Pure Accelerated Radiation Versus Concomitant Chemoradiation in Selected Cases of Locally Advanced Carcinoma Cervix: A Prospective Study

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Abstract

Objective This non-randomized study was conducted to assess and compare the response and safety of true accelerated radiation alone to concomitant chemoradiation in locally advanced squamous cell carcinoma of the uterine cervix.

Methods Sixty patients with locally advanced squamous cell carcinoma of the uterine cervix, FIGO Stages (2009) IB2–IIIB were non-randomized to receive six fractions per week of external beam radiation (EBRT) (will be henceforth referred to as Arm A or Study arm or pure accelerated radiation arm) and five fractions per week of EBRT and chemotherapy with inj cisplatin 40 mg/m² i.v. every

Monday during the course of EBRT (will be henceforth referred to as Arm B or Control arm or chemoradiation arm).

Results The median follow-up was 15 months in both the arms. The overall treatment time was 56.54 days for Arm A and 62.59 days for patients in Arm B (P value < 0.000**). The median EBRT time was 32.25 days in Arm A and 38.85 days in Arm B, a statistically significant delay for patients of chemoradiation Arm B (P value < 0.000**). The response assessment at the end of the study was not statistically different among the patients in both the treatment arms (P value 0.631).

Conclusion The early responses to treatment with pure accelerated EBRT are non-inferior to concomitant chemoradiation and the acute toxicities are lesser.

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Introduction

In Indian women, the uterine cervix is one of the leading sites of primary cancer. Poverty, ignorance, and lack of proper screening facilities are the root causes that most of the patients present to us in locally advanced stages. Traditionally, a judicious combination of external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) is the widely accepted primary modality of treatment for locally advanced carcinoma of the cervix.

Through the passage of time, with the advent of high energy machines, practice of radiotherapy with more precision, and with better understanding of radiobiological aspects, prospects of radio-curability have greatly increased. In spite of this, although in early stage disease this treatment achieves high cure rates, the result of conventionally fractionated primary radiotherapy alone is not very satisfactory in locally advanced cases.

To circumvent this problem, over the last three decades, different investigational procedures were attempted to increase the radiation response, namely altered fractionated schedule, radiosensitizers, hyperbaric oxygen, hyperthermia, and so on, but without any major benefit. On the basis of numerous notable studies in the late 1990s, concomitant chemoradiation with Cisplatin has become the “standard” treatment for advanced carcinoma cervix. Cisplatin added to radiation reduces the relative risk of death from cervical carcinoma by approximately 50 % by decreasing local failure and distant metastasis.

But, in elderly patients, patients with co-morbid medical conditions, poor performance status (PS), and those who refused chemotherapy, cytotoxic chemotherapy cannot be administered for which different strategy is required to enhance the effects of radiotherapy given as a single modality of treatment.

Prolongation of overall treatment time had detrimental effects on local tumor control in carcinoma cervix. Hence, the total duration of radiotherapy should ideally be as short as possible.

In our setting, many patients with advanced cervix cancer present to us with significant co-morbidities that preclude the use of chemotherapy along with radiation. Accelerated EBRT with six fractions per week is an effective alternative there. We conducted this study in locally advanced carcinoma cervix to compare treatment results of pure accelerated fractionation (AF) (six fractions per week) alone to that of concomitant chemoradiation.

Materials and Methods

Period of study: Accrual was started from Jan 1, 2009. Follow-up: updated till Aug 31, 2010. Type of study: prospective, nonrandomized, double arm, open label, interventional, and single institutional. Study population: All biopsy proven cases of locally advanced squamous cell carcinoma of the uterine cervix were eligible for this study. Inclusion criteria were: Biopsy proven cases of advanced squamous cell carcinoma of uterine cervix, Stage IB2–IIIB (as per FIGO 2009 Staging), age between 30 and 65 years with Karnofsky Performance Status (KPS) ≥ 70 , and adequate bone marrow function (Hb ≥ 10 g/dl; WBC $\geq 4,000/\text{mm}^3$; ANC $\geq 2,000/\text{mm}^3$; platelets $\geq 100,000/\text{mm}^3$). Signed study-specific informed

