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A Prospective Randomized Study Comparing Accelerated Radiotherapy Versus Conventional Concomitant Chemoradiation in Locally Advanced Carcinoma Cervix

Debottam Barman[1], Debasish Das[1], Bodhisattwa Dutta[2], Bithi Pal[1]

[1]Department of Radiotherapy, Medical College and Hospital, Kolkata, India
[2]Department of Radiotherapy, Chittaranjan National Cancer Institute, Kolkata, India

Corresponding author: Bithi Pal

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ABSTRACT

Introduction: In locally advanced carcinoma cervix (FIGO stage IB3-IVA) chemoradiation is the standard of care. But weekly concurrent chemotherapy can be poorly tolerated for elderly patients or patients with certain comorbidities. In this study efficacy and safety of accelerated radiotherapy is compared with definitive chemoradiation.

Methodology: Total 67 patients were enrolled, 32 patients had received accelerated radiotherapy alone and 35 patients had received chemoradiation, dose of radiation was 50Gy/25# in both arms. All the patients received HDR brachytherapy of dose 7Gy×3# to point A.

Objectives: Locoregional tumour control was the primary endpoint. Toxicity profile, Overall treatment time (OTT), Disease free survival (DFS) and Overall survival (OS) were the secondary endpoints. Unpaired t-test and chi square test were used for continuous and categorical variables.

Result: Tumour response was comparable in both arms. The median OTT was 54 days in accelerated radiotherapy arm which is significantly lesser compared to 62 days in chemoradiation arm (p-value <0.0001). Acute and late toxicities, DFS and OS were also comparable in both arms.

Conclusion: Accelerated radiotherapy is a feasible and safe treatment option for locally advanced carcinoma cervix with added benefit of lesser treatment time.

Keywords: Overall treatment time (OTT), Accelerated fractionation (AF), Tumour response.

INTRODUCTION

Among females, carcinoma of the uterine cervix is the 4th most common cancer worldwide and 2nd most common cancer in India as per GLOBOCAN 2022 data.[1] Definitive chemoradiation has become the standard of care for locally advanced carcinoma cervix supported by adequate level one evidence. [2,3,4,5,6,7,8] But cytotoxic chemotherapy is not well tolerated in older patients, patients with pre-existing compromised renal function, or other medical comorbidities. For such patients, an alternate treatment approach can be accelerated radiotherapy where total treatment duration is reduced by using more than one fraction a day, or more than five fractions a week. Accelerated repopulation is commonly encountered in carcinoma cervix. The onset of accelerated repopulation has been found to be shorter for carcinoma cervix (~19 days) in comparison to other carcinomas eg. 28 days in head and neck and 36 days for prostate respectively.[9] This may

explain the deterioration of tumour control and treatment outcome in patients with a prolonged duration of radiation treatment (done). So the radiobiological rationale of using accelerated radiotherapy is to shorten the overall treatment time (OTT) and to improve the treatment outcome for the patients of carcinoma cervix who will receive radiotherapy alone. In a country like India, where carcinoma cervix mainly affects women of lower socio-economic condition, reducing treatment duration may also lead to better compliance and treatment completion rate. In this study, we have compared the tumour response, toxicity, locoregional recurrence and survival in locally advanced carcinoma cervix treated with definitive chemoradiation (radiation 5days/weeks) and accelerated radiotherapy (radiation 6days/ weeks).

METHODOLOGY

In this prospective, randomized, single institutional, two armed study, all biopsy proven patients of carcinoma cervix, FIGO 2009 stage: Ib3-IVa attending the Department of Radiotherapy were eligible. Case accrual was done from January 2018 to April 2019 and followed up till December 2023. All the eligible patients belonged to the age group of 35-70 years, with ECOG performance status ≤2, with no prior exposure to cytotoxic chemotherapy, radiotherapy or pelvic surgery, with adequate bone marrow reserve (Hb:≥10gm/dl, WBC> 4000/mm^3, platelets: >1,00,000/mm^3). Patients with upfront metastatic disease, gross nodes and pregnancy were excluded.

