%)	0.2
	PD	0	0	
Nodal site*	CR	40 (54%)	48 (61%)	0.3
	PR	28 (38%)	21 (27%)	0.1
	SD	4 (5%)	6 (8%)	0.5
	PD	2 (3%)	3 (4%)	0.6
Primary + nodal site	CR	50 (58%)	55 (60%)	0.8
	PR	30 (35%)	32 (35%)	0.9
	SD	4 (5%)	2 (2%)	0.3
	PD	2 (2%)	3 (3%)	0.7
Objective response rate	CR + PR	80 (93%)	87 (95%)	0.6

*, CF-CRT (n=74), HF-CRT (n=78). CF-CRT, conventional concurrent chemoradiation; HF-CRT, hyperfractionated concurrent chemoradiation; n, number of patients; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3 Acute toxicity profile

Toxicity type	Toxicity grade	CF-CRT (n=98)	HF-CRT (n=102)	P value
Acute toxicity				
Mucosal toxicity	Grade 1 & 2	82 (84%)	68 (67%)	0.005*
	Grade 3 & 4	16 (16%)	34 (33%)	
Skin toxicity	Grade 1 & 2	78 (79%)	74 (72%)	0.2
	Grade 3 & 4	20 (21%)	28 (28%)	
Hematological toxicity (leucopenia)	Grade 1 & 2	34 (35%)	28 (27%)	0.1
	Grade 3 & 4	2 (2%)	6 (6%)	
Pharyngitis	Grade 1 & 2	78 (79%)	78 (76%)	0.5
	Grade 3 & 4	20 (21%)	24 (24%)	
Laryngitis	Grade 1 & 2	76 (77%)	74 (72%)	0.6
	Grade 3 & 4	10 (10%)	8 (8%)	
Salivary gland toxicity	Grade 1	18 (19%)	23 (22%)	0.4
	Grade 2	31 (32%)	29 (28%)	

*, indicates significant variable. CF-CRT, conventional concurrent chemoradiation; HF-CRT, hyperfractionated concurrent chemoradiation; n, number of patients.

Table 4 Late toxicity profile

Toxicity type	Toxicity grade	CF-CRT (n=80)	HF-CRT (n=82)	P value
Late toxicity				
Mucosal toxicity	Grade 1 & 2	50 (62%)	52 (63%)	0.1
	Grade 3	3 (4%)	8 (10%)	
Skin toxicity	Grade 1 & 2	38 (47%)	42 (51%)	0.8
	Grade 3	4 (5%)	4 (5%)	
Subcutaneous tissue toxicity	Grade 1 & 2	46 (57%)	49 (60%)	0.4
	Grade 3	6 (7%)	4 (5%)	
Pharyngitis	Grade 1 & 2	43 (54%)	41 (50%)	0.5
	Grade 3	5 (6%)	7 (8%)	
Salivary gland toxicity	Grade 1 & 2	47 (59%)	45 (55%)	0.5
	Grade 3	7 (9%)	9 (11%)	
Laryngitis	Grade 1 & 2	39 (49%)	37 (45%)	0.6
	Grade 3	2 (3%)	3 (4%)	

CF-CRT, conventional concurrent chemoradiation; HF-CRT, hyperfractionated concurrent chemoradiation; n, number of patients.

90-03 trial, with radiation schedules similar to that of ours, overall treatment time was 50 days in each arm (23).

Regarding concurrent chemotherapy, >60% of patients in both the treatment groups received 6 or more cycles of weekly cisplatin and approx. 90% patients in each group received at least 4 cycles of chemotherapy. In a similar study by Tallari RV *et al.*, all the patients received minimum 4 cycles of chemotherapy (1). Thus, as far as concomitant chemotherapy is concerned, delivering two radiation fractions a day in hyperfractionation had no impact on chemotherapy interruption.

The median follow up in our study was 7 months in the CF-CRT group (range, 1.5–20 months) and 7.2 months in the HF-CRT group (range, 1.5–18 months). We did not have a long follow-up due to limited study period.

