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REVIEW ARTICLE

PROSPECTIVE STUDY OF CONCOMITANT CHEMORADIATION VS ACCELERATED RADIOTHERAPY WITH INTERDIGITATED BRACHYTHERAPY IN CANCER CERVIX

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ABSTRACT

For decades, a synergistic combination of EBRT and Intracavitary Brachytherapy (ICBT) has been the widely accepted primary modality of treatment for carcinoma cervix. As already stated, concomitant chemoradiation using Cisplatin has become the accepted standard treatment for locally advanced cases. Although concomitant chemoradiation is the standard care, it cannot be administered safely in elderly patients and those with certain comobilities. An alternative radiation schedule, without chemotherapy, that can reduce treatment time is therefore required, especially in those patients who have contraindications to chemoradiations . Yoon SM *et al* have shown that in patients in whom chemotherapy cannot be used, radiation alone with 6 fractions per week instead of 5 have equivalent results without major toxicities. The aim of this study was to evaluate the feasibility and compare the efficacy of 6 fractions per week of external beam radiotherapy with conventional fraction size with interdigitated brachytherapy starting from third week of EBRT (a total of 5 fractions of interdigitated brachytherapy, each fraction comprising of 6 Gy each). In the test arm, accelerated EBRT is given to a total dose of 46 Gy in 23 fractions (Monday to Saturday 6 days a week) and interdigitated brachytherapy 6 Gy × 5 fractions. From the third week interdigitated brachytherapy is started and on that day EBRT was not given. On the control arm EBRT was given to 50 Gy in 25 fractions followed by intracavitary brachytherapy 7 Gy × 3 fractions. Concomitant Cisplatin was added along with EBRT. The main aim of the study is to assess and compare the response and safety of accelerated EBRT with interdigitated brachytherapy to concomitant chemo-radiation, which is the accepted standard today. The overall response was comparable in both arms at end of treatment and during the period of follow up. Although the percentage of complete responses were slightly higher in the chemo-radiation arm, this was not statistically significant. Moreover the difference in CRs seemed to diminish with time during follow up.The treatment time was also prolonged in the test Arm as most of the patients had repeated treatment breaks. An important aspect of our study was to assess the overall treatment time. It was found that a majority of patients in the study arm did not complete treatment within the stipulated time whereas many in the chemo-radiation arm had delays also. The rationale for accelerated fractionation (AF) is that reduction in overall treatment time decreases the opportunity for tumour cell regeneration during treatment and therefore increases the probability of tumour control for a given total dose. To conclude, findings from this study suggest that accelerated EBRT (six fractions per week) with interdigitatedbrachytherapy is an effective treatment for patients with locally advanced carcinoma of the uterine cervix and can be used as a possible alternative to concomitant chemo-radiotherapy in selected patients keeping in mind about slightly increased rectal and bowel toxicities. The early responses to treatment are non-inferior to concomitant chemotherapy and the acute toxicities lesser but in our study the Test Arm patients had many treatment breaks due to acute toxicities as a result the treatment time got prolonged in the Test Arm. So to conclude accelerated radiotherapy is a great alternative tool but the problem of acute toxicities must be bore in mind while using a conventional radiotherapy machine like Cobalt 60.

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INTRODUCTION

Carcinoma cervix is the common malignancy in women attending the Out Patients' Department of Radiotherpy, Medical College Hospitals, Kolkata. Most of them come from a lower socioeconomic class. Since there are no structure population based screening programme available, patients present to our OPD mostly in locally advanced stages.

For decades, a synergistic combination of EBRT and Intracavitary Brachytherapy (ICBT) has been the widely accepted primary modality of treatment for carcinoma cervix. As already stated, concomitant chemoradiation using Cisplatin has become the accepted standard treatment for locally advanced cases. Although concomitant chemoradiation is the standard care, it cannot be administered safely in elderly patients and those with certain comobilities. Moreover,

chemoradiation has the potential of increasing overall treatment time due to associated toxicities which has an adverse impact on disease outcome. An alternative radiation schedule, without chemotherapy, That can reduce treatment time is therefore required, especially in those patients who have contraindications to chemoradiations. Yoon *et al.,* (2006) have shown that in patients in whom chemotherapy cannot be used, radiation alone with 6 fractions per week instead of 5 have equivalent results without major toxicities.

The aim of the study

The aim was to evaluate the feasibility and compare the efficacy of 6 fractions per week of external beam radiotherapy with conventional fraction size with interdigitated brachytherapy starting from third week of EBRT (a total of 5 fractions of interdigitated brachytherapy, each fraction comprising of 6 Gy each). In the test arm, accelerated EBRT is given to a total dose of 46 Gy in 23 fractions (Monday to Saturday 6 days a week) and interdigitated brachytherapy 6 Gy × 5 fractions. From the third week interdigitated brachytherapy is started and on that day EBRT was not given. On the control arm EBRT was given to 50 Gy in 25 fractions followed by intracavitary brachytherapy 7 Gy × 3 fractions. Concomitant Cisplatin was added along with EBRT. The main aim of the study is to assess and compare the response and safety of accelerated EBRT with interdigitated brachytherapy to concomitant chemo-radiation, which is the accepted standard today.