All the eligible patients underwent thorough clinical examination for baseline recording of the local gynaecological findings and CEMRI scan of pelvis. Staging workup including CECT whole abdomen, and digital X-ray of chest or CECT thorax was done for all patients. Routine blood investigations including complete blood count (CBC), Liver function test (LFT), Renal function test (RFT), viral serology were also done for all patients. Ethical clearance was granted from the Institutional Ethical Committee before commencement.

All the eligible patients who met the selection criteria and gave informed consent were allocated randomly to one of the following arms using a computer generated random number table. In arm A patients received External beam radiotherapy (EBRT) of dose 50Gy in 25 fractions over approximately 4 weeks, treating 6 fractions per week from Monday to Saturday. The patients in arm B were treated with EBRT of total dose of 50Gy in 25 fractions over 5 weeks, treating 5 fractions per week from Monday to Friday along with weekly concomitant Inj.Cisplatin 40mg/m2. In both arms after EBRT completion, patients received High Dose Rate (HDR) Brachytherapy of dose regimen 7Gy weekly for 3 consecutive weeks with an aim of treatment completion by 7 weeks in arm A and 8 weeks in arm B.

EBRT was delivered by Theratron 780-C Telecobalt machine using the conventional 4 fields box technique. Dose was calculated at the midplane by SAD technique. No midline shielding was used. The upper border was kept at the level of L4-L5 vertebral interspace, and the lower border at the inferior border of the obturator foramen or ischial tuberosity depending on vaginal extension. For the AP-PA fields, 2 cm margin lateral to the true bony pelvis was taken as the lateral border. For the lateral fields, the anterior border was placed anterior to the symphysis pubis and the posterior border was placed upto third sacral vertebrae to include the presacral spaces. EBRT was expected to be completed in arm A and arm B within 29 days and 35 days respectively. HDR brachytherapy was administered after EBRT completion using Varian Gammamed Plus Remote Afterloading machine (Varian, Palo Alto, CA) using Ir^{192} isotope. Weekly clinical examination, CBC reports, biochemical profile were evaluated during treatment. A Hb ≥ 10 gm/dl, ANC > 2000/mm3 and platelet count > 1,00,000/mm3 were maintained by using oral

haematinics and transfusions of whole blood /blood components whenever required.

All the patients were followed up monthly for first six months after treatment completion, then 3-4 monthly for next two years, then biannually upto 5 years. Response assessment imaging was done 6 weeks after treatment completion. During each follow-up clinical examination was carried out along with annual cervical/vaginal cytology and imaging if indicated.

