RESEARCH ARTICLE

Impact of Treatment Time on Chemoradiotherapy in Locally Advanced Cervical Carcinoma

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Abstract

Background: Adverse effects of treatment prolongation beyond 8 weeks with radiotherapy for cervical cancer have been established. Clinical data also show that cisplatin increases the biologically effective dose of radiotherapy. However, there are no data on the effect of overall treatment time in patients with locally advanced cervical cancer treated with concomitant chemo-radiotherapy (CCRT) in an Indian population. The present study concerned the feasibility of concurrent chemotherapy and interspacing brachytherapy during the course of external radiotherapy to reduce the overall treatment time and compare the normal tissue toxicity and loco-regional control with a conventional schedule. Materials and Methods: Between January 2009 and March 2012 fifty patients registered in the Gynaecologic Oncology Clinic of Institute Rotary Cancer Hospital with locally advanced cervical cancer (FIGO stage IIB-IIIB) were enrolled. The patients were randomly allocated to treatment arms based on a computer generated random number. Arm I (n=25) treatment consisted of irradiation of the whole pelvis to a dose of 50 Gy in 27 fractions, and weekly cisplatin 40mg/m^2. High dose rate intra-cavitary brachytherapy (HDR-ICBT) was performed after one week of completion of external beam radiotherapy (EBRT). The prescribed dose for each session was 7Gy to point A for three insertions at one week intervals. Arm II (n=25) treatment consisted of irradiation of the whole pelvis to a dose of 50 Gy in 27 fractions. Mention HDR-ICBT ICRT was performed after 40Gy and 7Gy was delivered to point A for three insertions (days 23, 30, 37) at one week intervals. Cisplatin 20 mg/m^2/day was administered from D1-5 and D24-28. Overall treatment time was taken from first day of EBRT to last day of HDR brachytherapy. The overall loco-regional response rate (ORR) was determined at 3 and 6 months. Results: A total of 46 patients completed the planned treatment. The overall treatment times in arm I and arm II were 65±12 and 48±4 days, respectively (p=0.001). At three and six months of follow-up the ORR for arm I was 96% while that for arm II was 88%. No statistically significant difference was apparent between the two arms. The overall rate of grade ≥3 toxicity was numerically higher in arm I (n=7) than in arm II (n=4) though statistical significance was not reached. None of the predefined prognostic factors like age, performance status, baseline haemoglobin level, tumour size, lymph node involvement, stage or histopathological subtype showed any impact on outcome. Conclusions: In the setting of concurrent chemo-radiotherapy a shorter treatment schedule of 48 days may be feasible by interspacing brachytherapy during external irradiation. The response rates and toxicities were comparable.

Keywords: Cervical cancer - chemotherapy - treatment time - radiotherapy

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Introduction

Cervical cancer is the leading cause of death among women worldwide. In India majority of the patients present with locally advanced cervical cancer. Until NCI (National Cancer Institute) announcement in 1999 conventional treatment has been careful combination of external beam radiotherapy and intra-cavitary brachytherapy (ICBT). Following publication of the five randomized trials and one meta-analysis (Keys et al., 1999; Whitney et al., 1999; Morris et al., 1999; Rose et al., 1999; Peters et al., 2000; Green et al., 2001) concomitant chemo-radiotherapy (CCRT) has been the preferred treatment for locally advanced carcinoma of uterine cervix. Since then advances in cervical cancer therapy has remained stagnant despite new chemotherapy and radiotherapy and surgical techniques and a significant proportion of patients respond poorly to CCRT. Overall treatment duration has been found to be a significant predictor of treatment response. Several studies have demonstrated that prolonging overall treatment time with radiotherapy beyond 8 weeks results in increased pelvic failures and adversely affect overall

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survival (Grinsky et al., 1993; Perez et al., 1995; Chen et al., 2003). The poor outcome with RT prolongation is attributed to accelerated tumour cell repopulation resulting in poor local control.

