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Original Article

A Prospective Randomized Study to Assess the Feasibility and Compare the Acute Toxicity and Early Treatment Response in Locally Advanced Head-and-neck Patients Treated with Accelerated Fractionated Concurrent Chemoradiotherapy versus Conventional Chemoradiation

Shivani Chaparala[1,2], Laxman Pandey[1,3], Rajeev K. Seam[1], Kaalindi Singh[1,4]*, S. V. S. Bala[1], Deepika Malik[1,5], Maitry Acharya[1], Prudhvi Inampudi[1,6], Apurva Pandey[1,7], Kartik Kadia[1,8], Jameel Sherif[1]

[1]Department of Radiotherapy, MMIMSR, Mullana, Haryana, India
[2]Pranahita Multispeciality Hospital and Cancer Center, Guntur, Andhra Pradesh, India
[3]Department of Radiotherapy, Rohilkhand Cancer Institute, Bareilly, Uttar Pradesh, India
[4]Department of Radiotherapy, Shri Lal Bahadur Shastri Government Medical College and Hospital, Mandi, Himachal Pradesh, India
[5]Department of Radiotherapy, Sri Aurobindo Institute of Medical Sciences, Indore, Madhya Pradesh, India
[6]Department of Medical Oncology, GSL Medical College and General Hospital, Rajahmahendravaram, Andhra Pradesh, India
[7]Sparsh Orthopaedics and Cancer Care, Varanasi, Uttar Pradesh, India
[8]KJ Hospital Cancer and Superspeciality, Junagadh, Gujarat, India

Abstract

Background: To compare the acute toxicity and early treatment response in locally advanced head-and-neck cancer patients treated with accelerated fractionated radiotherapy with concurrent chemotherapy (AFCRT) versus conventional fractionation chemoradiation. **Materials and Methods:** Forty patients were randomized into two treatment arms. The prescribed dose to the high-risk planning target volume (PTV-HR) was 66–70 Gy at 2 Gy per fraction, 6 days a week. The intermediate-risk PTV (PTV-IR) received 59.4–63 Gy at 1.8 Gy per fraction, 6 days a week, and the low-risk PTV (PTV-LR) received 54–56 Gy at 1.69 Gy per fraction, 6 days a week for 33–35 fractions, respectively. In the control arm, the PTV-HR received 66–70 Gy at 2 Gy per fraction 5 days a week, the PTV-IR received 59.4–63 Gy at 1.8 Gy per fraction, 5 days a week, and the PTV-LR received 54–56 Gy at 1.69 Gy per fraction, 5 days a week for 33–35 fractions, respectively. Both arms received concurrent weekly chemotherapy at 40 mg/m^2. Toxicity was assessed per Radiation Therapy Oncology Group (RTOG) toxicity Common Terminology Criteria for Adverse Events (CTCAE) ver. 5 weekly during radiotherapy, 6 weeks posttreatment, and at 3 months. Response to treatment was assessed

Address for correspondence: Dr. Kaalindi Singh, Department of Radiotherapy, Shri Lal Bahadur Shastri Government Medical College and Hospital, Mandi, Himachal Pradesh, India.
E-mail: dr.kaalindisingh1987@gmail.com

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at 6 weeks and 3 months using the Response Evaluation Criteria in Solid Tumors 1.1 criteria. **Results:** All the patients in both study groups completed their treatment. The average number of chemotherapy cycles administered in both groups was five. The total amount of chemotherapy received in both groups was similar ($P = 0.249$). After 3 months of follow-up, 14 (70%) patients in the study group and 13 (65%) patients in the control group showed a complete response in the local and regional areas ($P = 0.898$). Progressive disease was observed in 1 (5%) patient in the study group and 4 (20%) patients in the control group ($P = 0.573$). Severe (grade 3 or higher) acute side effects were similar in both groups. Late side effects observed between 3 and 6 months after treatment were also comparable. Interestingly, there was a significantly higher incidence of weight loss (>10%) in the control group ($P = 0.020$). **Conclusion:** AFCRT was safe and feasible. The study arm had higher overall response rates with comparable toxicity with conventional chemoradiation. The findings suggest that AFCRT is a promising treatment option.

