Original Research Article

Prospective randomised study comparing concomitant chemo-radiotherapy using three weekly Cisplatin and biweekly 5- Fluoro-uracil versus weekly Paclitaxel in patients of locally advanced carcinoma cervix

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Abstract

India being the second most populous country in world, accounted for 25% of cervical cancer death according to GOLOBOCAN 2012. Although there are many agents available, the need for a model chemotherapy regimen which is effective and at the same time less toxic and has easy affordability is the current unmet need. We devised a study with the most commonly available and affordable drugs like Cisplatin, 5Fluoro-uracil and Paclitaxel. The main objective was to study the efficacy of concurrent chemo-radiotherapy in treatment of carcinoma cervix using two different regimens in terms of clinical response evidenced clinically as well as on imaging. Secondary objectives were to assess the progression free survival and overall survival. It was clearly evident that the response rate could be appreciated clinically in arm B over arm A, however this difference could not be justified by statistical methods. The toxicities observed in both the arms was comparable and in terms of progression free survival and overall survival the differences were not significant suggesting that the both the options could be considered in the treatment. Although the outcome looks promising prompting exploration of more such combination which are easily available in the rural hospitals, but due to smaller sample size and smaller follow up, a multi-institutional study with a larger sample size and a longer follow-up is definitely required to set the ball rolling in favor of combination chemotherapy including cisplatin and 5FU.

Key Words: Carcinoma cervix, Cisplatin, 5Fluoro-uracil, overall survival, progression free survival.

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INTRODUCTION

In 2012, according to GLOBOCAN, there were 527,600 new cervical cancer cases and 265,700 deaths reported worldwide[1]. Majority of global burden occurs in the less developed regions, where it amounts for 12% of all gynecological cancers. Carcinoma cervix is the most common female malignancy in India with crude incidence rate of 23.5 per 100,000 women per year and of the estimated 134,420 new cases each year, 72,825 women will die partially due to inadequacy of the current treatment[2-4] Radiotherapy is the mainstay of treatment for

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locally advanced cervical cancer. The ability of radiotherapy to cure locally advanced cervical cancer is limited by the size of the tumor because the doses required to treat large tumors exceeds the limit of radiation tolerance in normal tissue. Based on multi-centric trials favoring chemo-radiation compared to radiation alone for improved overall survival and reduce local and distant recurrence suggesting concomitant chemotherapy, National Cancer Institute issued a clinical alert stating that 'strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation in women who require radiation therapy in cervical cancer.[5] The reigning position of platinum agents in the treatment of advanced cervical cancer was questioned by the analysis of the Cochrane Collaboration meta-analysis in 2010, which showed that the benefit observed in previous concurrent chemo-radiotherapy based randomized trials may not depend on the use of platinum only[6]. A randomized study by Christie *et al*, confirmed that the addition of 5-FU to radiotherapy increased survival and local control[7]. However, the role of 5FU, as a radio-sensitizing agent is still severely underexploited, therefore, further research and trials are needed on a broader scale for its role to be stated as a chemotherapeutic agent used in treatment of carcinoma cervix in a concurrent setting. On the other hand, the role of taxanes has emerged recently in cervical cancer. Paclitaxel is a taxane based alkaloid from pacific yew (*Taxus brevifolia*)[8] which inhibits tubular aggregation[9,10]. Paclitaxel was found to have significant activityin solid tumors especially epithelial ovarian cancer, lung, and breast cancer[12]. Preclinical studies have shown a radio-sensitizing effect of paclitaxel in human cervical cancer cell lines[13]. Combination of cisplatin and paclitaxel has been used in metastatic or recurrent carcinoma of cervix in various phase II and III trials with an objective response rate of 36% to 46%. It was affirmed by these trials[14-16], that concomitant administration of cisplatin and paclitaxel was more effective than cisplatin alone in relapsed cases of advanced cervical cancer. These facts have lead many groups to investigate other drugs like paclitaxel in an attempt to improve on what can be achieved by Cisplatin alone. However little evidence is there to prove that Paclitaxel increase the overall response as compared to cisplatin[17]. However, in a rural Indian setting, where the standard treatment needs to be optimized with the primary drugs like cisplatin, 5FU and paclitaxel it becomes imperative to device an optimal regimen which can be used in a concomitant setting with radiotherapy to achieve maximum tumor control with minimum toxicity. This would not only improve compliance to the treatment owing to the less toxicity but also would lead to improved overall survival and quality of life.