Current RTOG (Radiation Therapy and Oncology Group) recommends completion of treatment within 8 weeks, however the impact of treatment time with concurrent chemotherapy has not been studied. This is pertinent as many factors including treatment related toxicities cause delay or prolongation of treatment time in cervical cancer especially in the setting of CCRT. There is no literature on the effect of overall treatment time in patients with locally advanced cervical cancer treated with CCRT from the Indian population.

Cancer care in developing countries is challenging for adequate infrastructure, specialist care, treatment costs, and access to tertiary care centre resulting in increased patient load in specialised centres. A significant proportion of our patients attend our centre from distant places and a gap between EBRT (external beam radiotherapy) and ICBT is frequently observed making treatment prolonged and protracted upto 10 weeks and beyond due to social reasons. Zamaniah et al. (2014) observed that nearly 30% exceeded the recommended 7 weeks for treatment completion due to various reasons. It was hypothesised that a shorter treatment time within the tolerance limit will accomplish the RTOG/GOG (Gynaecologic Oncologgy Group) recommendations of overall treatment time and might improve treatment compliance.

The current study aims to study the feasibility of concurrent chemotherapy and interspacing brachytherapy during the course of external radiotherapy to reduce the overall treatment time to 7 weeks and compare the normal tissue toxicity and loco-regional response with conventional schedule.

Materials and Methods

Patient selection

Between January 2009 and March 2012, fifty patients registered in Gynaecologic Oncology Clinic of Institute Rotary Cancer Hospital, All India Institute of Medical Sciences (AIIMS), with locally advanced cervical cancer (FIGO stage IIB-IIIB) were enrolled in this randomized controlled study. The patients were randomly allocated to treatment arms based on a computer generated random number. (Figure 1) Eligibility criteria included newly diagnosed cases of carcinoma cervix, biopsy proven squamous or adenocarcinoma, with Karnofsky performance status (KPS) 70-90 with adequate haematological and biochemical parameters and absence of obvious co-morbidities which can adversely affect treatment or outcome. The pre-treatment evaluation consisted of detailed history and clinical examination including routine haematological and biochemical investigations (kidney function tests and liver function tests), chest X- ray, cystoscopy, sigmoidoscopy and contrast enhanced computed tomography scan (CECT) of abdomen and pelvis. The study was approved by the Institute's Ethics Committee. Informed written consent was obtained before beginning of treatment.

Treatment schedule

Arm I (standard arm) received EBRT to a dose of 50 Gy in 27 fractions. It was delivered using four field box technique after simulation by Theratron 780C (Best Theratronics, Ottava, Canada) or by 6MV/15 MV photon by Linear accelerator (Elekta Medical Systems, Crawley, UK) in five and half weeks. ICBT was given after one week of completion of EBRT by Microselectron HDR