Specific objectives and end points of this study

Primary endpoint was assessment of loco-regional tumor response. Secondary Endpoints was Assessment of toxicities (acute and late) in this two group of patients including bladder, bowel ,rectal, vaginal mucosa, skin, haematological other non-haematological assessment of treatment time in days including, total time during EBRT, Gaps during EBRT, overall treatment time (OTT), gaps during overall treatment. The study design was presented and duly approved by the institutional ethics committee

MATERIALS AND METHODS

The study was started from October 2014 and the follow-up data was updated till September 2016. It was a prospective, non-randomized, two-arm single institutional study. All biopsy proven cases of locally advanced squamous-cell carcinoma of the uterine cervix attending the radiotherapy OPD were eligible for this study. The study design was presented and duly approved by the institutional ethics committee.

Study eligibility

Inclusion criteria (for both the study groups): No prior history of malignancy biopsy proven cases of locally advanced squamous cell carcinoma of cervix (defined as lesions from stage IB2 to stage IIIB.ECOG status 0-3.No prior history of exposure to cytotoxic chemotherapy or radiation. No prior pelvic surgery. No clinical or radiological evidence of metastasis at presentation. Adequate bone marrow function Hb > 10gm/dl; WBC > 4000 / mm^3 (ANC ≥ 2000 / mm^3.Informed and signed consent, in agreement with Helsinki declaration 1996, prior to study entry were mandatory.

Inclusion Criteria: Study group who received accelerated EBRT with interdigitated brachytherapy without any concomitant chemotherapy were included for the study.

Exclusion Criteria: (for both subsets): Patients aged more than 75 years and pregnant patients were excluded from the study. Those who had Karnofsky Performance Status < 70, those participating in any other study on cancer cervix, patients with prior pelvic radiation / surgery were also excluded from the study.

Study Protocol: The patients fulfilling the above criteria were put into their respective arms Control Arm and Test Arm. They were explained in details about the pros and cons and the consent forms were duly signed.

All eligible patients willing to participate in the study were divided into two groups / arms as below.

Test Arm: Patients who did not agree or were not fit for concomitant chemo-radiation, accelerated EBRT i.e. six fractions per week of external beam radiation therapy (EBRT) with interdigitated brachytherapy (starting from 3rd week of EBRT).

Control Arm: Patients received 5 fractions per week of radiation every Monday to Friday. Weekly injection of Cisplatin of dose 40 mg/m^2 IV with necessary pre-medications and adequate hydration was given on every Monday during external radiation.

Both groups received EBRT (External Beam Radiotherapy) to a total dose of 50 Gy in 25 fractions. The treatment would have to be completed in Arm A four weeks and in Arm B in five weeks.

Machine used in the treating patients wereTele-cobalt machine (Co60), Model : Theratron 780-C (Theratronics international Limited) with Source Length : 200 RMM. SSD : 80cm. Portals : Pelvic AP-PA portals were used if IFD was < 18cm and four field box technique if IFD was greater. Both fields were treated daily. Dose was calculated at midplane by SAD technique. Midline shielding was not done.

Fields: Upper Border: At the level of L4-L5 vertebral interface to include all the external iliac and hypogastric lymph nodes.When irradiation of common iliac lymph nodes was considered to be necessary, the upper margin was kept at L3-L4 interface, lower border in absence of any vaginal involvement, kept at the level of inferior border of the obturator foramen. In case of vaginal involvement, the lower border was extended to the vaginal introitus, lateral Borders was kept at 2cm lateral to the bony pelvic wall. During EBRT, patients were reviewed routinely (at least once every week) by clinical assessment and complete blood counts. Oral haematinics and transfusion of whole blood were given when required.

Brachytherapy: All patients in both arms received High Dose Rate Intracavitary Brachytherapy (HDR ICBT) immediately after EBRT. Time gap between end of EBRT and first application of Brachytherapy was kept to a minimum to shorten Overall Treatment Time. In the Test Arm, brachytherapy was started from the 2nd week of EBRT onwards, thereby interdigitating EBRT and ICBT. 6 Gy in five

fractions were given. On the day of interdigitation EBRT was not given. In the Control Arm, brachytherapy was started after completion of EBRT. The dose of 7 Gy in three weekly fractions was given. Brachytherapy in both the arms was given by HDR method as weekly fractions by Varian Gammamed Plus Remote After Loading machine using Ir192 isotope.