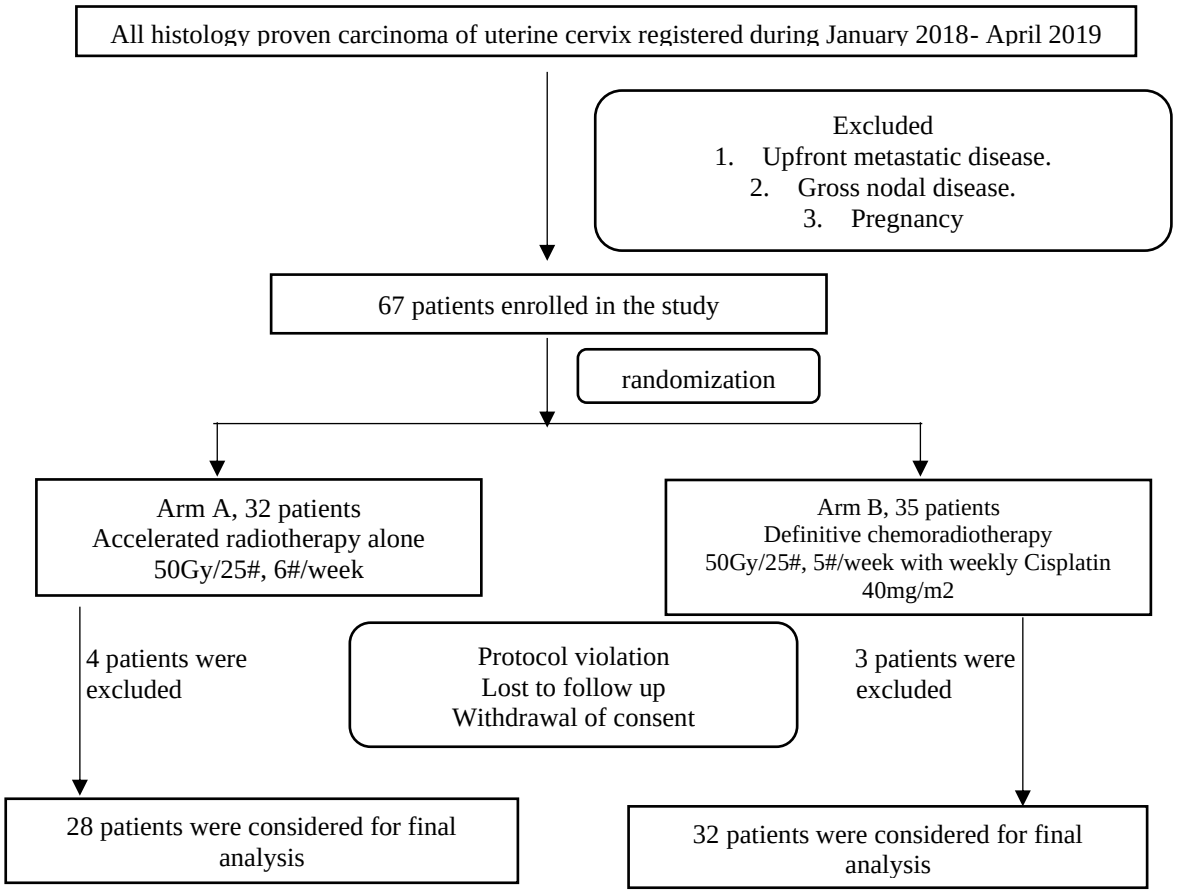
The primary endpoint of this study was to assess the locoregional tumour response. Toxicity profile, gap during treatment, overall treatment time (OTT), Disease free survival (DFS) and Overall Survival (OS) were included as secondary endpoints. Response was assessed using the Response Evaluation Criteria in Solid Tumours (RECIST) Criteria version 1.1 and Toxicity was reported using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[10,11]

Data were analysed using Statistical Package for Social Sciences, (SPSS Inc., Chicago, IL) software version 23.0. 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. In both situations 95% Confidence Intervals and p value <0.05 were considered significant. All reported p values are two tailed.

RESULTS

Case accrual

Initially all the histology proven carcinoma cervix patients registered in the Department of Radiotherapy from January 2018 to April 2019 were assessed for eligibility in this study. Then after applying the inclusion and exclusion criteria 67 patients were enrolled. After randomization, 32 patients were allocated to arm A and 35 to arm B. However, 4 patients in Arm A and 3 in Arm B failed to complete treatment and were consequently excluded from the study due to noncompliance with study protocol, lost to follow up and withdrawal of consent. Ultimately 28 patients in the Study Arm (Arm A) and 32 in Control Arm (Arm B) underwent the study.



Baseline patients' characteristics

Baseline patients' characteristics were comparable in both arms. The mean ages were 52years and 54.3 years in arm A and arm B respectively. Average number of children were 3 in both arms with a range of 2-6 in arm A and 1-6 in arm B. Majority of the patients were postmenopausal in both arms (85.7% in arm A and 81.3% in arm B). FIGO stage IIIB was the most common stage at presentation in both arms (53.6% in arm A, 53.1% in arm B). Median pre- treatment Haemoglobin was 10.8 gm/dl in Arm A (Range 10.0 - 12.1 gm/dl) and 11.0 gm/dl in Arm B (Range 10.1 - 12.7 gm/dl). As a randomized trial, baseline patient characteristics were similar and well balanced in both arms. The details are summarized in table no-1.