Keywords: Accelerated fractionation, concurrent chemoradiation, concurrent chemotherapy, conventional chemoradiation, locally advanced head-and-neck cancer

Introduction

Head-and-neck cancer (HNC) refers to a heterogeneous group of neoplasms arising from the upper respiratory and digestive tracts. HNC is the sixth most common cancer worldwide, with 890,000 new cases and 450,000 deaths in 2018. The incidence continues to rise and is anticipated to increase by 30% by the year 2030 (according to the GLOBOCAN data). Thus, it is a significant public health problem.[1,2] In India, head-and-neck squamous cell carcinoma accounted for nearly 21.3% of all cancers in 2021, constituting approximately 32.4% and 9.2% in males and females, respectively. In addition, over half of the cases were reported in patients between 45 and 64 years of age. Mortality in HNCs is at least half the incidence, driven by the late stage at diagnosis (60%–80% with advanced disease) and risk-associated behaviors with long-term health consequences.[3]

One of the critical causes of failure in HNC is accelerated repopulation of tumor clonogen, which usually starts around the 4th week of radiotherapy.[4] To counter this, researchers have tested accelerated radiotherapy, demonstrating promising results with increased rates of local control and disease-free survival compared to conventional fractionation.[5-8] Another method of enhancing tumor response is the addition of concurrent chemotherapy, which has a radio-sensitizing effect. Numerous randomized studies and meta-analyses have established the significant benefits of this approach in terms of local control, disease-free survival, and overall survival, offering a ray of hope in the fight against HNC.[9-14]

The aim of this study was to investigate the toxicities and potential benefits of combining chemotherapy with accelerated fractionation radiotherapy. We hypothesized that with modern radiotherapy techniques that minimize harm to healthy tissue, this approach could significantly improve disease control outcomes, offering a promising avenue for HNC treatment.

Materials and Methods

This study was carried out at the department of radiotherapy of a private cancer care center. The institutional protocol required obtaining Ethical Committee approval before starting the study. From December 2019 to April 2021, patients meeting specific criteria were enrolled. These criteria included being between 18 and 70 years old, having stage III-IVA, histologically confirmed squamous cell carcinoma of the oropharynx, hypopharynx, larynx, or occult primary with secondary neck nodes, a Karnofsky Performance Status (KPS) score over 70, normal blood biochemistry, and willingness to participate in the study. Patients with significant comorbidities that would hinder treatment according to the protocol, those who had previously received treatment for head-and-neck malignancy, and pregnant or lactating women were excluded from the study.

A convenience sample was selected for the study. All patients who met the inclusion criteria and did not meet any of the exclusion criteria between December 2019 and April 2021 were enrolled. Written informed consent was obtained from all the patients before receiving radiotherapy and chemotherapy. The enrolment in the two study arms was randomized using the computer-based methods.

Pre-treatment workup

All patients underwent a thorough history and physical examination, and the clinical findings were recorded on a clinical form in their treatment file. In addition, complete blood count and blood biochemistry analyses were performed. For disease staging and to rule out metastasis, positron emission tomography computed tomography (CT) was conducted for patients who could afford it. For the remaining patients, a chest X-ray, ultrasound of the abdomen, and regional contrast-enhanced CT (CECT) scan were performed. Magnetic resonance imaging (MRI) was carried out in certain cases where disease staging with a CECT scan was unclear. Furthermore, a comprehensive dental evaluation and nutritional assessment were conducted, and if necessary, a nasogastric tube was inserted before treatment initiation.

The disease was staged according to the AJCC 8th Edition.[15] However, patients with carcinoma of the oropharynx could not be stratified based on p16 status due to the unavailability of institutional testing and lack of affordability for testing in alternate centers.

Pretreatment simulation, planning, and treatment delivery

The patients were positioned supine and secured using a five-clamp thermoplastic cast, along with a base plate and

comfortable head support to ensure they remained still. To create a detailed plan, a multislice Phillips Brilliance Big Bore CT scanner was used to perform a contrast-enhanced CT scan with a 3-mm slice thickness, covering a range from 3 cm above the vertex to the tracheal bifurcation. The resulting images were transferred using the Digital Imaging and Communications in Medicine system to the Treatment Planning System (TPS; Monaco version 5.11.02) for further analysis and planning.

Delineation of regions of interest

Delineation of the regions of interest was done using ICRU 50 and 62 guidelines.[16,17] The gross tumor volume (GTV) consisted of both the primary (GTV-P) and nodal (GTV-N) volumes, which were initially assessed through physical examination, laryngoscopy, and CT/MRI scans. The clinical target volume (CTV) was divided into high, intermediate, and low-risk volumes. The high-risk volume (CTV-HR) included GTV-P and GTV-N with a 1 cm margin. The intermediate-risk volume (CTV-IR) encompassed high-risk areas near the tumor, including adjacent nodal regions, where microscopic tumor spread was anticipated. The low-risk volume (CTV-LR) included uninvolved nodes on both sides of the tumor, which were at lower risk of microscopic disease spread. A 5-mm margin was added to each CTV volume to create the planning target volume (PTV) to account for daily setup errors and organ movement. Organs at risk, such as the bilateral parotid glands, spinal cord, brainstem, brain, cochlea, eyes, lens, optic nerve, optic chiasma, uninvolved oral cavity, lips, pharyngeal constrictors, mandible, esophagus, and other relevant structures, were contoured based on the primary site. All contours were independently reviewed by two radiation oncologists before finalization.