Procedure in brief: The application was performed under deep sedation. The patient was positioned in the dorsal lethotomy position. Before the procedure started, the patient was reviewed to access response by a thorough gynecologic examination, assessing the present tumor response, the topography of the uterus and the organs at risk. This was repeated during all insertions (i.e. all fractions). After proper antiseptic dressing and draping, the patient was catheterized. The balloon of the bladder catheter was inflamed with radiopaque solution and was pulled towards the base of the bladder until it was placed at the bladder neck. All the applications were done using the Manshester or Fletcher system of applicators. After insertion of the applicator, a CT scan image was obtained in supine position with the applicators in place. After image acquisition, patient was taken back to the brachytherapy OT. Throughout these phases, positional accuracy of the applicators were ensured. The images were converted to DICOM format and transferred to the treatment planning system.

Varian Eclipse Brachytherapy Vision Software, was used for all 3D treatment planning. The bladder, rectum and distal part of the sigmoid colon, were considered as the Organs at Risk (OAR) were contoured. The reference points are identified on the CT scan based digitally reconstructed radiographs (DRR) were the bladder, the rectal points and Point A. The dose was prescribed at Point A. Although dose prescription should be done to a defined tumor volume and not to any applicator based point, this was not done. This is because of the fact that the GTV cannot be defined on CT scans. Although GTVs could not be exactly delineated, contouring of OARs could be easily done using CT Scans.

Follow-Up: The patients were followed-up by both gynecological and radiation oncologists with detailed physical and gynecological examinations. Papanicolaou smears and appropriate blood examinations and / or imaging studies. Initially, patients were followed every month (for first six months) and then every two months.

Response Assessment: Response was assessed using the Response Assessment in Solid Tumors (RECIST) Criteria (Therasse *et al.,* 2000) at the end of EBRT, end of treatment and during follow-up thereafter. Toxicity was reported using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (Cancer Therapy Evaluation Program).

Statistical Analysis: Data were assessed using Statistical Package for Social Sciences, (SPSS Inc., Chicago, IL) software version 14.0 and Medcalc version 11.0 [4, 5]. For continuous variables means / medians were compared with unpaired t-test and for categorical set of data, two groups were compared with chi-square test.

RESULTS

Initially our study started with 60 patients, 30 in each arm. Eventually it came down to 24 patients in arm Control Arm and 22 patients in Test Arm, after they did not match our inclusion and exclusion criteria as already mentioned earlier. Later 4 patients from the arm Controland 3 patients from Test Arm failed to comply the study the protocols and were excluded from the study. The reasons being refusing to take brachytherapy and other personal reasons. Eventually we were left with 20 patient from Control Arm and 19 patients from Test Arm. In this study, we sought out to find an effective treatment for these patients of our study group to the accelerated External Beam Radiation with interdigitated intra-cavitary brachytherapy. As EBRT and brachytherapy alone without concomitant cisplatin would be suboptimal as a treatment, we had to think of a device that would be optimal in delivering high dose to the tumour. Accelerated EBRT (6 days a week) and interdigitated brachytherapy starting from 3rd week of EBRT (total 5 fractions 6 Gy each) seems to be effective. Findings from this study suggest that pure accelerated EBRT (six fractions per week) with interdigitated brachytherapy is an effective treatment for locally advanced carcinoma cervix and can be possible alternative to selective patients.

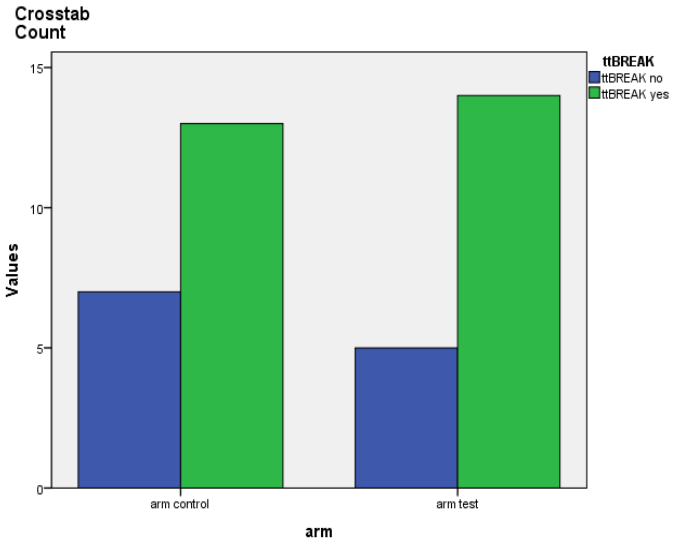

Figure 1. Treatment break

More number of treatment breaks in the study arm.

