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Ten years survival results of randomized study comparing weekly *vs.* triweekly cisplatin with concurrent radiation in locally advanced carcinoma cervix

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ABSTRACT

Background: The current standard of treatment for locally advanced cervical cancer is concurrent chemo-radiation with improved overall survival (OS) by 6% with manageable toxicities. The cisplatin 40 mg/m^2 given weekly is the widely practiced regimen for 4–6 cycles concurrently with irradiation.

Materials and methods: Two hundred and twelve patients with histologically proven squamous cell carcinoma of cervix with stages IIB to IIIB were enrolled between 2007–2011. External beam radiation dose of 45 Gy in 25 fractions was delivered over 5 weeks. Brachytherapy was delivered by manual afterloading cesium-137 (Cs137) low dose brachytherapy (LDR) using modified Fletcher suit intracavitary applicators to a total dose of 30 Gy to Point A or interstitial template to dose of 21 Gy/3 fractions with remote afterloading iridium-192 (Ir192) high dose brachytherapy (HDR). Patients were randomized to arm A receiving 40 mg/m^2 of concurrent cisplatin weekly and arm B receiving 100 mg/m^2 of concurrent cisplatin triweekly.

Results: One hundred and nine patients were randomized to weekly cisplatin and one hundred and three patients to triweekly cisplatin at the end of recruitment. At ten years, the OS was higher in the weekly arm (79.8%) compared to triweekly arm (70.9%). Disease free survival (DFS) was almost equal (76.1% and 73.8%) in the weekly and three-weekly arms. There is definite significance in overall DFS with patients receiving the cumulative cisplatin doses of more than 250 mg ($p = 0.028$). The patients with more than 45 years of age had better overall survival (OS) (79%) with statistical significance 31 ($p = 0.020$).

Conclusion: Both cisplatin based triweekly and weekly concurrent chemotherapy are equally effective in terms of OS and DFS.

Key words: concurrent chemoradiation; weekly cisplatin; triweekly cisplatin; survival of carcinoma cervix; cancer cervix

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Introduction

Globocan 2020 has stated that cervical cancer is one of the major causes of cancer mortality in women. The estimated incidence of new cases of cervical cancer is 604,127 and there are 341,831 new deaths due to cervical cancer [1]. The incidence is higher in low-middle income or low income countries accounting for 85% of locally advanced cervical cancer worldwide. Major challenges to combat this being sufficient resources for management and radiotherapy facilities [2]. Our national portal projected every year 122,844 women are diagnosed with cervical cancer and 67,747 die due to disease with cumulative risk of 1 in 75 females [3].

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The current standard of treatment for locally advanced cervical cancer is concurrent chemo-radiation with improved overall survival (OS) by 6% with manageable toxicities [4, 5]. The non-cisplatin multidrug combination chemotherapy regimens have proven inferior to cisplatin alone [6]. The optimal dose and scheduling of concurrent cisplatin has not been well defined. The commonly practiced regimen is weekly cisplatin of dose 40 mg/m^2 for 4–6 cycles concurrently with irradiation. In biologically similar locally advanced head and neck cancers, the three-weekly regimen of cisplatin is routinely used [7–10]. Only few authors have published their work comparing weekly versus three-weekly schedules. In view of high influx of cervical carcinomas in our institute, we wanted to study the effect on overall and disease-free survival (DFS) with these two schedules to optimize the patient load.

Materials and methods

Two hundred and twelve patients with histologically proven squamous cell carcinoma of cervix with stage IIB to IIIB (FIGO staging 2007) were enrolled from 2007 to 2011.

Inclusion and exclusion criteria

All patients having normal hematological, renal, hepatic, cardiac [electrocardioghraphy (ECG) and two-dimensional echocardiography (2D Echo)], glomerular filtration rate (GFR), audiometry parameters were randomized to receive weekly or three-weekly cisplatin along with radical radiotherapy. Radiological investigations, such as chest X-ray, contrast enhanced computed tomography (CT) scan of abdomen pelvis, were done to assess the loco-regional extent of the disease. The cases detected with breach in fat planes or frank infiltration of bladder and rectum on the computed tomography were subjected to cystoscopy and colonoscopy with biopsy.

The patients detected with paraaortic nodes of short axis diameter of > 1 cm, pelvic nodes greater than 3 cm and frank infiltration of the bladder or rectum on CT scan were excluded from the study. Subjects with uncontrolled diabetes mellitus/hypertension, active tuberculosis, human immunodeficiency virus (HIV)/hepatitis B surface antigen (HbsAg) were also excluded.