consent, in agreement with the Helsinki declaration 1996, prior to study entry was mandatory. The exclusion criteria for both subsets were: age ≥ 75 years with KPS < 70 ; pregnancy; history of pelvic surgery, malignancy, exposure to cytotoxic chemotherapy or radiation; clinical or radiological evidence of metastasis at presentation; and participation in any other study on cancer cervix. Pre-treatment evaluation included detailed history and physical examinations, complete hemogram, blood sugar, serum urea and creatinine, liver function tests, serum electrolytes, chest X-ray (CXR), ultrasonography (USG) of whole abdomen, contrast-enhanced computed tomography (CT) scan of abdomen and pelvis, biochemical and microbiological analyses of urine, cystoscopy, proctoscopy, and cardiological evaluation as and when indicated.

The patients who met the eligibility criteria were deemed fit to enter the study. The pros and cons of entering the study were explicitly explained to them in a language they understood best, and they were registered for the study only after they agreed to give informed consent.

All eligible patients willing to participate in the study were divided into two arms, Arm A (Study Arm) and Arm B (Control Arm). Baseline patient characteristics were similar and well-balanced in both arms (Tables 1, 2).

Patients of the Study Arm received six fractions per week of external beam radiation therapy (EBRT) only, from every Monday to Saturday (one extra fraction of EBRT on Saturday i.e., pure accelerated radiotherapy). Patients of the Control Arm (Arm B) received five fractions per week of EBRT from every Monday to Friday. A weekly injection of Cisplatin at the dose of 40 mg/m^2 iv with necessary premedication and hydration was given on every Monday during EBRT.

Both groups received EBRT to a total dose of 50 Gy in 25 fractions. The treatment was completed in 29 days (4 weeks and 1 day) in Arm A and in 35 days (5 weeks) in Arm B, using Telecobalt machine at a source-skin distance of 80 cm. Portals used were parallel opposing antero-posterior (AP) and postero-anterior (PA), but a four field box technique was used if the interfild distance exceeded 18 cm.

All patients in both arms received high dose rate intracavitary brachytherapy (HDR ICBT) immediately after completion of EBRT, delivered by tandem and vaginal applicators (ovoids) using Fletcher-Suit Delclos applicator system with Iridium 192 sources. Three consecutive weekly applications of 700 cGy each to point A (a point 2 cm lateral to the center of the uterine canal and 2 cm above from the mucous membrane of the lateral fornix of the vagina in the plane of the uterus) were done. Simple sterile gauze packing was introduced to ensure optimal separation between the applicators and the bladder

Table 1 Comparison of baseline categorical variables between the 2 arms

Parameters	Groups				<i>P</i> Value ^a
	Arm A (<i>n</i> = 28) (%)		Arm B (<i>n</i> = 27) (%)		
<i>Socio-economic status</i>					
Low	22	78.6	21	77.8	0.799
Middle (upper + lower)	4	14	5	18.5	
High	2	7.1	1	3.7	
<i>Contraceptive use</i>					
Yes	12	42.9	9	33.3	0.582 ^b
No	16	57.1	18	66.7	
<i>Menopausal status</i>					
Pre-menopausal	4	14.3	6	22.2	0.728 ^b
Post-menopausal	24	85.7	21	77.8	
<i>Average number of children</i>					
1	2	7.1	1	3.7	0.727
2	2	7.1	1	3.7	
3	6	21.4	4	14.8	
4	15	53.6	15	55.6	
5	3	10.7	6	22.2	
<i>KPS (%)</i>					
100	13	46.4	12	44.4	0.989
90	7	25.0	7	25.9	
80	8	28.6	8	29.6	
<i>Hemoglobin (gm/dl)</i>					
<12	13	46.4	12	44.4	0.883
>12	15	53.6	15	55.6	
<i>Creatinine clearance (ml/min)</i>					
50–59	9	32.1	10	37.0	0.765
60–69	14	50.0	14	51.9	
70–79	5	17.9	3	11.1	
<i>FIGO Staging</i>					
FIGO stage IIA	3	10.7	2	7.4	0.955
FIGO stage IIB	6	21.4	6	22.2	
FIGO stage IIIA	4	14.3	5	18.5	
FIGO stage IIIB	15	53.6	14	51.9	