MATERIALS AND METHODS

This study was a one year randomized prospective study, including sixty histologically proven patients of carcinoma cervix in a tertiary cancer institute in a rural Indian setting. The main objective of the study was to assess the efficacy of two different regimes of concurrent chemo- radiotherapy in a concurrent setting in treatment of carcinoma cervix in terms of compliance to treatment, toxicities and progression free survival (PFS). Patients were randomized into two different arms using central computerized randomization technique (consort diagram figure 1). The study arms were divided into arm A including patients receiving concurrent chemo-radiotherapy with weekly paclitaxel (60 mg/m^2) and arm B who received concurrent chemo-radiotherapy with three weekly cisplatin (50 mg/m^2) and biweekly 5- FU (500 mg/m^2). There were 29 patients in Arm A and 31 patients in Arm B. Both the chemotherapy schedules were studied along with concurrent radiotherapy in terms of progression-free survival (PFS), overall survival (OS) and the toxicities.

Inclusion Criteria

- Age < 70 years
- European Cooperative Oncology Group (ECOG) performance scale of 1 or 2
- Biopsy proven carcinoma of cervix.
- Stage IIB-IVA carcinoma cervix. Staging will be done as per International Federation of Gynecology and Obstetrics (FIGO) staging 2009.
- Normal hematological, renal and hepatic functions profile
- No prior chemotherapy or radiotherapy received.
- Signed written consent as per institutional regulation.

Exclusion Criteria

- Patient who has received chemotherapy or radiotherapy prior to this study will be excluded from the study.
- Patients not fulfilling the inclusion criteria are excluded from the study

A dose of 5000cGys in 25 fractions over 5 weeks was given by external beam radiotherapy (EBRT) either by two fields or four fields, during which weekly assessment of patients was done. After one week of completion of EBRT patients were assessed for brachytherapy and those appropriate were taken up for the treatment. Patients were reassessed for clinical response using the Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1) criteria. Radiation Therapy Oncology Group (RTOG)

toxicity criteria were used to access radiation induced toxicities. Patients were assessed by Magnetic Resonance Imaging (MRI) at the end of treatment and thereafter at six-weeks and at six-months for disease response and were categorized in following groups accordingly: Complete responders: Complete regression of lesion. Partial responders: More than 50% regression in lesion in maximum diameter. No responders: - Lesion regressed less than 50% in maximum diameter. During statistical analysis of the findings, we used SPSS (Statistical Package for Social Sciences) version 17. We also analyzed the data using cross-tables and have checked the significance using Chi-square test for different variables. For assessing the progression free survival and overall survival we used the Kaplan Meir curves. The strengths of this study were that it compared two schedules of chemotherapy which have not been explored before in a head on trial setting along with concomitant radiotherapy. A different dosing schedule which was considered less toxic and more manageable as well as treatment compliant was adopted. The other favorable aspect of our study was that the drugs chosen for the study has already demonstrated efficacy as first line drugs in treatment of carcinoma cervix and also had easy availability on a regular basis in a rural setting. The other most important strength of this study was that the drugs used in the study, were acceptable in terms of affordability, which has always been a limiting step in similar studies due to lack of any financial support from the institution or any medical companies. At the same time the drawbacks of the study were the small size of the study, as well as its limited follow-up period due to its time bound nature. Nevertheless, the results can always be reassessed after a longer follow-up for concrete analysis. We recommend that a long-term follow-up should be carried out to remove confounding factors and provide authenticity to the study.