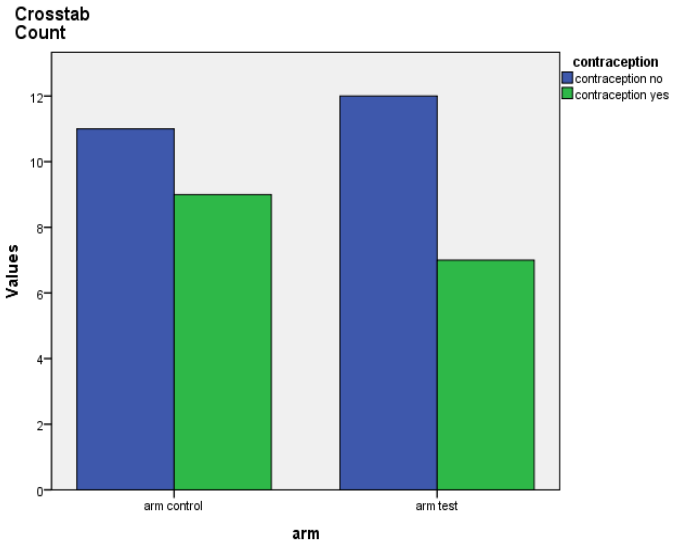

Figure 2. Contraception

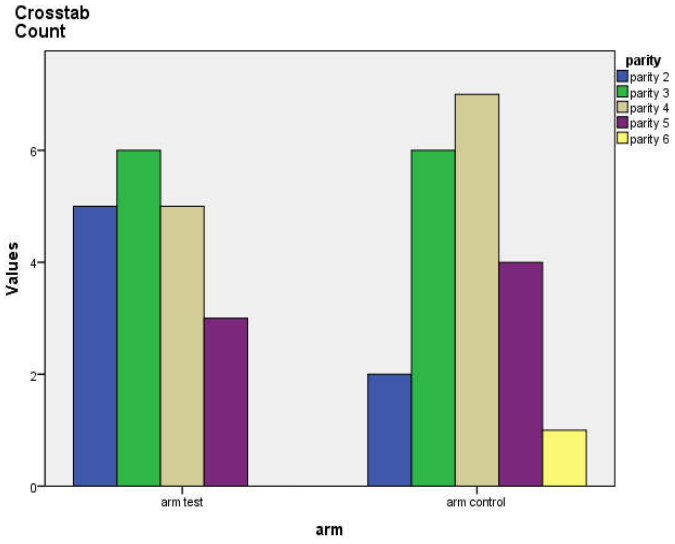

Figure 3. Parity in test arm and control arm

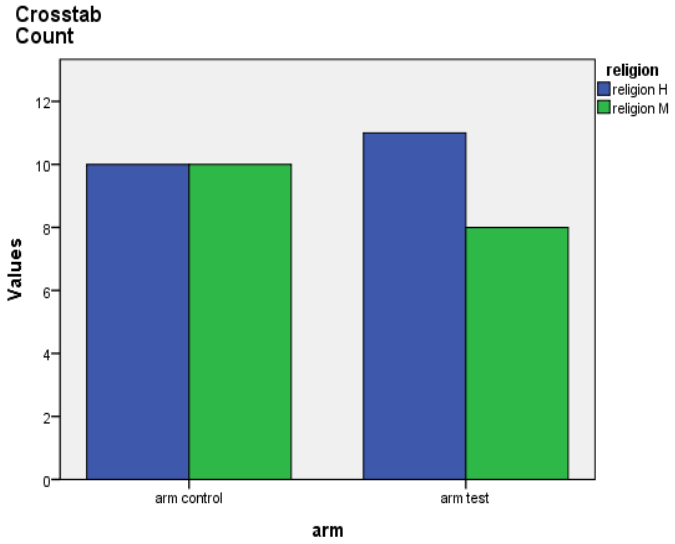

Figure 4. Religion

Stage

In our study stage *3B* was the most frequent in both the control and study group. A total of 21 cases of IIIB, 17 cases of IIB and 1 case of stage IIIA. No case of IIA was recorded.

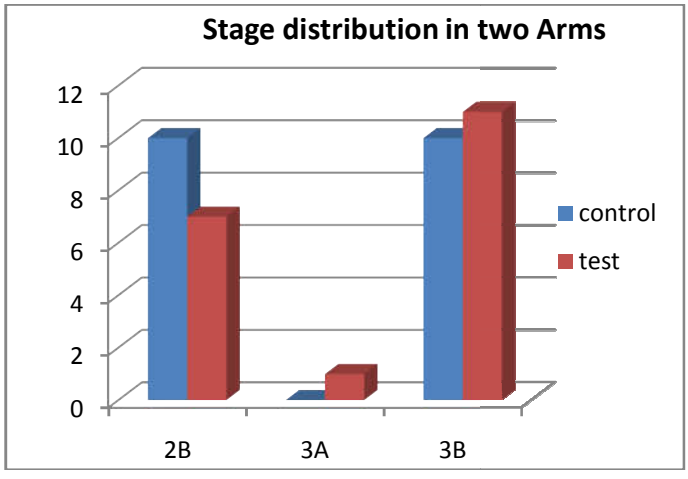

Figure 5

Table 1.