Any of them detected to have haemoglobin of less than 10 gm/dL at diagnosis were transfused with packed red blood cells to increase the haemoglobin to a minimum of 10 gm/dL and the same was maintained during the complete course of treatment.

Treatment course

Teletherapy

Teletherapy using Tele-cobalt machine was delivered following the bladder protocol in all the patients with advice to empty the bladder and drink 500 mL of water, half an hour prior to the treatment. Patients with antero-posterior separation of less than 20 cm were planned with parallel opposing, antero-posterior portals with the technique of source to skin distance (SSD) — 80 cm. The treatment fields were defined with 2D simulation placing the superior border at L4-L5 lumbar vertebral space, the inferior border at 2 cm beyond the lower extent of the disease and the lateral borders were at 1.5 cm beyond the pelvic brim on either side.

The patients with more than 20 cm abdominal separation were planned with the SAD four field box technique. In this technique limited cut CT scans were obtained, and target volume was traced in ratio of 1:1. External beam radiation dose of 45 Gy in 25 fractions was delivered over 5 weeks [equivalent total doses in 2 Gy fractions (EQD2) of 44.25 Gy and biological effective dose (BED) of 53.1 Gy to the tumor].

Brachytherapy

The manual after-loading low dose rate cesium-137 (Cs137) modified Fletcher Suit applicators were used to deliver intracavitary brachytherapy to a total dose of 30 Gy to point A following International Commission on Radiation Units & Measurements (ICRU) 38 guidelines. Patients unsuitable for intracavitary brachytherapy were treated with interstitial implant using Syed-Neblett Gynae-3 template with dose of 21 Gy in 3 fractions (7 Gy × 3frs, EQD2 29.76 Gy and BED of 35.7 Gy to the tumor) with remote after-loading high dose rate iridium-192 (Ir192). The planning systems used to plan interstitial brachytherapy (ISBT) was 2D Abacus or 3D Brachyvision (Eclipse v8.0).

Chemotherapy

Patients randomized to arm A received 40 mg/m2 of concurrent cisplatin once a week and arm B received 100 mg/m^2 of concurrent cisplatin once in three weeks. We intended to administer minimum of 4 cycles and maximum of 5 cycles of cisplatin in the weekly arm and 2 cycles in three-weekly arm to assess the impact of two schedules. Cisplatin was administered as intravenous infusion over 2 hours before radiation after adequate pre-medications which included dexamethasone 16mg, pantoprazole 40 mg, ondansetron 8 mg, mannitol 10 gm, potassium chloride 20 mEq, magnesium sulphate 20 mg/mL. All patients were hydrated with one liter of normal saline before and after cisplatin infusion. When total calculated cisplatin dose exceeded 70 mg per day, the total dose was divided and delivered over two consecutive days, in both arms.

Toxicity assessment

Weekly toxicity was assessed as per Radiotherapy Oncology Group (RTOG) grading and managed accordingly. The hematological and biochemical acute toxicities were evaluated every week, using the Common Terminology Criteria For Adverse Events (CTCAE) version 3.0.

Follow up

Overall treatment time was intended to be 49–51 days from the start of pelvic irradiation. All patients were followed up at 6 weeks, every 3 months for 3 years, every 6 months up to 5 years and yearly thereafter. At each visit they were evaluated clinically, heamatologically [compete blood counts, liver (LFT) and renal (RFT) function tests] and radiologically (ultrasound abdomen pelvis, chest X-ray).

Statistical analysis

Survival analysis was conducted with Kaplan-Meier estimates for categorical variables. Multivariate Cox Proportional Hazard analysis was used to identify significant variables in predicting OS and disease-free survival duration. Survival was calculated from the date of the start of external radiotherapy.

Ethical clearance

This study was approved by the scientific review board and ethical committee of our Institute.

Results

Of the total of 212 patients, 109 were randomized to the weekly cisplatin arm (Arm A) and 103 to the tri-weekly arm (Arm B) at the end of recruitment.