RESULTS AND ANALYSIS

At the time of analysis of the results, two patients were lost to follow up in arm A and arm B. In addition to this, in arm B, one patient was started on a different regime due to intolerance to chemotherapeutic agent and one patient expired during the treatment, leaving a total of 27 patients in each arm. Patients in both the study group were comparable with respect to age distribution. The mean age ± SD in Arm A was 51.41 ±9.544 years and in Arm B was 48.85 ± 10.007 years. In our study 60 % of patients were in fourth and fifth decade. Thirteen (48.1%) patients in Arm A and 17 (63%) patients in Arm B had ECOG PS of 1at presentation, whereas 14 (51.9%) patients in Arm A and 10 (37%) patients in Arm B had ECOG PS of 2. The most common histopathology was squamous cell variety found in 53 (98.15%) patients followed by its variants in 1(1.25%) patient. There were no cases of adenocarcinoma detected. The distribution of patients according to stage at presentation is documented in Table (1).

Treatment Profile: All the patients in the respective arms received radiotherapy with a combined dose of 80-85 Grays (Gys), delivered by EBRT and BRT. Arm A received concurrent chemotherapy with weekly Paclitaxel whereas patients in Arm B received concurrent chemotherapy with three weekly cisplatin and biweekly 5-FU.

1. It was evident that 17 (63%), less than two-third of the patients completed five cycles (desired number) of weekly Paclitaxel in Arm A. However, in arm B, more than two-thirds of the patients i.e. 24 (88.9%) patients completed more than two cycles (desired number) of Cisplatin and about 18 (66.7%) patients completed more than 7-8 cycles of planned 5FU regimen. Overall treatment delay was observed in a total of 22 (40.74%) patients. This difference of treatment time delay in both the groups was not statistically significant (p-value 0.857).

Toxicity Profile

1. Table (2) shows that incidence of treatment related GI toxicity. Majority of patients in both the groups, did not show symptoms of toxicity during first week of treatment. Most of the toxicities occurred beyond second week and were grade 2 irrespective of the chemotherapy agents used. The difference between the toxicities was not statistically significant (p-value. 233).
2. While on the acute hematological toxicity front, both the arms exhibited an uneventful first week, followed by grade 1 toxicity during the second week. From third week onwards, as expected, the toxicity increased but more so in Arm A than in Arm B. During fourth week of treatment almost all patients had grade 1 toxicity. The difference between the toxicity levels in both the Arms was not statistically significant (p-value 0.836). During fifth week of treatment, only 2 (7.4%) patients exhibited grade 3 toxicity, belonging to arm B.
3. In the case of chemotherapy induced neutropenia, it was evident that majority of patients in both the arms had grade 1 toxicity, but the percentage of patients having grade 2 toxicity increased especially in Arm A during the course of the treatment. During the entire treatment none of the patient progressed to grade 3 or 4 toxicity. The difference was statistically non-significant (p-value=. 217).

4. Patients requiring hospital admission for the management of chemotherapy related toxicities in both the arms are tabulated in Figure 2.

Tumor Response

Tumor response was assessed clinically with MRI at completion of treatment, at six weeks and subsequently at six-months of treatment completion.

1. Table number (2) shows that 19 (70.4%) patients in Arm A and 23 (85.2%) patients in Arm B had complete response at the completion of treatment (2A). The findings were consistent at six weeks and at six months of treatment with 19 (70.4%) patients in Arm A and 24 (88.9%) patients in Arm B showing complete response (Table 2B, 2C). Patients showing partial response there were 8 (29.6%) patients in Arm A and 3 (11.1%) patients in Arm B at treatment completion. The results were consistent at successive assessments. There is a difference of 18% in response rate in both the arms which was appreciated clinically at six months, however this difference is not statistically significant (p value=0.362) and therefore needs a larger sample size and a longer follow-up for validating our study.
2. Overall status of patients was assessed from enrollment of the first patient till the last follow up (table 4). Patients who were enrolled during initial period of study had longer follow up than the patients enrolled in later period of study. The overall status of the patients observed at six to eight months and beyond eight months was almost equal in both the arms. It was clear that the incidence of residual disease was appreciably high in arm A, almost double to that of arm B. Also the deceased patients in Arm A were twice in number to that of in Arm B.
3. In terms of progression free survival and overall survival, there was no significant difference among the two arms (p value > 0.05). The survival graph curve of arm B (Figure 3), is fairly better than arm A. But as seen in our study, at some or the other point both curves interchange, so one group is better for some period of time and at other point, the other group crosses it. In progression free survival, however, arm B is slightly better but not significantly. Also we can see mean survival time graph that the arm B is better than arm A.