^a All test by means of χ^2 , except were mentioned

^b Fisher's Exact test

Table 2 Baseline profile by means of continuous variables, comparison between the 2 groups by means of Independent t test

	Groups	Mean $\pm$ Std. error mean	95 % Confidence interval of the difference		P Value
			Lower	Upper	
Age (in years)	Arm A (n = 28)	50.46 $\pm$ 1.64	−3.80910	5.40434	0.730
	Arm B (n = 27)	49.66 $\pm$ 1.60			
Weight in kg	Arm A (n = 28)	54.21 $\pm$ 2.15	−4.29957	6.80222	0.653
	Arm B (n = 27)	52.96 $\pm$ 1.73			
Age of menarche (in years)	Arm A (n = 28)	12.82 $\pm$ 0.29	−1.39627	0.44653	0.306
	Arm B (n = 27)	13.29 $\pm$ 0.36			
Age of marriage (in years)	Arm A (n = 28)	20.25 $\pm$ 0.67	−1.29644	2.31495	0.574
	Arm B (n = 27)	19.74 $\pm$ 0.60			
Age of 1st child birth (in years)	Arm A (n = 28)	21.57 $\pm$ 0.62	−1.22213	2.06869	0.608
	Arm B (n = 27)	21.15 $\pm$ 0.53			

anteriorly and rectum posteriorly. The dose was prescribed to point A, point B, and 2 cc of rectum and bladder volumes (Table 3).

Response Assessment

Acute toxicities were assessed every week during EBRT and ICBT by means of the NCI common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and are listed in Table 5. Response was assessed by means of the response evaluation criteria in solid tumors (RECIST) older Version 1.0 at the end of EBRT, and after ICBT (i.e., completion of treatment) to determine immediate response to treatment. Thereafter, response was assessed every month on follow-up to 6 months, and every 2 months subsequently. Response assessment was done clinically and radiological investigations were used whenever appropriate.

The definitions used to define response are as follows: Complete response (CR) is the disappearance of all target lesions, partial response (PR) is at least a 30 % decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. Stable disease (SD) is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum longest diameter since the treatment started, and PD is defined as at least a 20 % increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions (all measurable lesions up to a maximum of five lesions per organ and ten lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline). Patients were followed up by both the radiation oncologist and the gynecologist with detailed physical and gynecological examinations (per speculum, per vaginal, and per rectal), and Papanicolaou smears, appropriate blood examination, and/or imaging studies. Initially, patients were followed up every month (for the first 6 months) and then every 2 months.

Statistical Analysis

Statistical analysis was done by means of SPSS version 17, Chicago. For categorical variables, Chi Square and Fisher Exact tests were used where applicable, while for continuous variables, the mean and standard deviation (SD) were compared by means of Independent samples *t* test with 95 % confidence interval (CI). All tests were two-tailed and *P* value <0.05 was taken as significant.

Results

Case accrual and baseline patient characteristics: After careful scrutiny toward the meeting of inclusion and exclusion criteria, 60 patients (30 in each arm) were selected for accrual. However, 2 patients in Arm A and 3 patients in Arm B failed to complete treatment and were consequently excluded from the study. Reasons included noncompliance with study protocol, refusal to undergo Brachytherapy, and personal reasons. Ultimately, 28 patients in the study arm (Arm A) and 27 patients in the control arm (Arm B) underwent the study.

The median number of concomitant chemotherapy cycles received by patients in Arm B was 4 (range 3–5). More than 90 % patients received all scheduled cycles as per protocol. All patients received 3 fractions of ICBT immediately on completion of EBRT using the Fletcher Suit Delclos system of Intracavitary Application. Median treatment delay between starting Brachytherapy and EBRT was 2 days in both arms (*P* = NS). The prescription dose of 7 Gy in 3 fractions by HDR could be delivered to all patients. A comparison of median dose to the critical organs—bladder and rectum—by Brachytherapy yielded similar results (*P* = NS) (Table 3).