Patient characteristics

Table 1 depicts the patient characteristics. All patients in both arms received planned total dose of radiation both by external beam radiation and brachytherapy. The mean overall treatment time was 50.02 and 50.07 days in arm A and arm B, respectively, with a range of 32–108 days. There were 193 (89.6%) patients who completed treatment within 60 days, 18 (8.5%) patients between 60 to 80 days and only 4 (1.9%) patients beyond 80 days. The treatment duration in 10.4% of patients (n = 22, > 60 days) was prolonged due to the time gap for recovery of the hematological or GI toxicities during the treatment. The planned dose of concurrent cisplatin was received by 66.07% in the weekly arm and 78.64% in the triweekly arm. The mean EQD2 of total point A dose delivered was 28.12 and 27.92 (BED: 34.3 Gy and 33.6 Gy), respectively, in the weekly and three-weekly arm (p = 0.717). The mean cumulative dose of cisplatin was higher in three-weekly arm: 262.62 mg *vs.* 227.16 mg in the weekly arm (p = 0.001).

Outcome

The OS and DFS was calculated at the end of 10 years of follow up ranging from 7 to 122 months with a mean follow up of 50 and 47 months, respectively.

Table 2 depicts the survival analysis of the cohort.

Overall survival

The OS (Fig. 1) was found to be higher in the weekly arm (79.8%) compared to the triweekly arm (70.9%). The probability of survival at 47 months was 78.3% and 56.4% at 98 months. The mean overall survival was 98.86 and 85.85 months in the weekly and three-weekly (p-value of 0.109), respectively. The cumulative survival at 78 months was 75.5% and 71.8% for the weekly and triweekly arms, respectively (p = 0.283).

Table 1. Patient characteristics

Characteristics		Arm A (109)	Arm B (103)
Age	Median	45	45
	Range	23–67	35–65
FIGO stage	IIB	52	46
	IIIB	57	57
RT plan	Two Fields	80	86
	Four Fields	29	17
	Parametrial Boost	1	1
Brachytherapy	LDR ICBT	97	88
	HDR ISBT	12	15
Overall treatment time	Mean	50.02	50.07
	Median	46	47
	Range	41–108	36–103
Cumulative chemotherapy dose [mg]	Mean	227.16 (± 56.9)	262.62 (± 72.3)
Point A dose	Median	28.1 (± 3.84)	27.9 (± 4.15)
Brachytherapy bladder dose	Median	19.9	19.3
Brachytherapy rectal dose	Median	15.5	15.8
Blood transfusion	Received	40	57
	< 2 pints	20	37
	> 2 pints	20	20

CDDP — cisplatin; FIGO — International Federation of Gynaecology and Obstetrics; ICBT —intracavitary brachytherapy; ISBT — interstitial brachytherapy; LDR — low dose rate brachytherapy; HDR — high dose rate brachytherapy; OTT — overall treatment time

Table 2. Survival

Survival		Weekly	Triweekly	p-value
OS	Over all	78.9%	70.9%	0.109
	Stg II B	82.7%	75.4%	0.107
	Stg IIIB	77.2%	65.2%	
	Cisplatin > 250 mg	227.16 mg	262.62 mg	0.256
DFS	Over all	76.1%	73.8%	0.605
	Stg IIB	76.9%	75.4%	0.599
	Stg IIIB	75.4%	71.7%	
	Cisplatin > 250 mg	227.16 mg	262.62 mg	0.028

OS — overall survival; DFS — disease free survival

The patients aged more than 45 years had better OS (79%) with statistical significance of p = 0.020 as compared to those aged below 45 years (58%).

Stage IIB *vs.* stage IIIB showed a slightly higher survival advantage in the weekly arm (82.7% and 77.2%) than in three-weekly arm (75.4% and 65.2% respectively). But the mean overall survival for stage IIB and IIIB was not significant in the weekly arm (98.3 and 96.1 months) as compared to the three-weekly one (96.108 and 68.878 months) (p-value = 0.107).

There was a trend towards reduced OS with prolonged overall treatment time but it was statistically insignificant (p-value of 0.265). Nor was there any significant survival advantage across the cumulative chemotherapy dose.

Disease free survival

The observed DFS probability at 78 months was 67% and 64% (p = 0.250), irrespective of any underlying factors. DFS (Fig. 2) was almost equal (76.1% and 73.8%) in the weekly and three-weekly