Table 1: Distribution of patients according to the disease stage. (Staging according to FIGO 2009)

FIGO STAGE	Patients in arm A		Patients in arm B		Total number of patients	
	n	%	n	%	N	%
2B	11	40.7	11	40.7	22	40.7
3A	3	11.1	1	3.7	4	7.4
3B	11	40.7	12	44.4	23	42.6
4A	2	7.4	3	11.1	5	9.3
Total	**27**	**100**	**27**	**100**	**54**	**100**

Table 2A:

Response	Arm A		Arm B		Total number of patients	
	N	%	n	%	n	%
Complete response	19	70.4	23	85.2	42	77.8
Partial response	8	29.6	3	11.1	11	20.4
Progressive disease	0	0	0	0	0	0
Stable disease	0	0	0	0	0	0
Died	0	0	1	3.7	1	1.9
Total	**27**	**100**	**27**	**100**	**54**	**100**

Distribution of patients according to tumor response at completion of treatment.

Table 2B:

Response at six weeks	Arm A		Arm B		Total number of patients	
	n	%	n	%	n	%
Complete response	19	70.4	24	88.9	43	79.6
Partial response	8	29.6	2	7.4	10	18.5
Progressive disease	0	0	0	0	0	0
Stable disease	0	0	0	0	0	0
Died	0	0	1	3.7	1	1.9
Total	**27**	**100**	**27**	**100**	**27**	**100**

Distribution of patients according to tumor response at 6 weeks of treatment

Table 2C:

Response at 6 months	Arm A		Arm B		Total number of patients	
	n	%	n	%	N	%
CR	19	70.4	24	88.9	43	79.6
PR	1	3.7	0	0	1	1.9
PD	5	18.5	2	7.4	7	13
SD	0	0	0	0	0	0
Died	2	7.4	1	3.7	3	5.5
Total	**27**	**100**	**27**	**100**	**54**	**100**

Distribution of patients according to tumor response at 6 months of completion of treatment.

Table 3:

PFS (months)	Arm A		Arm B		Total number of patients		p-value
	N	%	N	%	n	%	
<6	2	7.4	2	7.4	4	7.4	
6-8 months	9	33.3	7	26	16	29.6	.341
>8 months	16	59.3	18	66.6	34	63	
Total	27	100	27	100	54	100	
Mean± SD	10.15±3.708		11.15±3.929				
Median	10		11				

Distribution of patients according to Progression Free Survival till six months of follow up of the last patient enrolled in the study Arms.

Table 4:

	Arm A		Arm B		Percentage	
	n	%	n	%	N	%
No evidence of disease	19	70.4	24	88.9	45	83.3
Residual disease(Progressive disease)	6	14.8	2	7.4	6	11.1
Recurrent disease	0	0	0	0	0	0
Died of disease	2	7.4	1	3.7	3	5.6
Total	**27**	**100**	**27**	**100**	**54**	**100**

Overall status of the patients in the study arms till six months of follow up of the last enrolled patient.

Table 5

Group	Mean[a]			
			95% Confidence Interval	
	Estimate	Std. Error	Lower Bound	Upper Bound
1	9.556	.715	8.155	10.957
2	11.111	.765	9.612	12.610
Overall	10.333	.529	9.296	11.371

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	1.658	1	.198
Breslow (Generalized Wilcoxon)	2.188	1	.139
Tarone-Ware	2.042	1	.153

Test of equality of survival distributions for the different levels of Group.

Overall comparison of both study arms in terms of PFS.

