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Original Article

Oncology Section

Three-weekly Cisplatin versus Weekly Cisplatin Concurrently with Accelerated Radiotherapy Fractionation in Head and Neck Cancers: A Prospective Interventional Study

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ABSTRACT

Introduction: Concurrent chemoradiation is the standard of care for locally advanced head and neck squamous cell carcinoma. Cisplatin remains the primary radiosensitiser, enhancing tumour cell kill through multiple mechanisms. Altered fractionation, combined with concurrent chemotherapy, has demonstrated superior outcomes compared with conventional schedules. Accelerated fractionation is increasingly adopted; however, the optimal concurrent cisplatin schedule remains uncertain.

Aim: To compare acute toxicity and early treatment response between three-weekly and weekly cisplatin concurrently with accelerated fractionation in Head and Neck Cancers (HNC).

Materials and Methods: The present prospective interventional feasibility study was conducted in the Department of Radiation Oncology, Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala, Haryana, India. between 1st July 2021 and 30th June 2022. A total of 43 non-metastatic, histopathologically confirmed squamous cell carcinoma patients of the oropharynx, hypopharynx, and larynx (Stage II-IVB) were randomised using computer-based block randomisation into two arms. The three-weekly arm received accelerated radiotherapy (70 Gy in 35 fractions, six fractions per week) with cisplatin 100 mg/m^2 on days 1 and 22. The weekly arm received the same radiotherapy with cisplatin 40 mg/m^2 on days 1, 8, 15, 22, 29, and 36. Forty patients were analysed (20 per arm); Toxicities (dermatitis, mucositis, dysphagia, xerostomia, haematologic (using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0), renal parameters (using Kidney Disease: Improving Global Outcomes (KDIGO) criteria) and vomiting (using a predefined subjective clinical classification) were assessed and compared between the two arms. Response assessment was done and compared using the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. For Quality of Life (QoL) assessment and comparisons, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Head and Neck Module (35 items) (EORTC QLQ-H&N35) questionnaires were used. For comparison, 3-month outcomes were considered. Pearson's chi-square test was used to compare categorical variables. Continuous variables were compared using the unpaired Student's t-test. A p-value of <0.05 was considered statistically significant.

Results: The mean age of the study population was 54.50±8.4 years (42-70 years), 95% (38 out of 40) of patients were males. All patients in the three-weekly arm received 200 mg/m^2 cumulative cisplatin, whereas 90% in the weekly arm received >200 mg/m^2 (p=0.001). Radiotherapy interruptions occurred in 15% versus 5%, respectively. Median Overall Treatment Time (OTT) was similar (40.5 vs 41.5 days; p=0.98). At three months, complete response rates were 65% (three-weekly) and 50% (weekly) (p=0.66). Grade ≥3-mucositis was higher in the three-weekly arm (40% vs 25%; p=0.040). Xerostomia was significantly greater in the three-weekly arm at treatment completion and three months (p<0.05).

Conclusion: Both regimens were effective. Weekly cisplatin arm achieved higher cumulative dosing with a more favourable toxicity profile. Although response rates numerically favoured the three-weekly arm, differences were not statistically significant.

Keywords: Accelerated fractionation, Concurrent chemoradiotherapy, Concurrent cisplatin dosing

INTRODUCTION

Head and Neck Cancers are the sixth most common cancer worldwide, with 8,90,000 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) [1]. In India, head-and-neck squamous cell carcinoma accounted for nearly 21.3% of all cancers of which locally advanced HNCs constitute 68.5%; sometimes constituting around 80% in rural areas [2,3]. Concurrent chemoradiation forms the backbone of treatment of majority of such patients [4].