Crosstab					
			ARM		Total
			Control	Test	
Stage	3B	Count	0	1	1
		% within stage	0.0%	100.0%	100.0%
	2B	Count	10	7	17
		% within stage	58.8%	41.2%	100.0%
	3A	Count	0	1	1
		% within stage	0.0%	100.0%	100.0%
	3B	Count	10	10	20
		% within stage	50.0%	50.0%	100.0%
Total		Count	20	19	39
		% within stage	51.3%	48.7%	100.0%

Type of Applicator

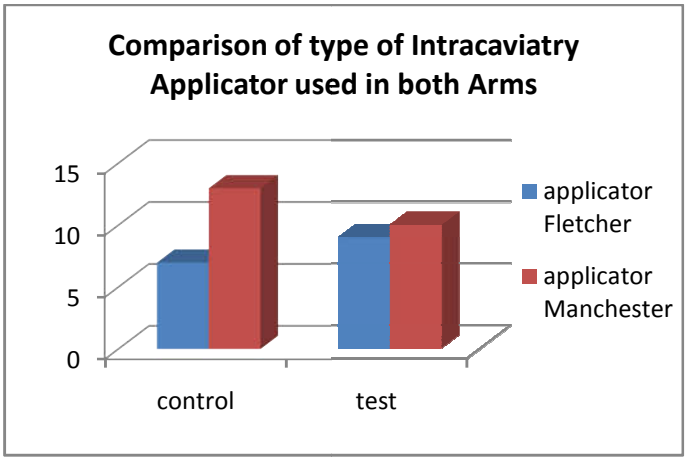

Figure 6

Table 2. Applicator Cross-tabulation

		Applicator		Total
		Fletchr	MANCHTR	
ARM	Control	7	13	20
	Test	9	10	19
Total		16	23	39

The applicators that was used in this study were Fletcher and Manchester System of Applicator. In the test Arm out of the 19 patients, 9 were treated with Fletcher system of applicator and 10 were by Manchester System of Applicator. In the control Arm out of total 20 patients, 7 were treated with Fletcher and 13 were treated with Manchester System of Applicators.

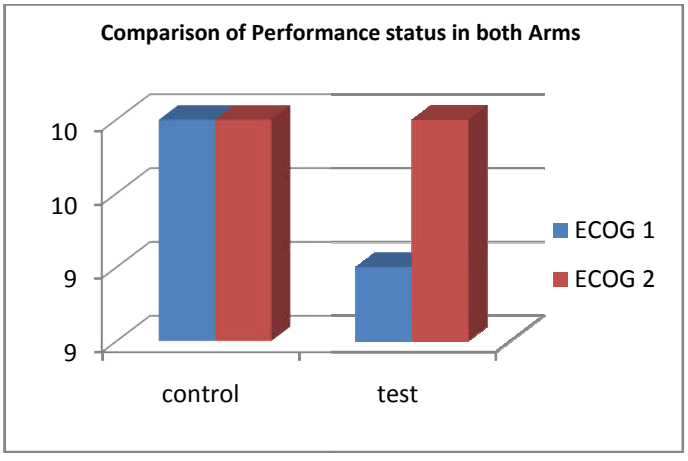

Fig. 7.

Table 3.

TOXICITY	Arm A	Arm B	P value
Anorexia all grades	18	19	P=0.792
Anorexia Grade 3	3	5	P=0.855
Nausea Vomiting All Grades	15	19	P=0.799
Nausea Vomiting Grade 2	3	1	P=0.145
Diarrhea All Grades	20	19	P=0.461
Diarrhea Grade 2	4	7	P=0.793
Enteritis/Colitis All Grades	12	17	P=0.518
Enteritis/Colitis Grade 3	0	2	P=0.530
Pain All Grades	12	15	P=0.951
Pain Grade 2	1	2	P=0.785
Cystitis/ Bladder Spasms All Grades	2	3	P=0.983
Vaginal Discharge All Grades	10	17	P=0.200
Vaginal Mucositis All Grades	10	16	P=0.323
Vaginal Mucositis Grade 3	2	3	P=0.874
Anemia All Grades	12	14	P=0.824
Anemia Grade 3	2	3	P=0.874
Elevated Serum Creatinine All Grades	3	6	P=0.569
Neutropenia All Grades	5	10	P=0.341
Fatigue All Grades	13	17	P=0.751
Weight Loss All Grades	5	9	P=0.540
Dermatitis All Grades	8	11	P=0.824

Table 4. ECOG Crosstabulation: ECOG

		ECOG		Total
		1	2	
Arm	Control	10	10	20
	Test	9	10	19
Total		19	20	39

The patients were mostly of ECOG performance status 1 and 2. In the control Arm 10 patients were of ECOG 1 and 10 were of ECOG 2. In the test arm, out of the total 19 patients, 9 were of ECOG 1 and 10 were of ECOG 2.