Table 6:

Group	Mean[a]			
			95% Confidence Interval	
	Estimate	Std. Error	Lower Bound	Upper Bound
1	18.857	.776	17.335	20.379
2	19.286	.661	17.990	20.582
Overall	19.006	.560	17.908	20.103

Table 7:

Overall Comparisons			
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	.614	1	.433
Breslow (Generalized Wilcoxon)	1.752	1	.186
Tarone-Ware	1.342	1	.247

Test of equality of survival distributions for the different levels of Group.

Overall comparision of patients in both the arms in terms of OS.

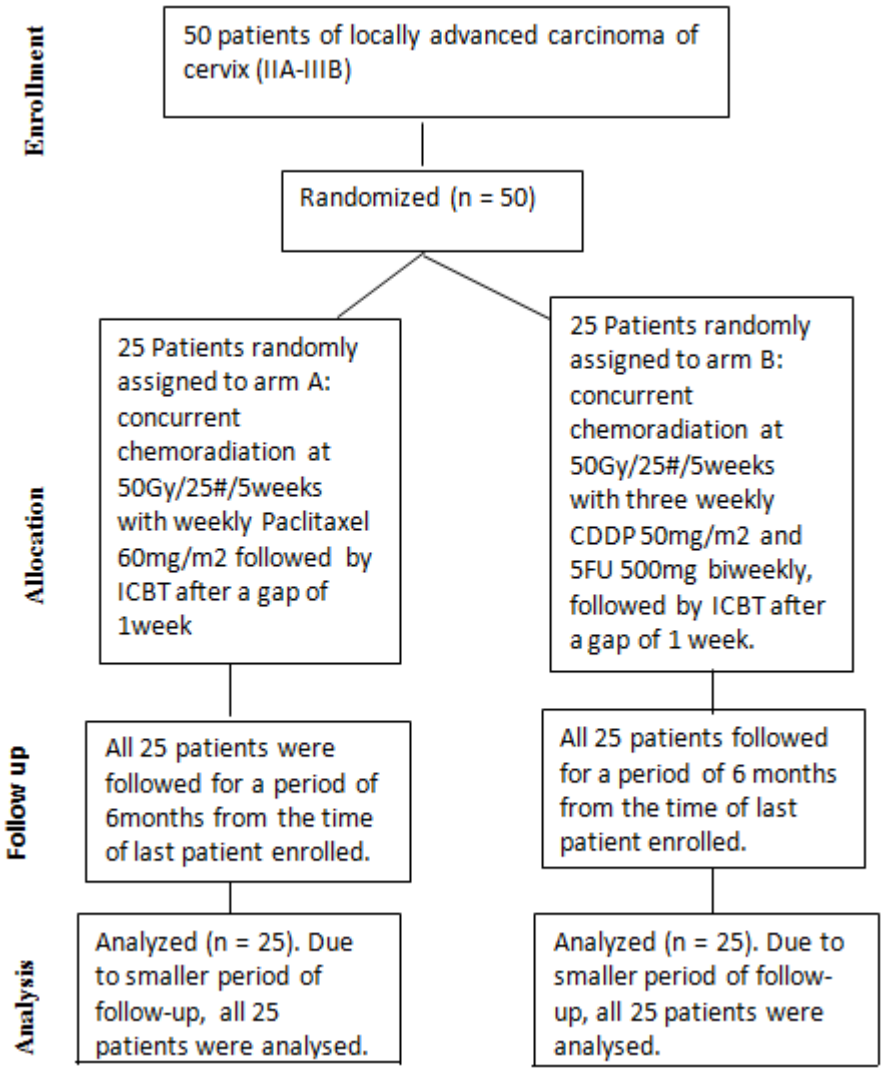

Figure 1: Consort Diagram depicting distribution of patients

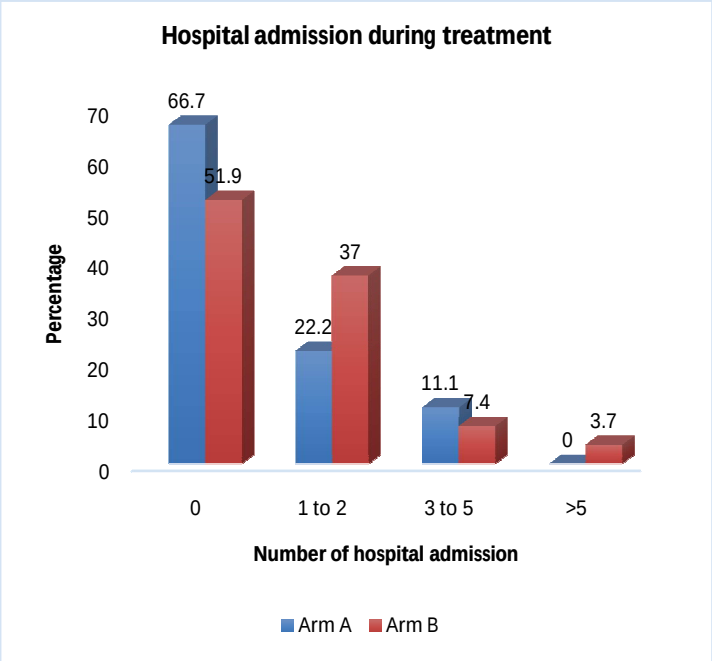

Figure 2: Representation of patients according number of hospital admission required during treatment

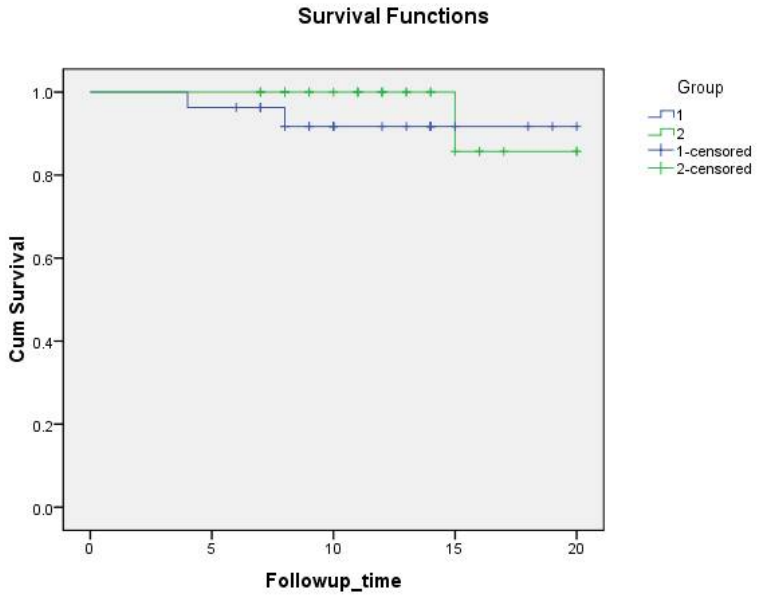

Figure 3: Survival functions of both study arms

An interchangeable pattern was seen suggesting arm B to be superior in the initial phase whereas arm A to be superior in the latter phase.

DISCUSSION

To reach to an academic consensus on the standard chemotherapy schedule, amidst the wide range of options available is a gigantic task in itself. The optimal choice of chemotherapy is still a grey zone in terms of carcinoma cervix with its varied sensitivity to variable drugs. Therefore, this study was undertaken to throw new light on the possible combinations of the most common and easily available drugs in the rural settings of Northern India which might prove to be more acceptable leading to increased compliance of the treatment. The most common reasons for local recurrence have been attributed to