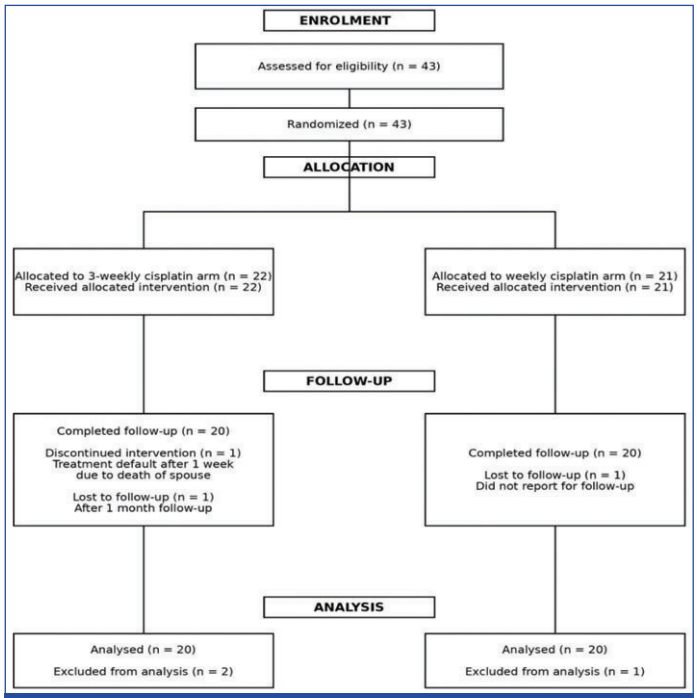
Among altered fractionation approaches, accelerated fractionation has gained increasing acceptance because it shortens the OTT and counteracts accelerated tumour repopulation during radiotherapy. The Danish Head and Neck Cancer Group (DAHANCA) 6 and 7 trials demonstrated improved locoregional control with six fractions per week compared with five fractions per week, establishing accelerated fractionation as an effective altered-fractionation strategy in head and neck cancer [5].

As accelerated fractionation is increasingly incorporated into routine practice, the optimal concurrent cisplatin schedule in this setting remains uncertain. Data evaluating these chemotherapy schedules in conjunction with accelerated radiotherapy are limited [6-9]. Therefore, the present study was designed to compare the acute toxicity profile of weekly versus three-weekly cisplatin administered concurrently with accelerated fractionated radiotherapy in patients with locally advanced head and neck squamous cell carcinoma. The primary endpoint was the incidence and severity of acute treatment-related toxicities up to three months after treatment completion. Secondary endpoints included treatment compliance, cumulative cisplatin dose delivered, overall QoL, and early tumour response assessed at three months.

MATERIALS AND METHODS

The present study was a prospective interventional feasibility study conducted in the Department of Radiation Oncology, Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala, Haryana, India. Patient recruitment was carried out from July 2021 to June 2022. The study protocol was approved by the Institutional Ethics Committee (IEC), MMIMSR, Mullana, Ambala (IEC approval number: 2018), Haryana, India.

Sample size: A total of 43 consecutive eligible patients with histopathologically confirmed squamous cell carcinoma of the oropharynx, hypopharynx, or larynx were enrolled and randomised. After exclusions due to treatment default and loss to follow-up, 40 patients (20 in each treatment arm) were available for final analysis, which have been demonstrated in the Consolidated Standards of Reporting Trials (CONSORT) flow diagram [Table/Fig-1].



[Table/Fig-1]: CONSORT flow diagram depicting patient enrolment, randomisation, allocation, follow-up, and analysis.

Inclusion criteria: Patients with histopathologically confirmed squamous cell carcinoma of the oropharynx, hypopharynx, or larynx, stage II-IVB disease, planned for radical concurrent chemoradiotherapy, patients with willingness to provide written informed consent, were included in the present study

Exclusion criteria: Eastern Cooperative Oncology Group (ECOG) performance status 3 and above, age >70 years, presence of distant metastasis, prior surgery, chemotherapy, or radiotherapy for the same malignancy, severe medical co-morbidities, pregnancy or lactation, pre-existing hearing impairment, pre-existing renal dysfunction.

Study Procedure

Pretreatment evaluation and data collection: All patients underwent detailed clinical evaluation including complete history, physical examination, direct or indirect laryngoscopy/endoscopy where indicated, complete blood counts, serum biochemistry, Contrast-Enhanced Computed Tomography (CECT) of the head and neck, chest radiography, and ultrasonography of the abdomen. Additional assessments included pure-tone audiometry, dental evaluation, nutritional assessment, and management of any dental pathology before treatment initiation.