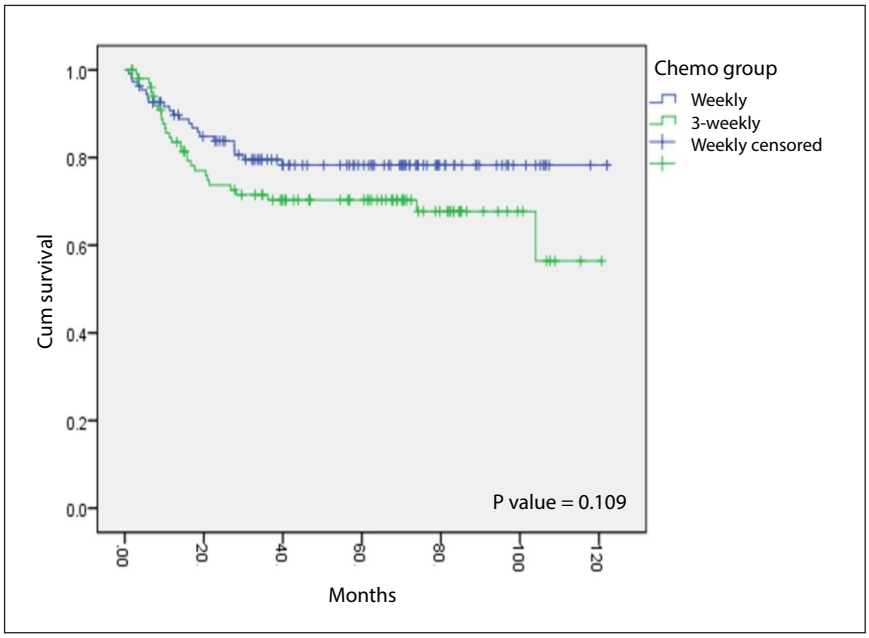

Figure 1. Carcinoma cervix weekly *vs.* 3-weekly cisplatin overall survival

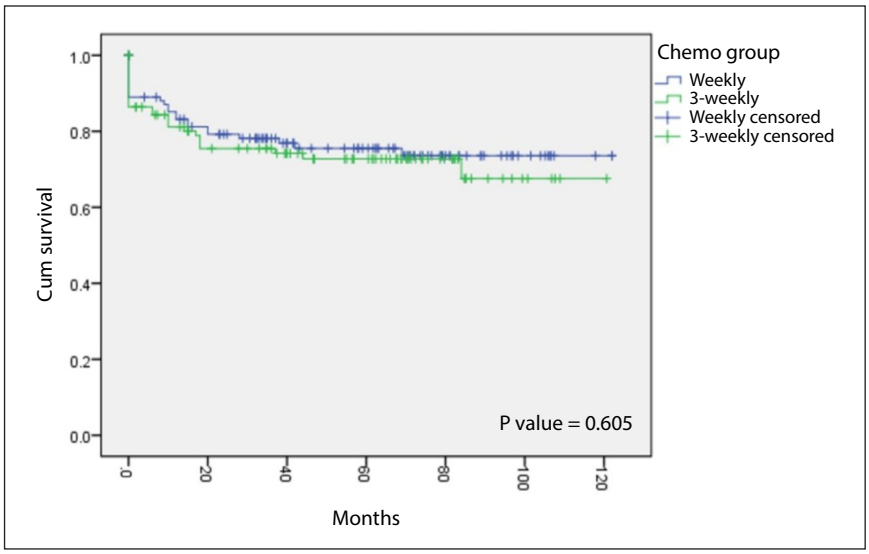

Figure 2. Carcinoma cervix weekly *vs.* 3-weekly cisplatin disease free survival at 10 years

arm with mean DFS of both regimens (103 months *vs*. 99 months, respectively) (p = 0.605).

There is a definite significance in overall DFS in patients receiving the cumulative cisplatin doses of more than 250 mg (p = 0.028). There was no significant change in DFS comparing stage IIB 76.9% *vs*. 75.4% and stage IIIB 75.4% and 71.7% in the weekly (106 and 87.46 month) and three-weekly arms (91.48 and 90.27 months, respectively) (p = 0.599).

Age had an influence on DFS. For patients aged below 45 years it was 70.8% and 67.8% (mean 87.5 and 102.7 months) and in those above 45 years, it was 84.1% and 81.8% (mean 67.4 and 98.9 months) in the weekly and three-weekly arm, respectively, at 10 years (p = 0.541).