incomplete treatments which in turn are caused mostly due to chemotherapy induced toxicities and increased overall treatment time (OTT). Patients receiving chemo-radiation have increased treatment-related toxicities as compared to those receiving radiation alone. Amongst them, the most common are nausea, enteritis, and hematologic toxicities. The most common reason for failure to complete chemotherapy as expected was gastrointestinal (GI) toxicity. There was no correlation between failure to complete planned chemotherapy and patient age, disease stage, radiotherapy treatment volumes or postoperative treatment (19). In a study by Jakubowicz *et al*, acute treatment-related toxicity grade 3 or 4 (WHO) occurred in 21.6% of patients including leucopoenia in 7.5%anemia in 5.0%, nausea and vomiting in 3.3%, diarrhea in 5.0%, and urinary tract infection in 0.8% (20). In our study, a total of 97.3% of patients completed treatment without any interruptions for treatment-related toxicity. Only two patients (3.4%) experienced a delay in brachytherapy for treatment-related toxicity. The common toxicities observed in our study were GI and hematological toxicities. However, this difference in the toxicities between the two chemo-radiation groups was not statistically significant (p-value. 440) irrespective of a combination chemotherapeutic schedule adopted in arm B. To emphasize, toxicities in both the arms were at an acceptable level and thereby offering an affordable. The other reason for increased recurrence rate is OTT. Median OTT of eight weeks is considered optimal by various investigators[21,22]. In our study, 17 (63%) patients in Arm A, and eighteen patients (66.7%) in Arm B, which amounts to more than two-thirds of the target population, completed their prescribed treatment in the desired time frame of eight to nine weeks. The mean treatment duration in both the study arms was 60-68 days which was longer than the standard accepted time period. The reasons behind this was that ours was a tertiary care set up with an ongoing academic program, many patients receiving treatment were from rural areas with compromised nutritional status and therefore needed time for nutritional build up or toxicity management. Also most of the patients were from low socioeconomic status and uneducated thereby undermining the importance of treatment. In the study, clinical response assessed at completion of treatment confirmed that there was a difference of 18% percent in the response rate between two Arms favoring arm B, however this difference was not statistically significant (p-value. 161). The clinical response attained at six weeks of treatment completion and at six months of follow-up was consistent. Frederick B *et al*,[23] in their study with concurrent chemo-radiotherapy with cisplatin and 5-FU observed complete disappearance of all clinical evidence of disease in 65 (86.7%) of patients, with the complete response and partial response rate of 93.3%. The findings were affirmed with our study results with arm B containing 5-FU and cisplatin regimen showing complete response rate of 88.9% and partial response rate of 95%. Whereas in defense for arm A, sufficient evidence was gathered by Kenji Umayahara *et al*, who in their study observed concurrent chemo-radiation with weekly paclitaxel and cisplatin showing complete response in 85% patients[24]. However, in our study, 70% complete response was seen in weekly paclitaxel arm. The reasons attributed for the slope in response rate could be because a single drug was used. Progression free survival and overall survival were also comparable in both the arms. The Kaplan Meir graph curves demonstrated an early survival advantage with Arm B initially, but in the latter part of the study Arm A took over and both the survival curves remained interchangeable during the time period of the study. However, in our study the main limitation was a relatively small sample size, which could be due to single institution study. Due to the study being conducted in a time bound manner, enrolment was conducted for one year only. Further due to the advanced stage presentation and poor nutritional status, about 18% patients did not have adequate regression of the disease at the completion of EBRT and therefore could not be included for brachytherapy. The answers to this problem lie in conducting more multi-institutional trials so as to overcome the problem of small sample size. The incorporation of positron-emission tomography based response-evaluation criteria (PERCIST) may improve accuracy of response assessment. Therefore, the results in both the studies re-affirmed that concomitant chemo-radiotherapy is the answer to locally advanced cervical carcinoma. There have been many chemotherapeutic agents which boast of high efficacy against the malignancy along with added radio-sensitizing property which are unfortunately not readily available or affordable at cancer centers in rural areas. However, there is still a persistent grey zone which needs re-exploration at every angle especially when it comes to a rural setup with limited resources. The results observed were definitely in favor of the arm including cisplatin and 5FU showing clinically appreciable complete response rate and also decreased progressive disease. However, the results cannot be validated on concrete grounds, as of now due to study limitations. So, based on these results we can conclude that this study very efficiently opens new horizons in terms of newer schedules of the commonly available chemotherapeutic agents which can be exploited with different dosing and schedules to offer treatment benefits to patients of advanced cervical carcinoma where treatment related toxicities and OTT

delay pose a major problem in attaining complete response due to poor performance status of patients hailing from rural backgrounds.

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