Menopausal status

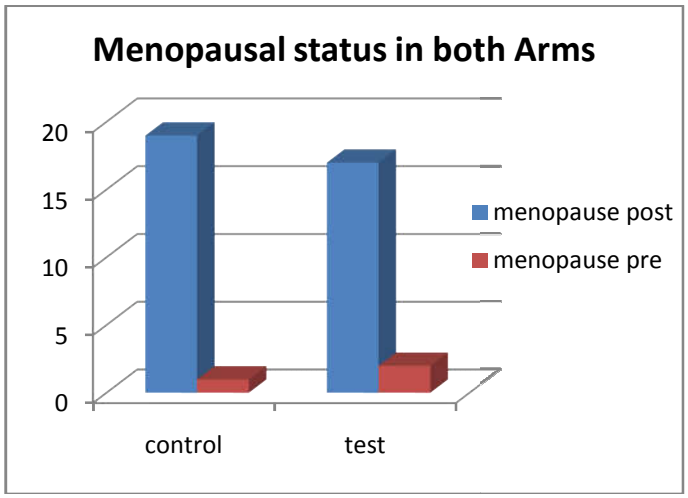

Figure 8.

Table 5. Treatment Breaks

Crosstab					
			Arm		Total
			Control	TEST	
tt BREAK	No	Count	7	5	12
	Yes	Count	13	14	27
Total		Count	20	19	39

13 patients of Control Arm had treatment breaks and 14 patients of Test Arm had treatment breaks

Table 6. Prior STD History

Crosstab					
			Arm		Total
			Control	Test	
STD history	no	Count	7	8	15
	yes	Count	13	11	24
Total		Count	20	19	39

Out of 19 patients in Test Arm, 11 had positive history of past sexually transmitted diseases and 13 patients in Control Arm had positive STD history.

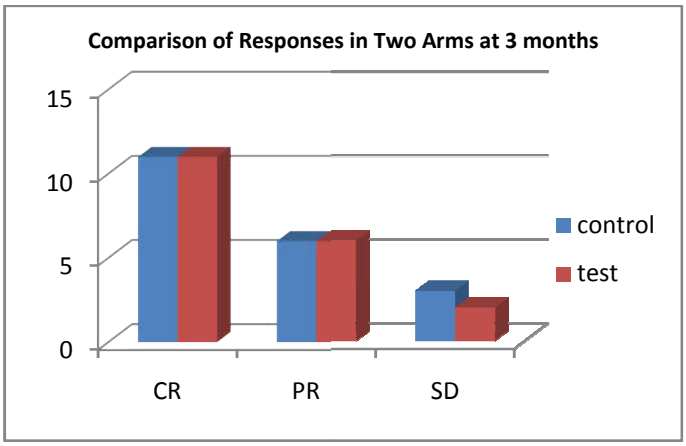

Figure 9.

Table 7. Response assessment at 3 months

Response at 3month			
	CR	PR	SD
Control	11	6	3
Test	11	6	2

The respond assessment at the end of 3 months was more or less similar on both the Arms as shown above.

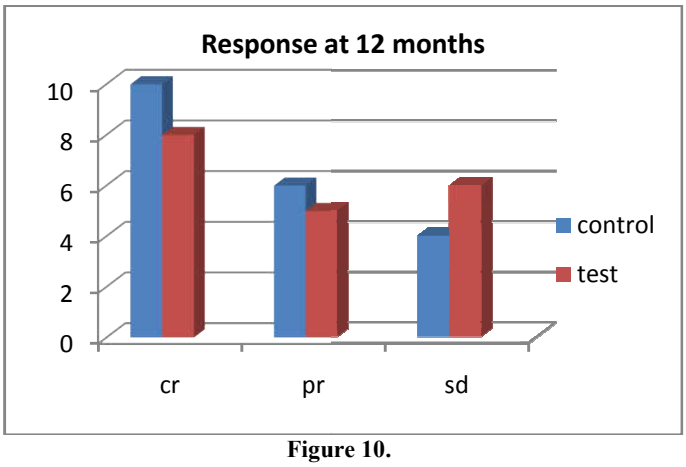

Figure 10.

Table 8.

	CR	PR	SD
Control	10	6	4
Test	8	5	6

At the end of 12 months, response assessment was done. The results are displayed on the above table. In the Control Arm, 10 patients had complete response (CR). Partial response (PR) in 6 and 4 had stable disease (SD).

On the Test Arm, 8 had complete response (CR), 5 had partial response (PR) and 6 had stable disease (SD). The different between the two Arms was not statistically significant.