Toxicities

Toxicities are captured in Table 3. Acute toxicities, such as leucopenia, were the most common he-

Table 3. Comparison of toxicities in weekly and three weekly arms

Reactions	Grade	Arm A N (%)	Arm B N (%)	p-value
Leucopenia	Low	57 (52)	63 (61)	0.574
	High	5 (4.5)	8 (7.7)	
Neutropenia	Low	48 (44)	45 (43.7)	0.804
	High	5 (4.6)	3 (2.9)	
Thrombocytopenia	Low	18 (16.5)	18 (17.5)	0.8
	High	1 (0.9)	2 (1.9)	
UGI	Low	45 (41.2)	54 (52.4)	0.03
	High	1 (0.9)	5 (4.9)	
LGI	Low	30 (27.5)	44 (42.7)	0.047
	High	1 (0.9)	0	
Cystitis	Low	0	0	0.234
	High	0	2 (1.9)	
Proctitis	Low	8 (7.3)	10 (9.7)	0.634
	High	4 (3.7)	2 (1.9)	

UGI — upper gastrointestinal; LGI — lower gastrointestinal

matological toxicities (p = 0.003). The upper GI and lower GI toxicity were marginally significant in the three-weekly compared to the weekly arm (p = 0.047).

Patterns of failure

Table 4 gives the comparison of death patterns and the recurrence patterns are depicted in Table 5 in both arms. The local recurrence rate at the end of 5 yrs and 10 yrs was 13% and 0.04% respectively, in the overall cohort. Eleven patients were disease free and lost to follow up after 2 years (0.52%).

Deaths

There were a total of 52 deaths in the study cohort of which 50 were seen within 5 years and there were three deaths not related to the disease. The percentage

Table 4. Patterns of failure

Event	Arm A	Arm B	Total
Local failure*	6	6	12
Distant metastasis	5	12	17
Pelvic recurrence	10	10	20
Unrelated to disease	1	2	3
Total deaths	22	30	52
Alive without disease	87	73	160

*Local failure = stable or progressive disease

Table 5. Recurrence

Recurrence	< 2 years		2–5 years		> 5 years		Total
	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B	
LR	7	6	2	2	0	1	18
Distant	3	7	1	4	0	0	15
LR & Distant	1	1	0	0	0	0	2

LR — local/pelvic recurrence

of deaths due to local failure was 0.057% (12 patients) and due to distant failure, 0.081% (17 patients).

Recurrence

Both loco-regional and distant metastasis were treated with palliative chemotherapy using multidrug regimens (paclitaxel + carboplatin being the most common regimen). Bone and Brain metastasis were treated with palliative radiotherapy. The dose schedules were chosen according to the site of presentation and their performance status which varied from 14.4 Gy/4 frs and 20 Gy/5 frs to 30 Gy/10 frs. Pain was managed as per the WHO guidelines along with supportive care by the Palliative care department.

In our cohort, two patients (one in each arm) with early recurrence were treated with multidrug chemotherapy, had a complete response and remained disease free thereafter (follow up for 85 and 90 months).

Distant metastasis

The presentations of distant metastasis was in various sites. In our cohort the most common single or multiple sites of distant metastasis observed was in the paraaortic (n = 6) and supraclavicular nodal region (n = 6). The other sites involved the liver (n = 3), lungs (n = 3), bone (n = 4) and brain (n = 1).

Discussion

Concurrent platinum based chemoradiation remained the standard of care in locally advanced cervical cancers, based on the beneficial results of 5 randomized trials [11–15]. Although the National Cancer Institute (NCI) alert was declared based on these randomized studies, the standard dose and schedules ofchemotherapy remained unanswered.

Chemotherapy dose and schedules were adopted anticipating poor compliance and effects of the treatment.

According to the randomized weekly *vs* tri-weekly cisplatin study conducted by Ryu et al. in 104 patients, three-weekly based concurrent chemoradiation was more effective and feasible in locally advanced cervical cancer [16]. Nagy et al. also concluded that the three-weekly arm yielded superior local control [17]. The only difference between our protocol and theirs was that the 100 mg dose was given over 5 days (20 mg/ m^2 for 5 days/every 3 weeks). In our study, we restricted the dose to 70 mg/day in three-weekly regime and the rest of the dose was delivered on the next day.

Akin retrospective study by Kinjyo et al. reported no significant difference in OS, DFS and distant DFS. The 5-year DFS was 88.5% and 87.9% and distant DFS was 83.9% and 84.1% in the triweekly and weekly arm ($p = 0.782$ and $p = 0.938$), respectively (18). Kinjyo used a similar protocol as Nagy et al. A 2-year complete response of 95.1% and 87.8% in tri-weekly and weekly arms were proclaimed by Panda et al. The three-weekly arm used 75 mg/m^2 unlike our study which used 100 mg/m^2. The author commented that the difference could be attributed to the higher peak concentration of cisplatin in the triweekly arm in which 2nd dose was delivered close to brachytherapy causing a synergistic effect of chemoradiation [19]. A similar study conducted by Preety et al. concluded that the triweekly arm was feasible and more effective. This study had its own limitations of limited follow up and a smaller cohort [20].