The median follow-up was 15 months in both the arms. The overall treatment time was 56.54 days for Arm A and 62.59 days for patients in Arm B (*P* value < 0.000**) (Table 4). The median EBRT time was 32.25 days in Arm A and 38.85 days in Arm B, a statistically significant delay for patients of chemoradiation Arm B (*P* value < 0.000**). The gap in treatment during EBRT was significant in Arm B (*P* value 0.023**). The first per protocol assessment of

Table 3 Mean dose (cGray) to rectum and bladder (mean ± SE)

Dose to organs at risk	Groups		95 % Confidence interval of the difference		<i>P</i> Value ^a
	Arm A (<i>n</i> = 28)	Arm B (<i>n</i> = 27)	Lower	Upper	
Dose to rectum per fraction (2 cc volume)	539.89 ± 5.06	546.85 ± 4.69	−20.83	6.91	0.319
Dose to bladder per fraction (2 cc volume)	647.61 ± 9.90	625.33 ± 9.19	−4.86	49.36	0.106

^a By means of independent *t* test for comparison of means

Table 4 Time parameters in the study (mean $\pm$ SE)

Time parameters	Groups		95 % Confidence interval of the difference		<i>P</i> Value ^a
	Arm A (<i>n</i> = 28)	Arm B (<i>n</i> = 27)	Lower	Upper	
Overall treatment time (in days)	56.54 $\pm$ 0.379	62.59 $\pm$ 0.56	−7.40166	−4.71209	0.000*
EBRT time (in days)	32.25 $\pm$ 0.39	38.85 $\pm$ 0.58	−8.00132	−5.20238	0.000*
Gap in treatment (in days)	2.18 $\pm$ 0.40	3.81 $\pm$ 0.57	−3.03477	−0.23772	0.023*
Follow-up time (in months)	15.10 $\pm$ 0.61	15.00 $\pm$ 0.63	−1.65560	1.86988	0.903

^a By means of independent *t* test for comparison of means* Significant *P* value **Fig. 1** Bar diagram showing the response rate at the last follow-up

response: The response assessment by means of the RECIST criteria was, however, not affected by treatment delays (interruptions during EBRT and overall treatment time) with no statistical difference in responses at the end of EBRT (*P* value 0.477) and at the end of the total treatment (*P* value 0.213). The response assessment at the end of the study: All patients were followed up regularly as per the study design. At the last follow-up, response was again assessed. The median follow-up duration was 15 months in both arms (range 10–19 months). The response assessment at the end of the study was not statistically different among the patients in both the treatment arms (*P* value 0.631) (Fig. 1) Acute toxicities were assessed by means of the CTCAE version 3.0 (Table 5). Grade 0 toxicities were not significantly different between the two arms, except for vaginal discharge which is higher in the study arm or Arm A. On the other hand, Grade 1 toxicities

for vaginal discharge and vaginal mucosities were significantly higher in the control arm or Arm B or chemoradiation arm. Grade 2 toxicities for both arms were not significantly different. Grade 3 vaginal mucosities were significantly higher in the chemoradiation arm. With the median follow-up of 15 months, there was no difference in the disease-free survival (Fig. 2) The median number of concomitant chemotherapy cycles received by patients in Arm B was 4 (range 3–5). More than 90 % patients received all scheduled cycles per protocol. All patients received 3 fractions of ICBT immediately on completion of EBRT. Median treatment delay between starting Brachytherapy and EBRT was 2 days in both arms (*P* = NS). The prescription dose of 7 Gy in 3 fractions by HDR could be delivered to all patients. A comparison of median dose to the critical organs—bladder and rectum—by brachytherapy yielded similar results (*P* = NS) (Table 4).

Discussion

Carcinoma of the cervix constitutes ~20 % of female cancer patients attending our Out Patients Department. Unfortunately, most of them hail from a lower socio-economic stratum and present in very advanced stages (mostly in stage IIIB), where the backbone of treatment is radiotherapy (usually EBRT followed by ICBT). Our institutional practice is to give about 50 Gy by EBRT followed by a high dose rate (HDR) ICBT to a total dose $\geq$ 80 Gy to point A.