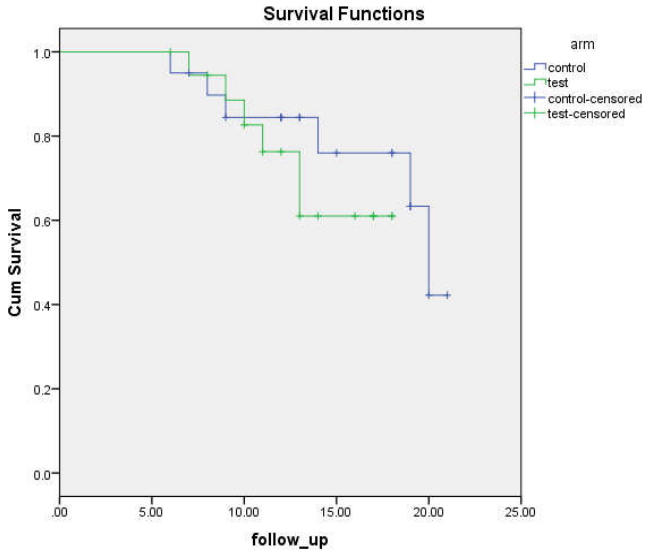

Figure 11

Disease free survival

A total of 39 patients, 20 in Control Arm and 19 in Study Arm underwent the study. Majority of them were of stage III B, post-menopausal and hailed from poor socioeconomic strata of our society. In Control Arm, patients received 50 Gy of EBRT in 25 fractions over 5 weeks with weekly Inj. Cisplatin per week whereas in Test Arm, patients received 46 Gy accelerated EBRT with interdigitated brachytherapy (6 Gy in 5 fractions) without concurrent Inj. Cisplatin. The overall response was comparable in both arms at end of treatment and during the period of follow up. Although the percentage of complete responses were slightly higher in the chemo-radiation arm, this was not statistically significant. Moreover the difference in CRs seemed to diminish with time during follow up. As expected, chemo-radiation was associated with a range of toxicities. The major acute toxicities noted were gastro-intestinal, genito-urinary, hematological and constitutional. Both the average number of Grade 3 and total (all grades)

Adverse Events were significantly higher in Control Arm. In contrast, patients in the study arm tolerated their treatment much better. The treatment time was also prolonged in the test Arm as most of the patients had repeated treatment breaks.An important aspect of our study was to assess the overall treatment time. It was found that a majority of patients in the study arm did not complete treatment within the stipulated time whereas many in the chemo-radiation arm had delays also. Although the difference in treatment time between the arms was only about a week, this was found to be statistically significant. Lastly, the radiobiological efficacy of accelerating radiation is proven with similar effective BEDs in both the arms and a lesser biologic dose wasted in Control Arm compared to Test Arm. Whether the encouraging short-term results of this study translate into simila 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 chemo radiations.

DISCUSSION

Carcinoma of the uterine cervix is one of the most common malignancies among female patients attending our Out Patients' Department. Over the years, we have been treating a large number of patients with Carcinoma Cervix. Unfortunately, most of them hail from the lower socio-economic strata of society and consequently present in very advanced stages. This is because of poverty, illiteracy, ignorance and social taboos coupled with lack of any well-organized, large scale, population based screening programs. Since many of the patients attending our center are of advanced stage, mostly in Stage III-B, the backbone of treatment is radiotherapy (usually EBRT followed by ICBT). Our institutional practice is to give about 50 Gy by EBRT followed by HDR ICBT to a total dose ≥ 80 Gy to point A. Concomitant chemo-radiation is now the standard treatment in locally advanced carcinoma cervix and cisplatin appears to be the ideal chemotherapeutic agent (Girinsky *et al.,* 1993) 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). Although, the absolute survival benefit was 12%maximal in early stage (I and II) disease (Green *et al.,* 2001). Moreover, a recent update from a pivotal 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 (Pignon *et al.,* 2009). There is no question about the benefit of chemo-radiation in cervical cancer, albeit at the cost of incremental toxicity. However, the best treatment of those patients who cannot tolerate chemo-radiation is not very clear. Traditionally, conventional radiation alone has been used in these subset of patients. Considering the fact that radiation alone is a suboptimal treatment in loco-regionally advanced cervical cancer, newer avenues to improve local control and perhaps survival should be sought in this group.

The cure rates of squamous cell carcinomas are highly dependent on overall treatment time, and this has been interpreted in terms of accelerated regeneration of tumor clonogens (Withers *et al.,* 1998). 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 approximately 0.6 Gy, on average, to offset clonogenic cell regeneration, again suggesting aclonogenic cell doubling time of 3.5 to 5 days (Bentzen and Thames, 1991). Many trials have conclusively proven overall treatment time to be a major determinant in outcome in cancer cervix (Delaloye *et al.,* 1996; Fyles *et al.,* 1992; Petereit *et al.,* 1995; Erridge *et al.,* 2002; Lanciano *et al.,* 1993; Girinsky *et al.,* 1993; Perez *et al.,* 1995). The usual recommendation is to complete treatment by 8 weeks (56 days) (Nag *et al.,* 2000). Petereit *et al*. have shown that the 5-year survival and pelvic control rates differed significantly with treatment times≤ 55 days vs. ≥ 55 days (Petereit *et al.,* 1995). Accelerated Radiotherapy seems 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 hyper-fractionation. This benefit should ideally be extended to those in whom concomitant chemotherapy is not possible because it gives

them tangible benefit over conventional radiation by reducing overall treatment time. In our study unfortunate many of the patients suffered acute toxicities and other non-compliance to treatment schedule as a result the treatment time was prolonged in the Test Arm.