Dose prescription

The simultaneous integrated boost-intensity modulated radiotherapy (IMRT) technique was used for most patients to deliver radiation. In the study arm, the high-risk PTV (PTV-HR) dose was 66–70 Gy at 2 Gy per fraction, 6 days a week. The intermediate-risk PTV (PTV-IR) received 59.4–63 Gy at 1.8 Gy per fraction, 6 days a week, and the low-risk PTV (PTV-LR) received 54–56 Gy at 1.69 Gy per fraction, 6 days a week for 33–35 fractions, respectively.

In the control arm, the PTV-HR dose was 66–70 Gy at 2 Gy per fraction, 5 days a week. The PTV-IR received 59.4–63 Gy at 1.8 Gy per fraction, 5 days a week, and the PTV-LR received 54–56 Gy at 1.69 Gy per fraction, 5 days a week for 33–35 fractions, respectively. Thus, in the study arm, treatment was administered 6 days a week, and in the control arm, treatment was given 5 days a week. A significantly higher number of patients in the study arm received 35 Gy of treatment ($P = 0.017$) [Figure 1]. The completion of 33 fractions of radiotherapy was considered treatment completion. For the patients who tolerated treatment well, two additional fractions were added at the same dose per fraction.

Chemotherapy

Chemotherapy was given in both arms, once weekly, on the 1st day of the week at a dose of 40 mg/m^2, after ensuring the patient was fit for chemotherapy and blood investigations were within the normal limits.

Treatment planning and delivery

Treatment planning used the Monte Carlo Algorithm. The plan was assessed according to the ICRU 83 guidelines for IMRT,[18] taking into consideration the dose-volume histogram, dose color wash, dose conformity, and heterogeneity indices to evaluate the quality of the plan. Doses to organs at risk were evaluated according to the LATE-QUANTEC criteria.[19] Quality assurance checks were performed for each patient before implementing the plan.

IMRT-volumetric modulated arc therapy was used for all patients, with beam energies of 6 MV and 15 MV for most patients. Treatment was administered using an Elekta Versa HD high-energy linear accelerator from Elekta Oncology Systems, Crawley, UK. During the 1st week of treatment, all patients underwent daily CBCT for the first three fractions, with adjustments made as needed. If the adjustments were within an acceptable range (<5 mm), treatment continued with imaging twice weekly. Replanning was conducted if there was significant weight loss or changes in the patient's body contour during treatment. The aim was to minimize or eliminate the treatment gaps due to adaptive replanning.

Data collection

Patients were reviewed weekly for toxicity assessments which were documented on a clinical pro forma. Radiation toxicities were graded according to Radiation Therapy Oncology Group (RTOG)/Chemotherapy-related adverse effects according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 toxicity grading.[20,21] The scores were based on the patient's subjective symptoms, objective examination findings, and treatment of the symptoms. Side effects of treatment that occurred within 90 days of the start of radiotherapy were considered acute effects. Those occurring or persisting more than 90 days after the start of radiotherapy were considered late effects. Among acute toxicities, skin, mucous membrane, pharynx, and laryngeal toxicities were noted once weekly while on treatment, at completion, and 6 weeks posttreatment. Among late toxicities, subcutaneous fibrosis, xerostomia, and dysphagia were assessed after 3 months from the completion of therapy until the last follow-up. Among chemotherapy-related toxicities, hematological and renal toxicities were documented. Weekly weight monitoring was done. Nasogastric tube insertion was done if the patients had Grade III oral mucositis or lost more than 10% of their body weight.

Responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECISTs) version 1.1[22] at 6 weeks and 3 months after completing treatment by clinical evaluation, endoscopy, and imaging, as appropriate [Figure 2].

Statistical analysis

Data were analyzed using the Chi-square and *t*-test, and P values were calculated. $P < 0.05$ was statistically