Concomitant chemoradiation is now the standard treatment in locally advanced carcinoma cervix and Cisplatin appears to be the ideal chemotherapeutic agent [1]. Green et al. analyzed data from 19 randomized trials comprising 4,580 patients and concluded that concomitant chemotherapy results in improved overall survival (RR 0.71; *P* < 0.0001) and progression-free survival (RR 0.61; *P* < 0.0001). However, the absolute survival benefit was 12 % maximum in early stage (I and II) disease [2]. Patients receiving chemoradiation had a higher incidence of grades 3 and 4 hematologic and gastrointestinal toxicities. Moreover, a recent update from a pivotal

Table 5 CTCAEv3 toxicity comparison between the 2 arms

Adverse events	Grade 0			Grade 1			Grade 2			Grade 3		
	Arm A	Arm B	P Value	Arm A	Arm B	P Value	Arm A	Arm B	P Value	Arm A	Arm B	P Value
Anorexia	3	3	0.962	16	13	0.504	5	5	0.949	4	6	0.446
Dermatitis	16	14	0.694	7	8	0.700	4	3	0.724	1	2	0.531
Lower GI	11	7	0.291	9	10	0.703	8	8	0.931	0	2	0.142
Bladder	19	17	0.703	7	8	0.700	2	2	0.970	0	0	0
Nausea and vomiting	8	7	0.826	8	5	0.380	8	8	0.931	4	7	0.281
Diarrhea	15	10	0.216	5	5	0.949	4	6	0.446	4	6	0.446
Fatigue	11	8	0.452	12	11	0.874	4	4	0.956	1	4	0.147
Hemoglobin	12	16	0.224	10	9	0.853	3	1	0.317	3	1	0.317
ANC	21	16	0.214	4	5	0.853	3	3	0.962	0	3	0.070
Creatinine	24	20	0.446	3	4	0.648	1	3	0.282	0	0	0
Vaginal discharge	15	7	0.036*	6	14	0.019*	7	6	0.808	0	0	0
Vaginal mucosities	15	8	0.072	4	11	0.028*	1	4	0.147	0	4	0.034*
Fever	23	19	0.304	4	7	0.281	1	1	0.979	0	0	0
Weight loss	21	17	0.496	6	8	0.485	1	2	0.531	0	0	0

ANC absolute neutrophil count

* Significant (χ^2 test). There were no grade 4 and 5 toxicities **Fig. 2** Disease-free survival by means of the Kaplan–Meier survival analysis by means of the Log rank test (P value 0.251) showing a median follow-up of 15 months; there was no difference in the disease-free survival

meta-analysis of chemotherapy in head and neck cancer has confirmed that the magnitude of the benefit from concomitant chemotherapy is less in older patients [3].

There is no question about the benefit of chemoradiation in cervical cancer, albeit at the cost of incremental toxicity.

However, the best treatment of those patients who cannot tolerate chemoradiation is not very clear. Traditionally, conventional radiation alone has been used in this subset of patients, which is a suboptimal treatment in locoregionally advanced cervical cancer. To improve local control and perhaps survival, newer avenues should be sought in this group.

The cure rates of squamous cell carcinomas are highly dependent on overall treatment time due to accelerated regeneration of tumor clonogens [4]. Studies of the increase in tumor control dose with increasing treatment time suggest that after a variable lag period, surviving tumor clonogens regenerate rapidly during fractionated radiation therapy to the extent that each additional day of treatment requires ~ 0.6 Gy, on average, to offset clonogenic cell regeneration, again suggesting a clonogenic cell doubling time of 3.5–5 days [5]. Many trials have conclusively proven overall treatment time to be a major determinant in the outcome in cervix cancer [6–11]. The usual recommendation is to complete treatment by 8 weeks (56 days) [12]. Petereit et al. [8] have shown that the 5-year survival and pelvic control rates differed significantly with treatment times of ≤ 55 days versus ≥ 55 days.

Accelerated radiotherapy seems to be a natural choice to circumvent the above two issues. By shortening treatment time, without any alteration of total dose or dose per fraction, treatment can be effectively completed earlier without incremental toxicities usually associated with other altered fractionation schedules like hyperfractionation. This benefit should ideally be extended to those for whom

concomitant chemotherapy is not possible because it gives them tangible benefit over conventional radiation by reducing overall treatment time.