Treatment protocol: Patients were randomised using computer-generated block randomisation into two treatment arms. Patients were randomised in a 1:1 ratio to either the three-weekly cisplatin arm or the weekly cisplatin arm using a computer-generated block randomisation sequence. A fixed block size of four was used to maintain balanced allocation between the treatment groups throughout the accrual period. The randomisation sequence was generated by an investigator who was not involved in patient recruitment or treatment allocation. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes which were opened only after patient enrollment and confirmation of eligibility.

Three-weekly Cisplatin arm: Accelerated radiotherapy to a dose of 70 Gy in 35 fractions (6 fractions per week) with concurrent cisplatin 100 mg/m^2 administered on Days 1 and 22.

Weekly Cisplatin arm: Accelerated radiotherapy to a dose of 70 Gy in 35 fractions (6 fractions per week) with concurrent cisplatin 40 mg/m^2 administered on days 1, 8, 15, 22, 29, and 36.

All patients underwent CECT simulation with three-mm slices from the vertex to the tracheal bifurcation on a Philips brilliance big bore CT simulator, using a 5 clamp thermoplastic cast and an adequate headrest. All patients were planned with volumetric modulated arc therapy and the simultaneous integrated boost technique for 70 Gy in 35 fractions at 2 Gy per fraction to the high-risk Planning Target Volume (PTV), 63 Gy in 35 fractions at 1.8 Gy per fraction to the intermediate-risk PTV, and 56 Gy in 35 fractions at 1.6 Gy per fraction to the low-risk PTV. Cisplatin was administered with adequate pre and post hydration and antiemetic prophylaxis and treatment.

Study parameters: The following toxicities were assessed: radiation dermatitis, oral mucositis, dysphagia, xerostomia, hearing loss, anaemia, neutropaenia, and acute kidney injury.

Cumulative cisplatin dose was also calculated by adding the dose per m^2 received by each patient. Comparison was made between number of patients in each arm receiving >200 mg/m^2.

Follow-up and outcome assessment: Patients were evaluated weekly during treatment and subsequently at six weeks, three months, six months, and one year following completion of radiotherapy. Acute and late toxicities were graded using CTCAE version 5.0 [10], while acute kidney injury was graded according to KDIGO criteria [11]. Tumour response was assessed using RECIST version 1.1 criteria [12]. QoL was evaluated using the EORTC QLQ-H&N35 questionnaire [13]. The QLQ-H&N35 incorporated seven multi-item scales that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact, and sexuality. In addition, 11 single-item scales assessed problems with teeth, opening the mouth, dry mouth, sticky saliva, coughing, feeling ill, use of pain killers, nutritional supplements, or a feeding tube, weight loss, and weight gain. The Linear transformation symptom scale for all the scales was calculated.

Assessment for vomiting was prospectively recorded according to its clinical impact on antiemetic requirements and treatment delivery. During treatment, assessment for vomiting was done in four categories as-No vomiting during and post-treatment, vomiting after chemotherapy controlled with antiemetics, vomiting not controlled with antiemetics, and vomiting leading to stoppage of chemotherapy and treatment. For the present analysis, outcomes at three months after treatment completion were considered.

STATISTICAL ANALYSIS

Data were entered into Microsoft Excel (Version 16.0) and analysed using Statistical Package for the Social Sciences (SPSS) software version 28. Continuous variables were expressed as mean±Standard Deviation (SD), while categorical variables were presented as frequencies and percentages. Pearson's chi-square test was used for comparison of categorical variables. Continuous variables were compared using the unpaired Student's t-test. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of the study population was 54.50±8.4 years (42-70 years), 38/40 (95%) of patients were males. The most common site of primary was the oropharynx 27/40 (67.50%), followed by the Larynx 8/40 (20%) and the Hypopharynx 4/40 (10%); 1 patient (2.5%) had an occult primary. 75% of patients in the study were of T2 and T3 stage (15 patients each). 15 (37.5%) patients belonged to N2 stage. Group-staging-wise, 9 patients (22.5%) were at Stage II, 7 (17.5%) at Stage III, 15 (37.5%) at Stage IVA, and 9 (22.5%) at Stage IVB; combined, 24 patients (60%) were at Stage IV [Table/Fig-2,3].