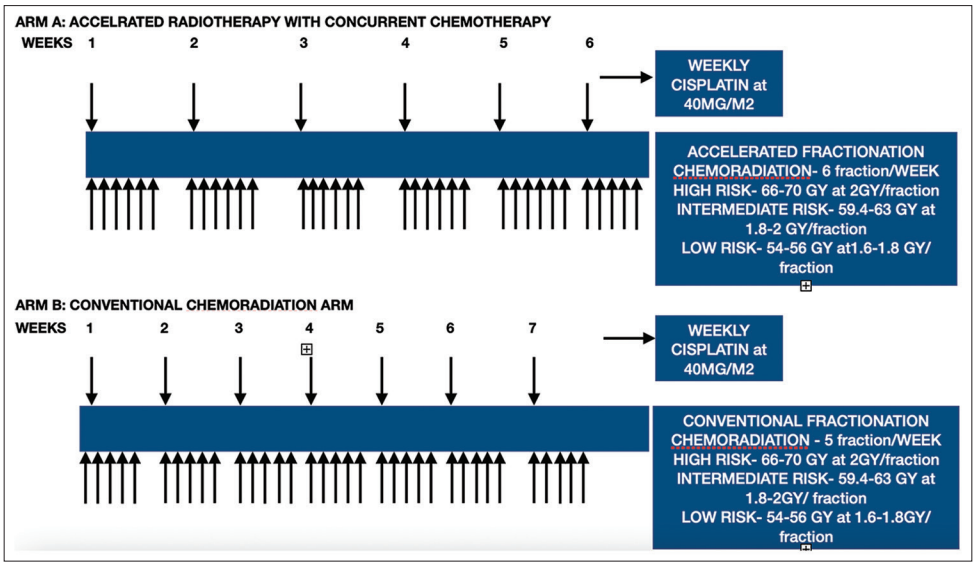

Figure 1: Pictorial study plan

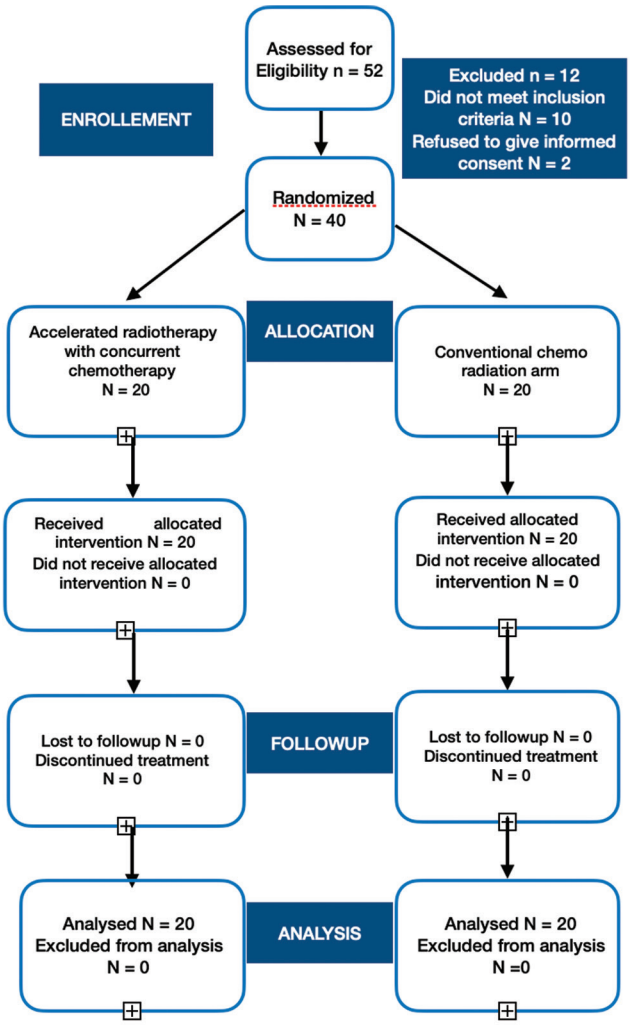

Figure 2: CONSORT Diagram of the study

significant. All analyses were done using the SPSS software version 21 (IBM Inc., Armonk, NY, USA).

Results

The research was carried out at a tertiary care cancer center. In this open-label, prospective study, 40 patients were randomly assigned to two groups using the computer-based randomization. All of the patients completed at least 33 fractions of treatment and were available for the analysis. The average age of the patients in the study group was 56 years, compared to 59 years in the control group. There were no significant differences in baseline patient and disease characteristics between the two groups [Table 1].

The median overall treatment time was 42.5 days (range 40–45 days) in the study group and 47 days (range 46–51.5 days) in the control group. Patients in the study group completed their treatment approximately 1 week earlier ($P = 0.001$). In both groups, patients received 4–6 cycles of weekly cisplatin at 40 mg/m^2. The cumulative dose of cisplatin was similar between the two groups ($P = 0.095$).

Response to treatment

During follow-up visits, all patients underwent clinical examinations and indirect/direct laryngoscopy. However, due to financial constraints, some patients were unable to undergo imaging to evaluate the response. The response classification was based on the RECIST 1.1 criteria, which included complete response, partial response, stable disease, and progressive disease. At 6 weeks of treatment, 70% (14) of the patients in the study arm showed a complete response, compared to 65% (13) in the control arm ($P = 0.898$). The treatment responses at 6 weeks and 6 months are summarized in Table 2. Subset analysis revealed no significant differences between the two arms in terms of site, T-stage, N-stage, and stage group. The pattern of failure regarding local, nodal, and metastatic spread was similar between the two arms ($P = 0.638$). In addition, while there were 20% more treatment failures in the control arm, this difference was not statistically significant ($P = 0.187$).