A meta-analysis of 8 prospective randomized trials conducted from 2007–2017 across India, Korea, Japan, United States and Romania was presented by Zhu et al. who stated that local relapse occurred less in the tri-weekly arm and recommended further randomized studies to support this hypothesis [21]. Another meta-analysis by Hong Yu et al. in 2019 found no statistical difference in odds ratio in 5-year overall survival in both arms. The authors came to the conclusion that the two schedules had their own advantages with no obvious differences [22].

Quasi experimental study was done by Hassan et al. in 80 patients which included locally advanced cervical cancers. The author concluded that tri-weekly chemoradiation was more compliant and convenient than the weekly arm [23].

Our study analogy is almost similar to the published literature summing up to the idea that although there is a marginal survival advantage with the triweekly arm, the overall OS and DFS do not differ significantly in both chemotherapy schedules. This study is unique from the rest of the published literature as the number of patients randomized is the largest (212) in comparison to other authors and follow-up is also the longest (10 yrs).

Although Nagy et al. enrolled 326 patients, their study design did not match ours nor did the established standard treatment [17]. Another distinctive feature is the adoption of chemotherapy dose of 100 mg/m^2 in the tri-weekly arm whereas majority of the studies have adopted 75 mg/m^2. This was in relation to the extrapolation of the schedules which are followed in head and neck cancer in view of common histopathology.

Although the cumulative dose of cisplatin in the three-weekly regimen was higher, we could not establish the correlation with the increase of distant failure in our cohort arm. None of the studies in the literature have published a follow up beyond 5 yrs; hence, it was not commentable.

The toxicity and compliance of this cohort of patients is already documented and published in the year 2021 [24]. A meta-analysis of six randomized and two retrospective studies, comparing tri-weekly *vs*. weekly cisplatin-based chemoradia- tion from 1990 to Dec 2017 published by Zu et al. found that tri-weekly cisplatin concurrent with radiation showed better compliance [21]. No sig- nificant difference was observed between the two arms with regard to acute adverse effects. The incidence of hematological toxicity was higher in the tri-weekly cisplatin arm, which is similar to the findings of our study. Finally, the authors recommend a tri-weekly over weekly cisplatin regimen for concurrent chemoradiation arm in patients with locally advanced cervical cancer given the better response of the disease and compliance.

In our study, all patients completed planned dose of radiation (teletherapy and brachytherapy) with gaps, whereas 66.07% of patients in the weekly arm and 78.64% in the triweekly one patients received planned dose of chemotherapy. This was owing to acute toxicities, namely leucopenia (0.7–3.8 × 10^9/L), neutropenia (0.5–1.5 × 10^9/L), and thrombocytopenia (33–98 × 10^9/L). The comparison of these toxicities in both arms was not statistically significant. As we aimed to assess the tolerance to the treatment, none of the patients received any granulocyte colony stimulating factors for improving blood counts. The majority of patients recovered within 2–3 weeks. The acute upper gastro-intestinal toxicity grade I and II was observed in 41.2% in the weekly arm and 52.4% in the tri-weekly arm, which was statistically significant ($p = 0.03$), and acute lower gastro-intestinal grade I and II reactions w seen in 27.5% in the weekly arm versus 42.7% in the tri-weekly arm just reaching statistical significance ($p = 0.047$). Although late rectal reactions (proctitis) were higher in the tri-weekly arm but not statistically significant. All the toxicities were managed conservatively.

Conclusion

In this study, both cisplatin based tri-weekly and weekly concurrent chemotherapy were equally effective in terms of overall survival and disease-free survival. The toxicities and compliance in both arms were comparable. On subgroup analysis there was no statistically significant difference according to both age and stage.

We observed that the cumulative cisplatin dose along with radiotherapy and the duration of the treatment seems to be the most important factor. Tri-weekly cisplatin based concurrent chemoradiation was associated with statistically non-significant haematological toxicity and significant acute upper and lower gastrointestinal toxicity which was managed conservatively. Therefore, in high volume centres and patients coming from distant places, triweekly cisplatin based chemotherapy can be adopted to lower chemotherapy related hospitalisation and associated financial burden to the patients.

Both cisplatin based triweekly and weekly concurrent chemotherapy are equally effective in terms of OS and DFS, this might also reduce the bed occupancy time thereby increasing the throughput of the set up.

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Conflicts of interest

None declared.

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