Variables	(Accelerated fractionation with concurrent three-weekly Cisplatin) n=20 (%)	(Accelerated fractionation with concurrent weekly Cisplatin) n=20 (%)	p-value
Age (Years)			
40-50	6 (30.0)	8 (40.0)	0.80
51-60	7 (35.0)	6 (30.0)	
61-70	7 (35.0)	6 (30.0)	
Gender			
Male	19 (95.0)	19 (95.0)	1.0
Female	1 (5.0)	1 (5.0)	
ECOG			
0	0	0 (0.0)	0.096
1	16 (80.0)	10 (50.0)	
2	4 (20.0)	10 (50.0)	
Smoker			
Yes	18 (90.0)	19 (95.0)	1.000
No	2 (10.0)	1 (5.0)	
Alcoholic			
Yes	15 (75.0)	9 (45)	0.105
No	5 (25)	11 (55)	

[Table/Fig-2]: Baseline characteristics.
Chi-square test for Age (3 categories); Fisher's exact test for Gender, Smoker, and Alcoholic; Fisher's exact test for ECOG

Variables	(Accelerated fractionation with concurrent three-weekly Cisplatin) n=20 (%)	(Accelerated fractionation with concurrent weekly Cisplatin) n=20 (%)	p-value
Primary tumour site			
Oropharynx	14 (70.0)	13 (65.0)	0.469
Larynx	5 (25.0)	3 (15.0)	
Hypopharynx	1 (5.0)	3 (15.0)	
Occult primary	0 (0.0)	1 (5.0)	
Histology			
Well diff	2 (10.0)	2 (10.0)	0.092
Moderate diff	13 (65.0)	11 (55.0)	
Poorly diff	5 (25.0)	2 (10.0)	
Unknown	0	5 (25.0)	
T stage			
T1	0 (0.0)	1 (5.0)	0.731
T2	7 (35.0)	8 (40.0)	
T3	8 (40.0)	7 (35.0)	
T4a	4 (20.0)	2 (10.0)	
T4b	1 (5.0)	1 (5.0)	
TX	0 (0.0)	1 (5.0)	
N stage			
N0	5 (25.0)	6 (30.0)	0.398
N1	1 (5.0)	4 (20.0)	
N2	8 (40.0)	7 (35.0)	
N3	6 (30.0)	3 (15.0)	
TNM stage grouping			
II	3 (15.0)	6 (30.0)	0.72
III	4 (20.0)	3 (15.0)	
IVA	8 (40.0)	7 (35.0)	
IVB	5 (25.0)	4 (20.0)	

[Table/Fig-3]: Tumour characteristics (N=40).
Statistical tests used: Chi-square test for all variables

In the 3-weekly arm, only two cycles were feasible concurrently with accelerated fractionation, as the radiotherapy course was completed in six weeks; thus, all patients received Cisplatin at a dose of 200 mg/m^2. In the weekly cisplatin arm, where six cycles were feasible, 90% of patients (n=18) received more than 200 mg/m^2 of cumulative cisplatin, and 10% (n=2) received 200 mg/m^2 of cumulative cisplatin, with statistical significance (p=0.001) [Table/Fig-4].