Patients' characteristic		**Arm A (n=28)**	**Arm B (n=32)**	**p-value**
Age (years)	Mean	52	54.3	0.44
	Median	52	54	
Weight (kg)	Mean	50.85	50.47	0.23
	Median	51	51.5	
Average no. of children		3	3	0.91
Contraceptive use	Yes	28.6%	25%	0.75
	No	71.4%	75%	
Menopausal status	Premenopausal	14.3%	18.7%	0.64
	Postmenopausal	85.7%	81.3%	
Age at Menarche (years)	Mean	12.5	11.8	0.02
	Median	12.5	12	
ECOG performance score	0	21.4%	28.1%	0.83
	1	53.5%	50.1%	
	2	25.1%	21.8%	
Pretreatment Hb%	Mean	10.7	10.9	0.23
	Median	10.8	11	
FIGO stage	IIB	25%	25%	0.89
	IIIA	10.7%	6.3%	
	IIIB	53.6%	53.1%	
	IVA	10.7%	15.6%	

Table- 1 showing Baseline patients' characteristics

Treatment time

The EBRT time, OTT and gap during treatment in both treatment arms are summarized in table-2. The differences were statistically significant ($p < 0.0001$). Treatment interruptions were due to acute toxicities (65.91%), holidays (9.09%), machine breakdown (6.81%), and miscellaneous other reasons (18.18%). The median number of concomitant chemotherapy cycles received by patients in Arm B was 5 (Range 4 – 6). More than 90% patients received all scheduled cycles per protocol.

Treatment time		**Arm A**	**Arm B**	**p-value**
EBRT time (days)	Median	32	39	<0.0001
	Range	29-36	35-44	
Overall Treatment Time (OTT) (days)	Median	54	62	<0.0001
	Range	49-63	57-68	
Gaps in OTT (days)	Median	7	9	<0.001
	Range	3-10	4-11	

Table- 2: Comparison of treatment time between two arms

Response assessment

Response assessment was done 6 weeks after treatment completion. In Arm A, 22 (78.6%) patients were in Complete Response (CR), 5 (17.8%) in Partial Response (PR) and 1 (3.6%) in Stable Disease (SD). In Arm B, 28

(87.4%) patients were in CR, 2 (6.3%) in PR and 2(6.3%) in SD. Summary is given in Table- 3.

Response		Arm A	Arm B	p-value
	CR	22 (78.6%)	28 (87.4%)	0.35
	PR	5 (17.8%)	2 (6.3%)	
	SD	1 (3.6%)	2 (6.3%)	

Table- 3: Response in both arms

Treatment related toxicities

Treatment related acute toxicities including dermatitis, gastrointestinal, genitourinary, haematological and constitutional symptoms were documented during treatment in both arms. Across the spectrum, toxicities were higher in arm B (chemoradiation arm). Grade 3/4 nausea and vomiting and dermatitis were higher in arm B compare to arm A which was statistically significant. Late toxicities including cystitis, proctitis, vesicovaginal fistula, vaginal stenosis, osteoradionecrosis of femoral head were also reported. All the toxicities are summarized in Table- 4.