On response evaluation, objective response rates (ORR) were 93% and 95% in control and study groups respectively (P=0.6). CR rates were 64% *vs.* 74% (P=0.1) at primary site and 54% *vs.* 61% (P=0.3) at nodal site in CF-CRT and HF-CRT groups respectively. No statistically significant difference was found between the two radiation schedules in terms of response to treatment. When response was assessed site-wise oropharyngeal cancer was found to be the most responsive tumor (highest percentage of complete response was seen in both treatment groups) (*Table 5*). These findings were consistent with the study by Tallari RV *et al.* (1). CR rates in their study were 64.6% *vs.* 76.6% at primary site & 68.7% *vs.* 80.8% at nodal site in CF-CRT & HF-CRT respectively (P=0.19) though their patients were subjected to concurrent chemoradiation after 3 courses of induction chemotherapy. In our study, 5 patients (2 in conventional fractionation and 3 in hyperfractionation) had overall progressive disease (P=0.7). Four of them had disease progression at primary/nodal site while 1 patient (belonging to HF-CRT group) developed distant metastasis to lung and later died of disease complications.

We observed significantly higher rate of acute severe mucositis (grade 3 & 4) with HF-CRT compared to CF-CRT (P=0.005). Other similar studies have also reported mucous membrane as the most common site of severe acute reaction, even in some studies mucositis was the dose limiting toxicity (21,24). In our study mucositis was one of the causative factors for prolonged OTT in patients of hyperfractionated RT. This was our major concern since the start of this study as we were aware that both concomitant chemotherapy and hyperfractionated radiotherapy could potentially increase acute toxicities. There was no significant difference in the frequency of late effects reported in the two treatment groups. This finding was concordant with the fact that hyperfractionation did not cause an increase in late toxicity (25).

We at this moment cannot comment on locoregional

Table 5 Disease response site-wise

Subsite	Treatment response	CF-CRT (n=86)	HF-CRT (n=92)
Oral cavity (n=59)	CR	17 (56%)	21 (72%)
	PR	11 (37%)	7 (24%)
	SD	2 (7%)	1 (4%)
	PD	0	0
Oropharynx (n=84)	CR	26 (72%)	38 (79%)
	PR	8 (22%)	9 (19%)
	SD	2 (6%)	1 (2%)
	PD	0	0
Hypopharynx (n=5)	CR	1 (33%)	1 (50%)
	PR	2 (67%)	1 (50%)
	SD	0	0
	PD	0	0
Larynx (n=30)	CR	11 (65%)	8 (61%)
	PR	5 (29%)	5 (39%)
	SD	1 (6%)	0
	PD	0	0

CF-CRT, conventional concurrent chemoradiation; HF-CRT, hyperfractionated concurrent chemoradiation; n, number of patients; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

control and survival outcome of the two radiation protocols because of our limited study period but in future we may update these long-term results with the same patients once we will have enough follow up.

Thus, we can say that hyperfractionated concurrent chemoradiation (HF-CRT) results in more acute mucositis with no better response rate, rather conventional concurrent chemoradiation is better compared to hyperfractionated chemoradiotherapy. Hyperfractionated radiation regimens also have some logistic disadvantages, both patient-related as well as hospital-related. It is usually inconvenient for the patients to come twice a day for each day treatment or to wait for 6 long hours for the second fraction. These often add to their stay/transportation costs with simultaneous detriment to their daily source of earning. This protocol ultimately doubles the patients' load over the treatment machine along with prolongation of the working hours of our RT technicians; all these are certainly not desired in a resource-restrained setting like ours. We can rather go for accelerated radiation plans which have the theoretical advantage of accelerating the overall treatment time.

Conclusions

Based on our results we conclude that though HF-CRT is equally effective but still does not have a therapeutic benefit over conventional concomitant chemoradiation and should be avoided in low resource settings.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://jxym.amegroups.com/article/view/10.21037/jxym-21-34/rc

Trial Protocol: Available at https://jxym.amegroups.com/article/view/10.21037/jxym-21-34/tp

Data Sharing Statement: Available at https://jxym.amegroups.com/article/view/10.21037/jxym-21-34/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jxym.amegroups.com/article/view/10.21037/jxym-21-34/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Ethical Committee (EC/NEW/INST/2020/904) and informed consent was taken from all the patients.