Table 1: Patient and disease characteristics

Characteristic	Study arm, *n* (%)	Control arm, *n* (%)	*P*
Age			
40–50	8 (40)	4 (20)	0.366
51–60	6 (30)	7 (35)	
61–70	6 (30)	9 (45)	
Gender			
Male	19 (95)	20 (100)	0.311
Female	1 (5)	0	
Karnofsky performance status			
90	10 (50)	6 (30)	0.197
80	10 (50)	14 (70)	
Smoking			
Smoker	19 (95)	20 (100)	0.311
Nonsmoker	1 (5)	0	
Alcohol consumption			
No	9 (45)	9 (45)	1
Yes	11 (55)	11 (55)	
Site			
Oropharynx	13 (65)	7 (35)	0.311
Larynx	3 (15)	7 (35)	
Hypopharynx	3 (15)	4 (20)	
Unknown primary	1 (5)	2 (10)	
Total	20 (100)	20 (100)	
Grade			
Well-differentiated	2 (10)	0	0.212
Moderately-differentiated	11 (55)	13 (65)	
Poorly differentiated	2 (10)	0	
NOS	5 (25)	7 (35)	
T-stage			
Tx	1 (5)	2 (10)	0.264
T1	1 (5)	2 (10)	
T2	8 (40)	2 (10)	
T3	7 (35)	10 (50)	
T4A	2 (10)	4 (20)	
T4B	1 (5)	0	
N stage			
N0	6 (30)	2 (10)	0.409
N1	4 (20)	4 (20)	
N2	7 (35)	11 (55)	
N3	3 (15)	3 (15)	
Stage group			
I	0	1 (5)	0.825
II	6 (30)	4 (20)	
III	3 (15)	3 (15)	
IVA	7 (35)	5 (25)	
IVB	4 (20)	5 (25)	

NOS: Not otherwise specified

Toxicity assessment

Toxicities were compared using the RTOG criteria, and the highest grade toxicity observed was compared [Table 3]. In most patients, acute toxicities appeared 2–3 weeks after radiation treatment. The median time of onset of acute toxicity symptoms was 18 days in the study arm and 17 days in the control arm. Late toxicities observed included xerostomia, laryngeal reactions, and subcutaneous fibrosis. There were no significant differences between the two groups in terms of the incidence and severity of acute and late toxicities.

Weekly monitoring of weight loss during treatment revealed that a significantly higher number of patients in the control arm lost >10% of their body weight from baseline ($P = 0.020$). However, there was no significant difference between the two groups in feeding tube placement (7 [35%] patients in the study arm vs. 8 [40%] patients in the control arm, $P = 0.744$). Tube placement was carried out during the 4th week of treatment in both groups.

Discussion

In this study, accelerated radiotherapy with concurrent chemotherapy was shown to be achievable with comparable acute toxicity to conventional concurrent chemoradiation. A nonsignificant 5% benefit in locoregional control (LRC) at 3 months' follow-up was observed in the accelerated fractionated radiotherapy with concurrent chemotherapy (AFCRT) group compared to the conventional fractionation chemoradiation (CFCRT) group (overall complete response: 70% vs. 65%; $P = 0.736$). The complete response rates for local disease in the AFCRT and CFCRT groups were 75% and 80%, respectively ($P = 0.796$), and the complete response rates for nodal disease in the AFCRT and CFCRT groups were 75% and 70%, respectively ($P = 0.796$). The rates of local and nodal failure were 20% in both groups. The incidence of systemic metastasis was similar in both groups at 15%.

In previous studies, accelerated RT has yielded a small but significant benefit in LRC and overall survival in patients with head-and-neck squamous cell carcinoma.[5,8,23] Adding concurrent chemotherapy to radiotherapy has also been shown to improve the control rates achieved with radiotherapy due to its radio-sensitizing effects and control of micrometastasis.[9,10] Based on these findings, this study was designed to investigate the feasibility, tolerability, and efficacy of combining accelerated fractionated radiotherapy (AFRT) with concurrent chemotherapy.

In a prospective study conducted in India, Gupta *et al*.[24] compared accelerated radiotherapy with conventional chemoradiotherapy. They found a complete response rate of 62.1% in the accelerated radiotherapy group and 70.1% in the concurrent chemoradiotherapy group ($P = 0.402$) at a median follow-up of 12 months. In our study, the complete response in the accelerated chemoradiotherapy group at 3 months was higher than that in the accelerated radiotherapy arm of the aforementioned study and was comparable to the concurrent chemoradiation arm. However, a direct comparison is not feasible due to the shorter follow-up period in our study.