Acute Toxicities		Arm A	Arm B	p-value
Anorexia	All grades	25 (89.3%)	28 (87.5%)	0.84
	Grade 3	4 (14.3%)	6 (18.7%)	0.64
Nausea and vomiting	All grades	20 (71.4%)	25 (78.1%)	0.05
	Grade 3	1 (3.6%)	9 (28.1%)	0.04
Diarrhoea	All grades	16 (57.2%)	21 (65.6%)	0.55
	Grade 3	1 (3.6%)	6 (18.7%)	0.42
Pain	All grades	18 (64.3%)	21 (65.6%)	0.53
	Grade 3	2 (7.2%)	5 (15.6%)	0.55
Genitourinary	All grades	17 (60.7%)	20 (71.4%)	0.32
	Grade 3	9 (32.1%)	11 (34.4%)	0.95
Anemia	All grades	17 (60.7%)	21 (65.6%)	0.56
	Grade 3	2 (7.2%)	5 (15.6%)	0.58
Dermatitis	All grades	10 (35.7%)	16 (50%)	0.35
	Grade 3	1 (3.6%)	3 (9.4%)	0.03
Late Toxicities		Arm A	Arm B	p-value
Cystitis	Grade 1 or 2	2 (7.2%)	5 (15.6%)	0.5
	Grade 3 or 4	0 (0%)	0 (0%)	
Proctitis	Grade 1 or 2	0 (0%)	3 (9.4%)	0.13
	Grade 3 or 4	2 (7.2%)	2 (7.1%)	
Vesicovaginal fistula	Grade 1 or 2	0 (0%)	0 (0%)	0.64
	Grade 3 or 4	1 (3.6%)	1 (3.1%)	
Vaginal stenosis	Grade 1 or 2	1 (3.6%)	1 (3.1%)	0.64
	Grade 3 or 4	0 (0%)	0 (0%)	
Osteoradionecrosis of femoral head	Grade 1 or 2	0 (0%)	0 (0%)	0.51
	Grade 3 or 4	0 (0%)	1 (3.1%)	

Table- 4: toxicities in both arms

Survival outcome

The median follow-up was 34months. The median DFS and OS and 3years DFS and OS for both arms are summarized in the following Table-5. Kaplan-Meire survival curves are also depicted in fig no-1,2.

Survival Outcome	Arm A	Arm B	p-value
Median DFS	36 months	33.5 months	
Median OS	36 months	34.5 months	
3years DFS	77.8%	71.6%	0.84
3years OS	76.7%	74%	0.86