References

1. Tallari RV, Singh OP, Yogi V, et al. Five versus ten fractions per week radiotherapy in locally advanced head and neck cancer. J Cancer Res Ther 2017;13:224-9.
2. Budach V, Stuschke M, Budach W, et al. Hyperfractionated accelerated chemoradiation with concurrent fluorouracil-mitomycin is more effective than dose-escalated hyperfractionated accelerated radiation therapy alone in locally advanced head and neck cancer: final results of the radiotherapy cooperative clinical trials group of the German Cancer Society 95-06 Prospective Randomized Trial. J Clin Oncol 2005;23:1125-35.
3. Pignon JP, Bourhis J, Domenge C, et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet 2000;355:949-55.
4. Al-Sarraf M, Pajak TF, Marcial VA, et al. Concurrent radiotherapy and chemotherapy with cisplatin in inoperable squamous cell carcinoma of the head and neck. An RTOG Study. Cancer 1987;59:259-65.
5. Pignon JP, Bourhis J, Domenge C, et al. Chemotherapy added to locoregional 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.
6. Horiot JC, Le Fur R, N'Guyen T, 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. Overgaard J, Hansen HS, Specht L, 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.
8. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006;368:843-54.
9. Bourhis J, Sire C, Graff P, 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.
10. Beitler JJ, Zhang Q, Fu KK, 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.
11. Budach W, Hehr T, Budach V, et al. 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.
12. Lacas B, Carmel A, Landais C, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group. Radiother Oncol 2021;156:281-93.
13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
14. 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;31:1341-6.
15. Denaro N, Russi EG, Merlano MC. Strategies for non-resectable head and neck cancer. Curr Treat Options Oncol 2013;14:492-504.
16. Withers HR, Taylor JM, Maciejewski B. The hazard

of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 1988;27:131-46.
17. Ng CE, Keng PC, Sutherland RM. Characterization of radiation sensitivity of human squamous carcinoma A431 cells. Br J Cancer 1987;56:301-7.
18. Gatenby RA, Kessler HB, Rosenblum JS, et al. Oxygen distribution in squamous cell carcinoma metastases and its relationship to outcome of radiation therapy. Int J Radiat Oncol Biol Phys 1988;14:831-8.
19. Herchenhorn D, Dias FL. Advances in radiochemotherapy in the treatment of head and neck cancer. Rev Hosp Clin Fac Med Sao Paulo 2004;59:39-46.
20. Hall Eric J, Giaccia Amato J. Radiobiology for the Radiologist. 6th edition. Philadelphia: Lippincott Williams and Wilkins, 2006:378-97.
21. Karasawa K, Matsumoto F, Ito S, et al. Hyperfractionated radiotherapy with concurrent docetaxel for advanced head and neck cancer: a phase II study. Anticancer Res 2012;32:4013-8.
22. Jeremic B, Milicic B, Dagovic A, et al. Radiation therapy with or without concurrent low-dose daily chemotherapy in locally advanced, nonmetastatic squamous cell carcinoma of the head and neck. J Clin Oncol 2004;22:3540-8.
23. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J Radiat Oncol Biol Phys 2000;48:7-16.
24. Thejaswini B, Nanda R, Aradhana K, et al. Hyperfractionated radiotherapy and concurrent chemotherapy in locally advanced hypopharyngeal cancers-an institutional experience. Int J Med Res Rev 2016;4:1017-23.
25. Liu Y, Kou C, Bai W, et al. Altered fractionation radiotherapy with or without chemotherapy in the treatment of head and neck cancer: a network meta-analysis. Onco Targets Ther 2018;11:5465-83.

doi: 10.21037/jxym-21-34
Cite this article as: Alam Z, Khan M, Siddiqui SA, Akram M, Alam MS, Hussain MAB. Hyperfractionated concurrent chemoradiation against conventional concurrent chemoradiation in locally advanced head and neck carcinoma: a prospective randomised trial. J Xiangya Med 2022;7:2.