Dose	(Accelerated fractionation with concurrent three-weekly Cisplatin) n=20 (%)	(Accelerated fractionation with concurrent weekly Cisplatin) n=20 (%)	p-value
Cumulative cisplatin dose (mg/m^2)			
200	20 (100)	2 (10.0)	<0.001*
201-250	0 (0.0)	15 (75.0)	
251-300	0 (0.0)	3 (15.0)	

[Table/Fig-4]: Cumulative cisplatin dose (N=40).
Statistical test used: Chi-square test. *p<0.001 indicates statistically significant difference

In the three-weekly cisplatin arm, radiotherapy was interrupted for three patients (15%). The reason for interruption in all these patients was grade III or higher oral mucositis. In the weekly cisplatin arm, one patient (5%) had treatment interruptions due to radiotherapy toxicity, due to grade III or higher mucositis. During treatment, grade 1 acute renal toxicity was observed in 45% vs 15% (n=9 out of 20 vs n=3 out of 20), respectively, in the 3-weekly and weekly cisplatin arms, a statistically significant difference. Three patients (15%) had a delay in chemotherapy due to renal toxicity (Grade II) in the 3-weekly arm. In the weekly cisplatin arm, one patient was given only three cycles of chemotherapy due to persistently deranged kidney function test, and one patient was given a gap of 15 days between the chemotherapy cycles due to deranged creatinine levels, which was conservatively managed.

The median Overall Treatment Time (OTT) was 40.5 days in the 3-weekly cisplatin arm and 41.5 days in the weekly cisplatin arm and was statistically insignificant (p=0.98).

Response Evaluation

The response trend at three months seemed to favour the 3-weekly cisplatin arm numerically but was statistically insignificant (p=0.66) [Table/Fig-5].

Locoregional response at three-months	(Accelerated fractionation with concurrent three-weekly Cisplatin) n=20 (%)	(Accelerated fractionation with concurrent weekly Cisplatin) n=20 (%)	p-value
Complete Response (CR)	13 (65.0)	10 (50.0)	0.66
Partial Response (PR)	4 (20.0)	4 (20.0)	
Progressive Disease (PD)	1 (5.0)	3 (15.0)	
Stable Disease (SD)	2 (10.0)	3 (15.0)	

[Table/Fig-5]: Response assessment at 3 months.
Statistical test used: Chi-square test

During RT, mucositis was significantly higher in the three weekly cisplatin arm, with 95% (n=19) versus 60% (n=12) having Grade 2 and higher mucositis (p=0.04) [Table/Fig-6].

At 3-month follow-up, in the 3-weekly cisplatin arm, 60%(n=12) patients had grade 1 xerostomia and 10% (n=2) patients had grade 2 xerostomia, while in the weekly cisplatin arm, 20%(n=4) patients had

Variables	Highest grade	Toxicity during RT and at treatment completion		p-value
		Accelerated fractionation with concurrent 3 weekly Cisplatin n=20 (%)	Accelerated fractionation with concurrent weekly Cisplatin n=20 (%)	
Radiation dermatitis	0	0	0 (0.00)	0.323
	1	11 (55.0)	15 (75.0)	
	2	9 (45.0)	5 (25.0)	
	3	0 (0.0)	0 (0.0)	
Oral mucositis	0	0 (0.0)	0 (0.0)	0.040**
	1	1 (5.0)	8 (40.0)	
	2	11 (55.0)	7 (35.0)	
	3	8 (40.0)	5 (25.0)	
Pharyngeal dysphagia	0	3 (15.0)	7 (35.0)	0.26
	1	9 (45.0)	7 (35.0)	
	2	7 (35.0)	3 (15.0)	
	3	1 (5.0)	3 (15.0)	
Laryngeal reactions	0	11 (55.0)	14 (70.0)	0.127
	1	7 (35.0)	2 (10.0)	
	2	2 (10.0)	4 (20.0)	
Xerostomia	0	3 (15.0)	11 (55.0)	0.036**
	1	14 (70.0)	7 (35.0)	
	2	3 (15.0)	2 (10.0)	
Anaemia	0	11 (55.0)	16 (80.0)	0.222
	1	7 (35.0)	2 (10.0)	
	2	2 (10.0)	2 (10.0)	
Neutropaenia	0	14 (70.0)	17 (85.0)	0.453
	1	6 (30.0)	3 (15.0)	
	2			
Acute kidney injury	0	11 (55.0)	17 (85.0)	0.085
	1	9 (45.0)	3 (15.0)	

[Table/Fig-6]: Toxicity assessment at RT completion and at six weeks follow-up.
Statistical test used: Fisher's exact test (Freeman–Halton extension)

grade 1 xerostomia and 25%(n=5) patients had grade 2 xerostomia, which was statistically significant (p=0.035) [Table/Fig-7].