The rationale for accelerated fractionation (AF) is that reduction in overall treatment time decreases the opportunity for tumor cell regeneration during treatment and therefore increases 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 dose fractions is sufficient for complete repair to take place (Ahamed Anesa). Strategies to accelerate radiation be divided into two categories: (i) Pure Accelerated fractionation regimens, with reduced overall treatment time without concurrent changes in the fraction size or total dose and (ii) Hybrid Accelerated fractionation, 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 accelerated fractionation regimes tested in randomized clinical trials which include : (a) accelerated with dose reduction, (b) accelerated with split course, and (c) accelerated with concomitant boost [20].The benefit of Accelerated (6 fractions per week) radiation have been conclusively proven in the DAHANCA Trials by Overgaard *et al* (2003). 1,485 patients with head and neck carcinomas of all stages were treated with 6 vs 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).Overall 5-year loco-regional control rates improved (70% vs. 60%; p = 0.0005) and improved disease-specific survival (73% vs. 66%; p = 0.01) but not overall survival. As squamous cell cervix cancers behave clinically and radio-biologically in a similar fashion to their head and neck counterparts, Yoon *et al*. (2006) extended the AF schedule to cervical cancer. The findings from this Phase I/II trial were that "six fractions per week of external beam radiotherapy 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 chemo-radiotherapy in elderly patients or in patients with co-morbidity".

In Pure AF, however, the Biological Effective Dose (BED) remains same compared to a similar conventional schedule (as total dose and dose/ fraction are not changed, see Equation 1below). This is opposed to hyper-fractionation where the use of small dose fractions allows higher total doses to be administered within the tolerance of late-responding normal tissues, and this translates into a higher BED to the tumor. However this is not absolutely true, because BED does not incorporate treatment time which is shortened in AF.BED = nd [1 + d/α/β] ….. Eqn. 1, (Dale and Jones, 2008) where n is the number of fractions, d is the dose per fraction and α/β (often called fractionation sensitivity) is a measure of how a specific tissue will respond to fractionation and dose rate and may be called Total Physical Dose (TD) and [1+d/α/β] may be called Relative Effectiveness (RE). Over the years, however, it has been realized that BED does not tell the full story since it disregards time, a pivotal element of treatment delivery. To circumvent this problem, modifications to the BED formula have been suggested. Considering tumor repopulation at a continuous (exponential) rate throughout treatment, the net effect depends on treatment duration(T) and the effective tumor doubling time teff (in unit of days). As a consequence of this, the equation of BED can be modified as, BED = TD × RE – RF

Where TD and RE are as in Eqn. 1 and RF is a measure of the biological dose 'wasted' in combating repopulation [22]. Thus Eqn. 1 above has to be modified to Eqn. 2 below: BED = nd [1 + d/α/β] – 0.693/α.teff (T- Tk) …….. Eqn. 2

Where T is the Total treatment time and Tk is the time from when repopulation starts. The entity0.693/α.teff can be simply expressed as a constant K, the required dose equivalent of repopulation per day. For rapidly proliferating tumors, like cervical cancers the value of K is approximately 0.6Gy/day (considering α = 0.3 Gy-1 and teff = 3.5 – 5 days).

In summary, therefore, the radiobiological efficacy of Pure AF in Carcinoma Cervix can be demonstrated over conventional radiation alone and one would hope to translate this into tangible clinical tumor control. In our study, although the shortening of treatment time was not achieved due to repeated treatment breaks but the results were clearly non-inferior to the standard arm. Complete Response appeared to be relatively higher in the chemotherapy 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 longer follow up. This is not an unexpected finding, and we found that the prolongation in overall treatment time was due to these adverse events in the majority of patients. It facilitates earlier initiation of treatment for more patients by reducing the waiting period and ensures optimization of limited resources. Although findings from our study vindicate the non-inferiority of accelerated radiation with interdigitated brachytherapy, the results need to be viewed with cautious optimism. This is because our study is plagued by some drawbacks including small sample size, short follow up period and inherent biases of single-institutional trials and treatment breaks in Test Arms due to radiation toxicities as our patients were often not able to tolerate this intensified radiation schedule. Our trial offers an exciting prospect which might be an alternative option in selected patients who have contraindications to chemo-radiation. With larger sample size and proper patient selection the outcome would be much better. To conclude, findings from this study suggest that accelerated EBRT (six fractions per week) with interdigitated 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 chemo-radiotherapy in selected patients keeping in mind about slightly increased rectal and bowel toxicities. The early responses to treatment are non inferior to concomitant chemotherapy and the chemotherapy induced toxicities lesser but overall treatment time, which is of paramount importance for treatment success, is increased due to treatment breaks in the Test Arm. This method provides a rational and feasible alternative to conventional chemo-radiation in patients of locally advanced cervical cancer who have contraindications to chemotherapy. However, these findings are 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 results should therefore be accepted with the caveat that chemo-radiation is still the best option in those who can tolerate it and newer approaches should only be reserved in selected patients and special circumstances.

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