The poorer outcomes in our study compared to previous studies can be attributed to a higher percentage of stage IVB patients – 20% in the accelerated chemoradiotherapy arm and

Table 2: Response assessed at 6 weeks and 3 months in study and control arm

Site	Response	Study, *n* (%)	Control, *n* (%)	*P*
Response at 6 weeks				
All sites	CR local	16 (80)	16 (80)	0.898
	CR nodal	16 (80)	15 (75)	
Response at 3 months				
All sites	CR local	15 (75)	16 (80)	0.796
	CR nodal	15 (75)	14 (70)	
	Overall CR (nodal + local)	14 (70)	13 (65)	0.573
	PR	2 (10)	3 (15)	
	SD	3 (15)	0	
	PD	1 (5)	4 (20)	
Oropharynx	CR	10 (77)	4 (57)	0.357
	NCR (PR + PD)	3 (23)	3 (43)	
	Total	13	7	
Larynx	CR	2 (67)	4 (57)	1.000
	NCR (PR + PD)	1 (33)	3 (43)	
	Total	3	7	
Hypopharynx	CR	1 (33)	3 (75)	0.741
	NCR (PR + PD)	2 (67)	1 (25)	
	Total	3	4	
Unknown primary	CR	1 (100)	2 (100)	1.000
	NCR (PR + PD)	0	0	
	Total	1	2	

CR: Complete response, PD: Progressive disease, SD: Stable disease, PR: Partial response, NCR: Non-CR

25% in the conventional chemoradiotherapy arm – compared to only 3% of patients with stage IVB in the above mentioned study, who were all in the chemoradiotherapy arm. Advanced nodal disease was also more prevalent among our patients; 15% of patients in both the study and control arms presented with N3 disease, compared to only 2.9% in the abovementioned study, where all cases were in the concurrent chemoradiation arm.

In the DAHANCA trial, Overgaard *et al*.[23] demonstrated a statistically significant improvement of 10% in the 5-year loco-regional tumor control rate for the accelerated fractionation group compared to the conventional radiotherapy group (70% vs. 60%; $P = 0.0005$). In their study, 33% of the patients in the AFRT group were stage IV and 36% in the CFCRT group were stage IV. In contrast, our study had a higher proportion of stage IV patients, with 55% in the AFCRT arm and 50% in the CFCRT arm.

In addition, nodal positivity was observed in 42% of the patients in the AFRT group and 44% in the CFCRT group in the DAHANCA study. In comparison, 70% of the patients in the AFCRT arm and 90% in the CFCRT arm in our study were node positive, which is nearly double the rates reported in the previous study.

Hemanth *et al*.[25] prospectively compared AFCRT with CFCRT. During the initial follow-up, 68% of the participants in the CFCRT group achieved a complete response, compared to 96% in the AFCRT group ($P = 0.003$). At a median follow-up of 17 months, the loco-regional control rate was 86% in the CFCRT group compared to 90% in the AFCRT group. Although disease-free survival was slightly higher in the AFCRT group, this difference was not statistically significant ($P = 0.59$).

In their study, 20.5% and 5.9% of the patients in the AFCRT and CFCRT groups had stage IVB disease, respectively, compared to 20% and 25% our study. In addition, N3 disease was present in 11.8% of the patients in the AFCRT group and none of the patients in the CFCRT group in Hemanth *et al*.'s[25] study, compared to 15% of the patients in each arm in our study.

Therefore, the poorer outcomes observed in our study may be attributed to a higher percentage of stage IVB and advanced nodal stage patients compared to previous studies. The late presentation of these patients could be due to a lack of awareness in the region. Many patients prefer indigenous treatment methods and often seek medical attention only after their condition has worsened.

In the DAHANCA study, the 5-year LRC rates for glottic, supraglottic, and pharyngeal cancers were 76%, 56%, and 51%, respectively ($P < 0.0001$). The IAEA study from developing countries reported a 5-year LRC of 46% for laryngeal cancer, 37% for pharyngeal cancer, and 25% for oral cavity cancer ($P < 0.0001$). In our study, at a median follow-up of 3 months, the complete response rates for oropharyngeal, laryngeal, and hypopharyngeal cancers were 77%, 67%, and 33% in the AFCRT arm ($P = 0.447$), and 57%, 57%, and 75% in the CFCRT arm ($P = 0.652$). It was observed that oropharyngeal and laryngeal cancer had better response rates in the AFCRT group. In comparison, hypopharyngeal cancer had a better response rate in the CFCRT group, although these