Table-5: Survival Outcome in both arms

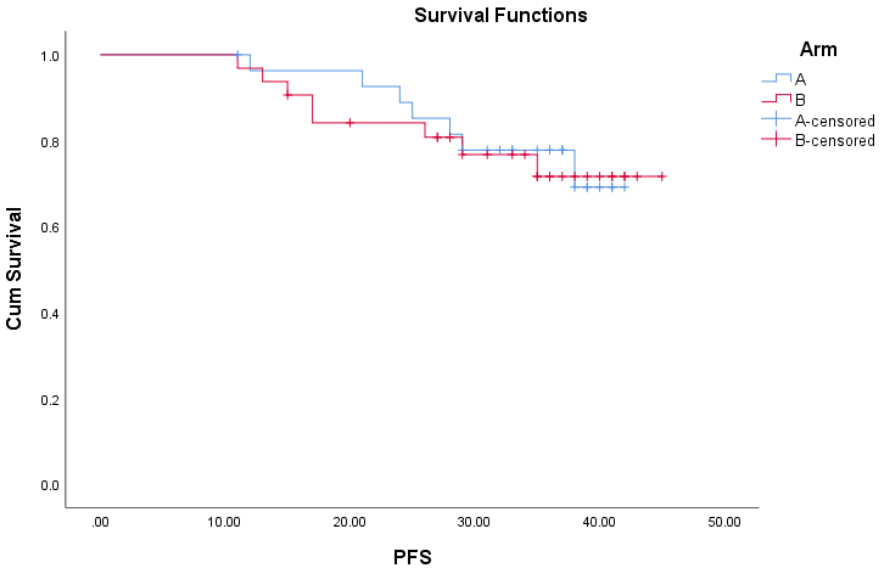


Fig no-1

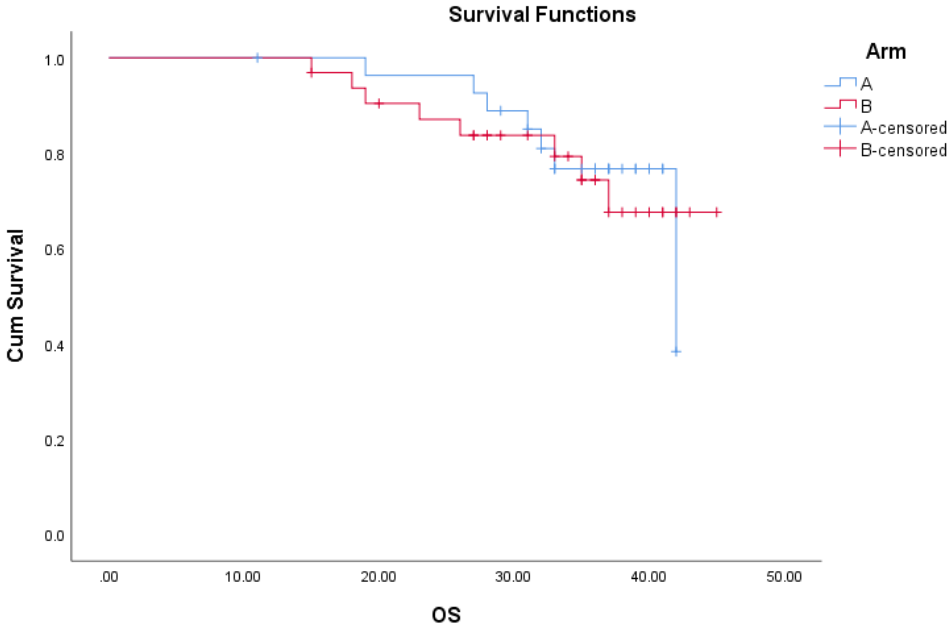


Fig no-2

DISCUSSION

In locally advanced carcinoma cervix radical chemoradiation with cisplatin as concurrent chemotherapy is the definitive treatment.[2,3,4,5,6,7,12] Meta-analysis of 19 randomized controlled trials strengthen the fact that concomitant chemoradiation has improved the survival, both OS and PFS.[13] Literature also suggests that the maximum survival benefit can be achieved in earlier stages of the disease, and that a higher incidence of grade 3 or 4 toxicities occur in patients receiving chemoradiation compared to radiation alone.[13] Being a nephrotoxic agent cisplatin must be used with caution in stage III and IV where the incidence of hydronephrosis could be as high as 46%.[14] In case of elderly patients, patients with multiple comorbidities, poor performance and nutritional status, administration of concurrent chemotherapy can become challenging. Many studies including the DAHANCA-6/7 have already showed that accelerated EBRT is beneficial in Head and

Neck carcinoma (HNC) due to reduced OTT which ultimately provide therapeutic gain.[15,16] These results can potentially be extrapolated in carcinoma cervix due to similar radiobiological properties with HNC. In pure accelerated fractionation (AF), the Biological Effective Dose (BED) remain same as that of conventional fractionation. But the limitation of BED is that it does not incorporate the treatment time, which is shortened in AF.

BED= nd(1+ d/α/β)…. Equation 1[17]

Thus the equation of BED has been modified to include the treatment time(T), tumour doubling time(teff) and time at which the repopulation start(T_k).

BED = nd (1 + d/α/β) − 0.693/α.teff (T–Tk) …. Equation 2[17]

The entity 0.693/α.teff can be expressed as constant K and is found to be 0.6 Gy/day, dose to overcome accelerated repopulation of tumour cells if treatment time extends beyond T_k.[18] So the simplified equation of BED is as following

BED = nd (1 + d/[α/β]) −0.6 (T-21) …. Equation 3[17]

Data from this study show that patients in the 6 fractions per week radiation alone arm completed treatment earlier than those in the chemoradiation arm. The treatment gaps were also lesser. Although small in terms of absolute value, the delays in the chemoradiation arm were statistically significant. Considering the fact that patients who were older and had comorbidities (for which they were denied chemotherapy) can be selectively included in the 6fractions arm, the results are definitely encouraging. If we translate this into equation 1 above, we will find that the BED is 50 × 1.2 or 60Gy in both arms (considering α/β value of 10). However, if we incorporate the median treatment time (during EBRT in both arms – 32 days in Arm A and 39 days in Arm B), we will get different BEDs of 53.4Gy in Arm A and 49.2Gy in Arm B (from equation 3). The biologic dose wasted in Arm A is only 6.6Gy compared to 10.8Gy in Arm B.