Toxicity 3 months after treatment completion	Highest grade	(Accelerated fractionation with concurrent 3 weekly cisplatin) n=20 (%)	(Accelerated fractionation with concurrent weekly cisplatin) n=20 (%)	p-value
Radiation dermatitis	0	19 (95.0)	20 (100.0)	1.000
	1	1 (5.0)	0 (0.0)	
Oral mucositis	0	19 (95.0)	20 (100.0)	1.000
	1	1 (5.0)	0 (0.0)	
Pharyngeal dysphagia	0	14 (70.0)	17 (85.0)	0.563
	1	3 (15.0)	2 (10.0)	
	2	3 (15.0)	1 (5.0)	
Laryngeal reactions	0	11 (55.0)	14 (70.0)	0.809
	1	5 (25.0)	3 (15.0)	
	2	3 (15.0)	2 (10.0)	
	3	1 (5.0)	1 (5.0)	
Xerostomia	0	6 (30.0)	11 (55.0)	0.035*
	1	12 (60.0)	4 (20.0)	
	2	2 (10.0)	5 (25.0)	
Anaemia	0	19 (95.0)	17 (85.0)	0.603
	1	1 (5.0)	2 (10.0)	
	2	0 (0.0)	1 (5.0)	
Neutropaenia	0	18 (90.0)	19 (95.0)	1.000
	1	2 (10.0)	1 (5.0)	
Acute Kidney injury	0	17 (85.0)	19 (95.0)	0.603
	1	3 (15.0)	1 (5.0)	
Subcutaneous fibrosis	0	10 (50.0)	11 (55.0)	1.000
	1	10 (50.0)	9 (45.0)	

[Table/Fig-7]: Toxicity assessment at 3 months follow-up.
Statistical test used: Fisher's exact test (Freeman-Halton extension)

During treatment, assessment for vomiting was done in four categories as- No vomiting during and post-treatment, vomiting after chemotherapy controlled with antiemetics, vomiting not controlled with antiemetics, vomiting leading to stoppage of chemotherapy and treatment. Respectively, for the 3-weekly and weekly cisplatin arms, the observed ratios (10%, 55%, 20%, 15% vs 15%, 45%, 30%, 10%) were statistically insignificant (p=0.80) across all four categories [Table/Fig-8].

Vomiting grade	(Accelerated fractionation with concurrent 3 weekly cisplatin) n=20 (%)	(Accelerated fractionation with concurrent weekly cisplatin) n=20 (%)	p-value
No vomiting during or after treatment	2 (10%)	3 (15%)	0.80
Vomiting after chemotherapy controlled with antiemetics	11 (55%)	9 (45%)	
Vomiting not controlled with antiemetics	4 (20%)	6 (30%)	
Vomiting leading to stoppage of chemotherapy/treatment	3 (15%)	2 (10%)	

[Table/Fig-8]: Vomiting assessment during treatment.
Statistical test used: Chi-square test

Quality of Life

The EORTC QLQ-H&N35 assessment demonstrated no significant differences between the two treatment arms across any symptom domain [Table/Fig-9].

DISCUSSION

The optimal concurrent cisplatin schedule with radiotherapy remains controversial. Randomised trials and meta-analyses have reported conflicting findings regarding efficacy, toxicity, and treatment compliance [14-17]. While the Tata Memorial trial by Noronha V et al., demonstrated superior locoregional control with three-weekly cisplatin compared with weekly administration [15], the phase III randomised controlled trial of weekly versus three weekly cisplatin and radical radiotherapy in locally advanced head and neck squamous cell carcinoma (CONCERT trial) reported non-inferiority of weekly cisplatin with comparable survival outcomes [17]. Similarly, meta-analyses have generally shown no consistent survival advantage for either schedule, although differences in toxicity profiles and cumulative cisplatin dose delivery have been observed [16]. Concurrent cisplatin-based chemotherapy administered with accelerated radiotherapy was also evaluated in a prospective single-arm study of patients with advanced unresectable head and neck cancers and demonstrated encouraging treatment outcomes with acceptable feasibility [18].