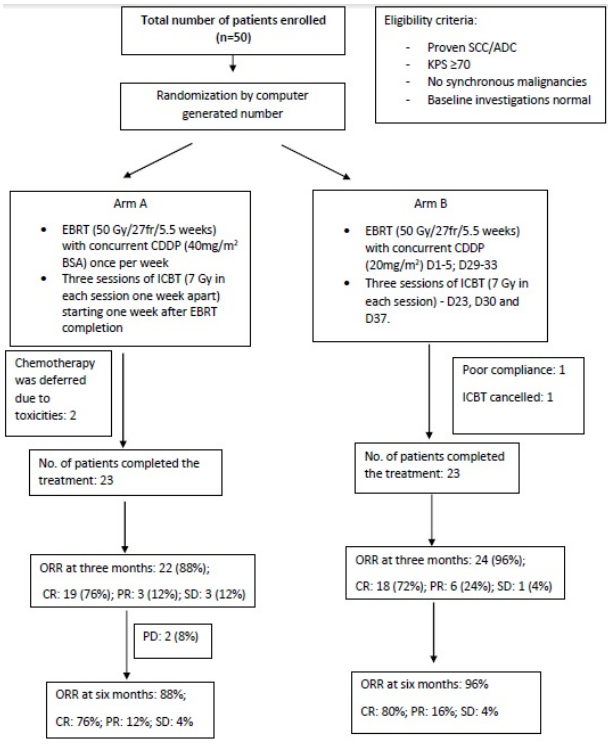

Figure 1. Showing the CONSORT Diagram of the Study

Table 1. Showing the Patient Characteristics in Both Treatment Arms

Characteristics	Arm I (n=25)	Arm II (n=25)	p Value
Mean Age (Years)	51.8±8.9	48.8±9.1	0.24
KPS			
≤80	6	5	0.99
>80	19	20	
Stage			
II	6	7	0.74
III	19	18	
Tumour size (cm)			
≤4	9	11	0.78
>4	16	14	
Lymph node metastasis			
Yes	5	11	0.128
No	20	14	
Parametrial invasion			
Unilateral	2	3	0.99
Bilateral	23	22	
Histopathology			
SCC	25	24	0.99
ADC	0	1	
Hemoglobin (Hb) level			
≤10	5	6	0.99
>10	20	19	

unit, Nucletron, an Elekta company (Elekta, Stockholm, Sweden). A total of 21 Gy in 3 fractions one week apart was given to point A. Cisplatin was administered concurrently every week at a dose of 40mg/m^2 during the course of EBRT.

Arm II (study arm) received EBRT to a dose of 50 Gy in 27 fractions. It was delivered using four field box technique after simulation by Theratron 780C (Best Theratronics, Ottava Canada) or by 6MV/15 MV photon by Linear accelerator (Elekta Medical Systems Crawley, UK).in five and half weeks. ICBT was delivered after 40 Gy of external radiation by HDR Microselectron to point A. Patients received three sessions of ICBT on day 23, 30 and 37. A total of 21Gy in 3 fractions one week apart was given to point A. Cisplatin 20 mg/m^2 body surface area/ day was administered from D1-5 and D24-28. EBRT was not delivered on the day of brachytherapy.

Table 2. Treatment Duration in Two Arms (in days)

	Arm I		Arm II		*P*
	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	
EBRT time	39 (31-63)	42±8.1	40 (34-46)	40±3	0.36
BT time	14 (9-21)	15±2.3	14 (13-21)	15±2.3	0.59
OTT	61 (54-101)	65±12.1	49 (42-60)	48±4.2	0.001

Table 3. Showing Treatment Response in Two Arms at 3 and 6 Months

Response	Arm I f (%)	Arm II f (%)	p value
At 3 months			
CR	19 (76%)	18 (72%)	
PR	3 (12%)	6 (24%)	
SD	3 (12%)	1 (4%)	
PD	0	0	
ORR (CR+PR)	22 (88%)	24	0.34
At 6 months			
CR	19 (76%)	20 (80%)	
PR	3 (12%)	4 (16%)	
SD	1 (4%)	1 (4%)	
PD	2 (8%)	0	
ORR (CR+PR)	22 (88%)	24 (96%)	0.6

Treatment modification

Chemotherapy dose was reduced to 75% for absolute neutrophil count (ANC) of 1000-1500/mm^3 and platelet count of 75,000 -100,000. Radiotherapy and chemotherapy was withheld if ANC was below 1000/mm^3 and platelet below 75,000 till counts recovered.

Evaluation of treatment Response and toxicity

Patients were monitored during the course of EBRT every week with haematological investigations and clinical examination for acute treatment related morbidities. Toxicity grading was prepared according to RTOG and CTCAE (Common terminology criteria for adverse events) version 4. Tumour response to external beam radiotherapy was recorded by pelvic examination before first brachytherapy session.

Treatment Time

Overall treatment time (OTT) was taken from first day of EBRT to last day of HDR brachytherapy.