Table 3: Comparison of early and late toxicity between study and control arm

Toxicity	Grade	Study, *n* (%)	Control, *n* (%)	*P*
Acute toxicity during treatment				
Oral mucositis	0	1 (5)	1 (5)	0.117
	I	7 (35)	1 (5)	
	II	7 (35)	9 (45)	
	III	5 (25)	9 (45)	
Radiation dermatitis	0	5 (25)	1 (5)	0.150
	I	12 (60)	11 (55)	
	II	3 (15)	7 (35)	
	III	0	1 (5)	
Pharyngeal dysphagia	0	7 (35)	2 (10)	0.283
	I	7 (35)	10 (50)	
	II	3 (15)	3 (15)	
	III	3 (15)	5 (25)	
Laryngeal toxicity	0	14 (70)	12 (60)	0.663
	I	2 (10)	4 (20)	
	II	4 (20)	4 (20)	
Hematological toxicity	No toxicity	16 (80)	16 (80)	0.766
	Anemia	4 (20)	3 (15)	
	Neutropenia	3 (15)	4 (20)	
Nephrotoxicity	0	17 (85)	11 (55)	0.111
	I	2 (10)	7 (35)	
	II	1 (5)	2 (10)	
Toxicity assessed at 6 weeks				
Radiation dermatitis	0	20 (100)	18 (90)	0.147
	I			
Oral mucositis	0	20 (100)	20 (100)	1.00
	0	13 (65)	13 (65)	0.506
Pharyngeal dysphagia	I	5 (25)	7 (35)	
	II	1 (5)	0	
	III	1 (5)	0	
Laryngeal toxicity	0	15 (70)	10 (50)	0.420
	I	2 (10)	5 (25)	
	II	2 (20)	3 (15)	
	III	1 (5)	2 (10)	
Xerostomia	0	13 (65)	8 (40)	0.274
	I	4 (20)	6 (30)	
	II	3 (15)	6 (30)	
Anemia	0	18 (90)	19 (95)	0.597
	I	1 (5)	1 (5)	
	II	1 (5)	0	
Neutropenia	0	17 (85)	17 (85)	0.677
	I	3 (15)	3 (15)	
	II	1 (5)	0	
Renal toxicity	0	19 (95)	19 (95)	1.000
	I	1 (5)	1 (5)	
Subcutaneous fibrosis	No	11 (55)	11 (55)	1.000
	Yes	9 (45)	9 (45)	
Late toxicity assessed after 3 months				
Radiation dermatitis	0	20 (100)	20 (100)	1.000
Oral mucositis	0	20 (100)	20 (100)	1.000
Pharyngeal toxicity	0	17 (85)	14 (70)	0.193
	I	2 (10)	1 (5)	
	II	1 (5)	5 (25)	

Contd...

Table 3: Contd...

Toxicity	Grade	Study, *n* (%)	Control, *n* (%)	*P*
Laryngeal toxicity	0	14 (70)	10 (50)	0.453
	I	3 (15)	2 (10)	
	II	1 (5)	1 (5)	
	III	1 (5)	3 (15)	
	IV	1 (5)	4 (20)	
Xerotomia	0	11 (55)	8 (40)	0.617
	I	4 (20)	6 (30)	
	II	5 (25)	6 (30)	
Anemia	0	17 (85)	19 (95)	0.486
	I	2 (10)	1 (5)	
	II	1 (5)	0	
Neutropenia	0	19 (95)	18 (90)	0.548
	I	1 (5)	2 (10)	
Subcutaneous fibrosis	0	14 (70)	16 (80)	0.460
	I	6 (30)	4 (20)	

differences were not statistically significant due to the short follow-up period.

Toxicities vary considerably in different studies depending on the treatment technique used (conformal and conventional) and the irradiated tumor volume (and surrounding normal tissue). However, most studies have reported increased incidence and severity of RT-induced acute complications in the accelerated radiotherapy arm.

Hemanth *et al*.[25] observed an increase in Grade 2 and Grade 3 skin reactions in the accelerated arm compared to the conventional arm (89% vs. 61%; $P = 0.38$), but the increase was not statistically significant. Acute grade 2 and grade 3 mucositis was also higher in the accelerated arm compared to the conventional arm (99% vs. 75%, $P = 0.49$). However, radiation-induced late morbidity did not differ significantly between the groups.