A relatively new concept in chemoradiation biology is that of a chemotherapy equivalent biologic effective dose (CBED). This predicts a ~2 Gy10 equivalence for each cycle of chemotherapy such as single agent Cisplatin when used weekly during radiotherapy. This would mean a 10Gy advantage for chemoradiation patients in Arm B, thereby increasing the BED to 59.2Gy. Again this proves the benefit of using AF which can achieve a BED similar (albeit slightly lesser) to chemoradiation than using radiation alone.

Yoon et al. conducted a prospective study to investigate the efficacy and toxicity of accelerated EBRT followed by HDR brachytherapy.[19] 3years OS, Locoregional and Distant metastasis free survival were 74.7%, 87.8% and 84.7% respectively in their study. A similar prospective study by Kumar et al. on 46 patients of locoregionally advanced cervical cancer, had compared survival between accelerated EBRT and conventional EBRT with both arms receiving concurrent chemotherapy.[20] The 3years DFS and OS were 69.5% vs 72.7% (p-value:0.73) and 63% vs 68% (p-value:0.45) in both arms. In this study 3years DFS and OS were also comparable in both arms. In one retrospective analysis 3years survival was 73.7% in carcinoma cervix patients treated with chemoradiation, which is close with this present study (76.7% in arm A, 74.4% in arm B).[21]

Another study by Roy et al. had shown the OTT to be 56.54 days for accelerated EBRT alone and 62.59 days for conventional chemoradiation, whereas the median EBRT duration to be 32.25 days and 38.85 days in accelerated vs conventional chemoradiation.[22] This result closely corroborates with the present study.

During our follow up, 10.7% patients in arm A and 12.7% patients in arm B had developed late toxicities of grade 3 or 4. Late toxicities of grade 3 or 4 reported by Eifel et al and Vale et al. are 12.6% and 10% respectively. [23,24]

In the present study, the accelerated EBRT was found to be comparable to conventional

chemoradiation in terms of local tumour control. Grade 3 acute toxicity was higher in chemoradiation arm, whereas the late toxicities were comparable in both arms. In a developing country like ours, where delivering treatment under numerous resource constraints is a major challenge, shortening treatment time is beneficial. It facilitates earlier initiation of treatment for more patients by reducing the waiting period and ensures optimization of limited resources.

Although this study suggests the equal efficacy of accelerated radiation, the results need to be viewed with cautious optimism. Some pitfalls of this study were small sample size, short follow up period and inherent biases of single-institutional trials. Also, we were unable to use the current FIGO staging for this trial as the planning, academic and ethical approvals, and part of the accrual were done prior to the 2018 FIGO update in the staging of cervical cancer. This study offers an exciting prospect which might be an alternative option in selected patients who have contraindications to chemoradiation and needs further validation from larger trials in future.

CONCLUSION

To conclude, this study suggests that EBRT using AF schedule alone followed by HDR brachytherapy is an effective treatment for patients with locally advanced carcinoma cervix and can be used as a possible alternative to chemoradiation in selected patients. The early responses to treatment are comparable to chemoradiation and the less acute toxicities. Moreover, the OTT is significantly reduced with accelerated radiation. This method provides a rationale and feasible alternative to conventional chemoradiation in patients of locally advanced carcinoma cervix who are unfit for chemotherapy. Further multicentre, controlled, randomized phase III trials will be needed to prove the benefit of the shortening OTT and compare the efficacy with chemoradiation.

Declaration by Authors

Ethical approval: Approved by Institutional Ethics Committee, Medical College, Kolkata (Reg no: ECR/287/Inst/WB/2013) with ref no. MC/Kol/IEC/Non-spon/600/10-2017.

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