The rationale for AF is that reduction in overall treatment time decreases the opportunity for tumor cell regeneration during treatment and, therefore, the probability of tumor control for a given total dose. Because overall treatment time has little influence on the probability of late normal tissue injury, a therapeutic gain should be realized provided the size of dose per fraction is not increased and the interval between fractions is sufficient for complete repair to take place [13]. Strategies to accelerate radiation can be divided into two categories: (i) pure AF regimens with reduced overall treatment time without concurrent changes in the fraction size or total dose and (ii) hybrid AF regimens with reduced overall treatment time in conjunction with changes in other parameter(s) such as the fraction size, total dose, and time distribution. Three forms of hybrid AF regimens tested in randomized clinical trials include: (a) accelerated with dose reduction, (b) accelerated with split course, and (c) accelerated with concomitant boost [14].

The benefit of accelerated (six fractions per week) radiation has been conclusively proven in the DAHANCA Trials by Overgaard et al. where 1,485 patients with head and neck carcinomas of all stages were treated with 6 versus 5 fractions of conventional radiation per week (i.e., completion of treatment was achieved in 6 vs. 7 weeks by giving an extra fraction each week) [14]. Overall, 5-year locoregional control rates improved (70 vs. 60 %; $P = 0.0005$) and improved disease-free survival (73 vs. 66 %; $P = 0.01$), but not overall survival. As squamous cell cervix cancer behaves clinically and radiobiologically in a similar fashion to its head and neck counterparts, Yoon et al. [15] extended the AF schedule to cervical cancer. The findings from the phase I/II trials were “six fraction per week of EBRT and HDR brachytherapy is an effective treatment for patients with a carcinoma of the uterine cervix and can be used as a possible alternative to concomitant chemoradiotherapy in elderly patients or in patients with co-morbidity.”

In our study, although the shortening of treatment time did not translate into improved local control or reduced recurrence, the results were clearly non-inferior to the control arm. CR appeared to be relatively higher in the control arm, but the difference seemed to be dwindling with time. Whether the similar short-term response is carried forward with time or, more importantly, survival rates are similar can only be ascertained with a longer follow-up.

Another major finding of our study was the consistently increased grade 3 acute toxicities in the chemoradiation or control arm. We assumed that the prolongation of overall treatment time was the cause behind these adverse events in the majority of patients. In a developing country like

ours, where delivering treatment under numerous resource constraints is a major challenge, shortening treatment time has other benefits. It facilitates earlier initiation of treatment for more patients by reducing the waiting period, and insures optimization of limited resources.

Although findings from our study vindicate the non-inferiority of accelerated radiation, the results need to be viewed with cautious optimism. Though our study is plagued by some drawbacks including small sample size, short follow-up period, and inherent biases of single-institutional trials, our trial offers an exciting prospect which might be an alternative option in selected patients who have contraindications to chemoradiation, and we hope that our results will be validated in larger trials in the future to better serve these patients.

Conclusion

To conclude, findings from this study suggest that pure accelerated EBRT (six fractions per week) alone followed by HDR brachytherapy is an effective treatment for patients with locally advanced carcinoma of the uterine cervix and can be used as a possible alternative to concomitant chemoradiotherapy in selected patients. The early responses to treatment are non-inferior to concomitant chemotherapy and the acute toxicities lesser. Moreover, overall treatment time, which is of paramount importance for treatment success, is significantly reduced with accelerated radiation. This method provides a rational and feasible alternative to conventional chemoradiation in patients with locally advanced cervical cancer who have contraindication to chemotherapy. However, this finding is not conclusive as a result of the small sample size and the relatively short follow-up period, which are major drawbacks of this study. The result should, therefore, be accepted with the caveat that chemoradiation is still the best option in those who can tolerate it and newer approaches should only be reserved for selected patients and special circumstances. Whether the encouraging short-term results of this study translate into similar long-term response and overall survival without significant late toxicities remains an unanswered question. Further, multicenter, controlled, randomized phase III trials will be needed to prove the benefit of the shortening overall treatment time and compare the efficacy with chemoradiation.

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