Furthermore, a feasibility study by the DAHANCA group evaluating accelerated hyperfractionated radiotherapy with concurrent cisplatin and nimorazole in p16-negative head and neck cancers showed that although acute toxicity was pronounced, late toxicity remained acceptable and three-year outcomes were encouraging [19].

In a multi-center retrospective study, significantly more patients received a cumulative cisplatin dose of ≥200 mg/m^2 with a 3-weekly schedule than with weekly dosing. It also did not show an association between a cumulative cisplatin dose ≥200 mg/m^2 and improved outcomes [14]. The apparent difference between our findings and those reported by Helfenstein S et al., may be explained by the radiotherapy fractionation schedule employed. In studies

Domain	Baseline			3 months follow-up		
	(Accelerated fractionation with concurrent 3 weekly cisplatin) n=20 (median score) range	(Accelerated fractionation with concurrent weekly cisplatin) n=20 (median score) range	p-value	Accelerated fractionation with concurrent 3 weekly cisplatin) n=20 (median score) range	(Accelerated fractionation with concurrent weekly cisplatin) n=20 (median score) range	p-value
Pain	26 (0-100)	10 (0-78)	0.95	13 (0-83)	6 (0-42)	0.92
Swallowing	36 (0-100)	33 (0-100)	0.74	60 (13-93)	63 (17-100)	0.78
Teeth	60 (13-93)	53 (13-89)	0.99	53 (8-93)	46 (17-83)	0.98
Mouth opening	63 (17-100)	56 (13-100)	0.86	63 (8-100)	50 (8-83)	0.90
Dry mouth	36 (33-100)	40 (33-100)	0.78	66 (25-100)	36 (33-100)	0.82
Sticky saliva	46 (33-100)	43 (33-100)	0.86	56 (8-93)	46 (33-100)	0.85
Senses problems	26 (0-17)	23 (0-83)	0.98	30 (0-100)	26 (0-100)	0.92
Coughing	13 (0-67)	10 (0-100)	0.59	20 (0-67)	26 (0-67)	0.85
Felt ill	30 (0-100)	26 (0-100)	0.76	13 (0-100)	26 (0-100)	0.78
Speech	26 (0-78)	23 (0-78)	0.99	30 (0-78)	26 (0-100)	0.90
Social eating	33 (0-80)	30 (0-93)	0.72	56 (8-93)	63 (8-92)	0.93
Social contact	66 (13-86)	73 (13-93)	0.96	83 (13-100)	86 (13-93)	0.82
Sexuality	70 (17-100)	63 (17-100)	0.67	73 (17-83)	70 (0-83)	0.78
Use of pain killers	63 (0-100)	56 (0-100)	0.49	46 (0-100)	63 (0-100)	0.88
Nutritional supplements	26 (0-78)	30 (0-83)	0.21	50 (0-100)	53 (0-100)	0.92
Feeding tube	3 (33-100)	3 (32-100)	0.70	6 (0-100)	6 (0-100)	0.86
Weight loss	63 (0-100)	46 (0-100)	0.23	70 (0-100)	73 (0-100)	0.53
Weight gain	13 (0-67)	26 (0-100)	0.99	6 (0-67)	13 (0-67)	0.85

[Table/Fig-9]: Linear transformation scores for QOL at baseline and at 3 months follow-up.
Statistical test used: Mann-Whitney U test (Wilcoxon rank-sum test)

using conventional fractionation, the overall treatment duration is sufficiently long to permit administration of three cycles of high-dose cisplatin (Days 1, 22, and 43), allowing many patients to achieve cumulative doses of 300 mg/m^2 [14]. In contrast, accelerated fractionation shortens the OTT to approximately six weeks, effectively limiting the three-weekly regimen to two cycles and a cumulative dose of 200 mg/m^2. Conversely, the weekly schedule can still deliver up to six cycles during this treatment period. Therefore, accelerated fractionation alters the treatment-delivery dynamics and may favour achievement of higher cumulative cisplatin doses with weekly administration, as observed in the present study. Another randomised controlled trial showed that the weekly arm received a higher cumulative cisplatin dose (>200 mg/m^2) than the 3-weekly arm, but the difference was not statistically significant [17].