In our study, the accumulated dose per week (12 Gy AFCRT vs. 10 Gy CCRT) did not result in a higher incidence or severity of acute toxicities. Grade 2 and 3 dermatitis was seen in 15% and 0% of the patients in the study arm and 35% and 5% in the control arm, respectively, with a *P* value of 0.150. In addition, grade 2 and grade 3 mucositis was seen in 35% and 25% of the patients in the study arm and 45% each in the patients in the control arm, respectively, with a $P = 0.117$. A non-significant increase in late grade 4 laryngeal toxicity was observed in the study arm (5% vs. 20%, $P = 0.453$). The nasogastric tube dependency rate was lower in the study arm, although it was not statistically significant (15% vs. 25%; $P = 0.283$). Adherence to RT was the same in both groups, with fewer radiation-induced treatment interruptions in the study arm (5% vs. 15%; $P = 0.475$). Mucositis, when present, was transient and resolved within 6 weeks in all patients. In previous studies including DAHANCA and Hemanth *et al*.'s,[25] acute reactions persisted longer. The lower toxicities in our study may have been due to modern radiation techniques, close monitoring during treatment, timely nutritional intervention by introducing a nasogastric tube, and supportive care. All patients in both arms were admitted in the 3rd week of treatment when the onset of radiotherapy-related acute toxicity is anticipated, and completed the remaining treatment as inpatients. These patients were monitored daily for RT-related side-effects, and appropriate interventions were introduced.

From a planning perspective, the oral cavity and lips were outlined as organs at risk during radiation therapy planning, and constraints were set to minimize oral toxicity. This toxicity is a major factor contributing to reduced intake and weight loss in patients. In addition, dysphagia-associated respiratory structures were outlined in all patients with specific constraints as per the LATE QUANTEC prescribed for them.

We found that a significantly higher dose could be delivered in the accelerated radiotherapy group. The patients in the conventional arm experienced a greater number of (>10%) weight loss events compared to the accelerated arm, and this difference was statistically significant ($P = 0.020$). Patients with head and neck conditions often experience progressive weight loss throughout their treatment. The higher documented weight loss in the conventional treatment group may be attributed to a longer duration of both treatment and hospital stay. In contrast, patients in the study group were admitted for a shorter period due to their reduced treatment time.

Although weight loss may have continued in the weeks following treatment completion, it likely went unrecorded, since most patients were discharged once deemed fit at the end of their treatment. This could have led to documentation bias, resulting in significantly more weight loss reported in the control group.

There was no significant difference between the two groups regarding feeding tube placement, with 7 patients (35%) in the study group and 8 patients (40%) in the control group requiring tubes ($P = 0.744$). For the patients who had feeding

tubes inserted after radiation therapy, tube removal typically occurred around 3–4 days post treatment in both groups.

The median overall treatment time was 42.5 days in the accelerated treatment arm and 47 days in the conventional arm. This was slightly higher compared to previous studies such as IAEA (40 and 47 days) and DAHANCA (39 and 46 days) due to the contemporaneous COVID-19 pandemic during the study period.

This study has several limitations, including being conducted at a single center, a small sample size that limited significant findings, and a short follow-up period for assessing the long-term response rates and late toxicities. In addition, only fit patients with a KPS score >70 were selected, which may not fully represent the broader population of patients visiting the head and neck outpatient department. Due to the small sample size, factors that could have impacted outcomes in these patients could not be analyzed. Although a subset analysis was performed, no significant results emerged, likely due to the limited sample size.

On the other hand, the study also has several strengths, including its prospective randomized design. It assessed a promising modification to the established standard of care treatment. Both patient groups had balanced characteristics, and the optimal dose fractionation and chemotherapy schedule were effectively delivered. The study evaluated toxicities and responses according to the protocol, establishing that accelerated fractionation with concurrent chemotherapy can be administered to fit patients with comparable acute toxicities and early treatment responses when compared to conventional chemoradiation.

Unlike most previous studies on this topic, a high percentage of patients presented in advanced stages, which is often seen in rural societies in developing countries. This study underscores the need for enhanced treatment measures for these patients to improve the outcomes. However, larger prospective randomized studies with longer follow-up periods are necessary to investigate the benefits of this regimen in locally advanced HNC and to establish it as a standard of care.

Conclusion

In conclusion, it was evident from this study that accelerated fractionation with concurrent chemotherapy is feasible and well-tolerated. The study also showed an improved overall locoregional response with accelerated fractionation chemoradiation, although the difference was not statistically significant. The results are encouraging, and more extensive studies with longer follow-ups are needed to establish the absolute benefit of this regimen. Accelerated radiotherapy with concurrent chemotherapy is a reasonable option in busy departments with high turnover; however, careful patient selection is crucial for optimal results.

Ethical approval

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its amendments, it was approved by Institutional Ethical Committee of Maharishi Markendeshwar Institute of Medical Sciences and Research, Mullana, Ambala. Approval No. IEC-1673; Approval date: 13/03/2020. Written informed consent was obtained from the patient for the publication of this case report, including any relevant images. The patient was informed about the purpose of the report and gave consent for its dissemination in medical literature while ensuring anonymity.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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