The findings of the present study revealed no statistically significant difference in locoregional response rates between the two accelerated fractionation arms. Notably, the three-weekly arm demonstrated a numerically higher complete response rate (65%) at three months. In the phase III trial by Noronha V et al., the 2-year locoregional control rate was significantly higher with three-weekly cisplatin than with weekly cisplatin (73.1% vs. 58.5%, p=0.014), establishing the three-weekly regimen as the reference standard. Furthermore, the median progression-free survival was 28.6 months in the three-weekly arm compared with 17.7 months in the weekly arm, although overall survival did not differ significantly between groups [15].

The ConCERT trial demonstrated that weekly cisplatin was non-inferior to three-weekly cisplatin, with no significant differences in locoregional failure, progression-free survival, or overall survival. The median time to locoregional failure did not differ significantly between the weekly and three-weekly arms (not reached vs. 21.23 months; p=0.45), while median progression-free survival (20.66 vs. 20.60 months; p=0.46) and overall survival (25.46 vs. 30.50 months; p=0.59) were also comparable [17]. The absence of a statistically significant difference in response rates in the present study, despite a numerical advantage favouring the three-weekly schedule, lies between the findings of these two landmark trials and supports the growing evidence that both regimens remain effective treatment options when delivered concurrently with radiotherapy. Differences in radiation schedules, patient populations, and study endpoints should, however, be considered when interpreting these comparisons.

Mucositis and xerostomia were significantly more pronounced in the three-weekly arm, consistent with previous studies reporting higher rates of acute mucosal toxicity with high-dose three-weekly cisplatin regimens [14,15].

Quality-of-life assessment using the EORTC QLQ-H&N35 questionnaire demonstrated comparable outcomes between the weekly and three-weekly cisplatin arms across most evaluated domains. No statistically significant differences were observed in pain, swallowing, speech, social eating, social contact, or other symptom scales at baseline or at three months following treatment. The only notable difference was a higher dry-mouth score in the three-weekly cisplatin arm, consistent with the higher incidence of xerostomia observed clinically in this cohort. These findings are broadly consistent with the quality-of-life analysis from the randomised trial by Noronha V et al., which demonstrated similar longitudinal QoL outcomes between weekly and three-weekly cisplatin schedules despite differences in treatment delivery and toxicity profiles [15]. Likewise, the ConCERT trial reported that weekly cisplatin was non-inferior to the conventional three-weekly regimen without any clinically meaningful deterioration in patient-reported outcomes [17]. The comparable QoL results observed in the present study, together with similar locoregional response rates between treatment arms, suggest that both cisplatin schedules provide equivalent patient-reported functional outcomes when administered concurrently with accelerated radiotherapy.

The present study supports the feasibility of both regimens in the context of accelerated fractionated radiotherapy. The choice of regimen should therefore be individualised based on patient comorbidities, nutritional status, and treatment intent.

Limitation(s)

However, the small sample size was a key limitation, and the follow-up duration is too short for long-term survival and late toxicity analyses.

CONCLUSION(S)

Both once-weekly (40 mg/m^2) and once-three-weekly (100 mg/m^2) cisplatin regimens were effective. The weekly cisplatin arm achieved higher cumulative dosing and a more favourable toxicity profile, and although early response rates were numerically higher in the three-weekly arm, the differences were not statistically significant. Further randomised controlled studies with larger sample sizes and longer follow-up periods are needed to establish the appropriate cisplatin schedules for concurrent use with accelerated fractionation in head-neck cancers.

Data availability statement: The datasets generated during and/or analysed during the current study is available from the corresponding author on reasonable request.

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