Follow-up

After completion of treatment patients were followed up in clinic after 4 weeks, 12 weeks, 3 months, 6 months and every 6 months thereafter. The median follow up was 15 months (range:7.4-59 months). The median follow-up for arm I and II are 14.2 and 15.2 months respectively. The period was calculated from the completion of treatment. A general clinical and pelvic examination was performed during each follow-up. Radiological imaging in the form of chest X-ray, abdominal ultrasound and CT scan of abdomen and pelvis and biopsy of a recurrent tumour was carried out in the presence of clinical symptoms and signs necessitating the investigation. Overall response assessment was done using revised RECIST (response evaluation criteria in solid tumours) criteria version 1.1. Overall response rate (ORR) was defined as sum of complete response (CR) and partial response (PR)

Statistical Analysis

Clinico-pathological attributes, treatment response, overall treatment time and toxicities between two arms were compared with chi-square/ Fisher exact test and independent "*t*" test (as applicable) using STATA 11.2 (Stata Corp, College Station, Texas 77845, USA). p- value <0.05 was considered to be significant.

Table 4. Showing the Pattern of Toxicities in Two Arms

Toxicity		Arm I				Arm II				p value (Grade 3/4 toxicities)
		Gr1	Gr2	Gr3	Gr4	Gr1	Gr2	Gr3	Gr4	
Haematological	Anaemia	2	1	0	0	3	2	0	0	-
	Neutropenia	0	3	3	1	1	2	4	0	0.99
	Thrombocytopenia	1	2	0	1	4	0	0	0	0.99
GI	Nausea vomiting	10	4	0	0	14	6	0	0	-
	Diarrohea	8	7	1	0	8	8	0	0	0.99
GU		5	4	1	0	8	6	0	0	0.99

Results

The patient characteristics in both arms are detailed in Table 1. The distribution of patients in the two arms were uniform with no significant difference Majority of the patients presented in stage IIIB (74%). Were squamous cell carcinomas (98%), clinical tumour size of ≥4 cm (60%) with no clinical lymph nodes (68%), and haemoglobin levels above 10 mg/dl (78%) with bilateral parametrial involvement. The clinico-pathological attributes and prognostic parameters were similar in both arms.

Forty six patients completed the planned treatment. Chemotherapy was deferred in two patients in arm I due to haematological toxicity and hydroureteronephrosis. One patient did not receive ICBT due to gross residual after external beam radiotherapy and was treated with three dimensional conformal radiotherapy. One patient in arm II did not complete chemotherapy due to poor compliance. The overall treatment time in arm I and arm II are 65±12 and 48±4 days respectively (Table 2).

At 3 months following completion of treatment in arm I 22 (88%) patients responded, complete response 19 (76%), partial response 3 (12%). In arm II 24 (96%) responded complete response 18 (72%), partial response-6 (24%), improved complete response rates were observed in arm II (96% vs. 88%) at 6 months. However the difference of overall response rate in two arms did not reach statistical significance (Table 3). In arm I two patients developed progressive disease. One of them developed a distant metastasis to lung and other developed multiple peritoneal deposits and retroperitoneal lymph node metastasis. Both of them were referred to hospice care.

Grade ≥3 haematological toxicity was observed in 5 patients (20%) in arm I (neutropenia: 4; thrombocytopenia: 1) as compared to 4 (16%) arm II (neutropenia: 4) in arm II. Patients received blood transfusion, antibiotics and colony stimulating factors as per necessity. One patient developed grade 3 diarrhoea and grade 4 haematuria in arm I. No grade ≥3 non-haematological toxicity was observed in arm II. Comparison of grade ≥3 toxicities between two arms did not confer any statistical significance (Table 4)

Discussion

The present study is an attempt to study the role of overall treatment time in patients with locally advanced cervical cancer treated with concomitant chemo-radiotherapy. Despite the small sample size, our study highlights the beneficial role of treatment completion in the recommended 8 weeks time in terms of loco-regional control and outcome. The morbidity in both arms were comparable and within acceptable limits.

Overall treatment duration has been a significant predictor of loco-regional response and survival in advanced cervical cancer (Fyles et al., 1992; Grinsky et al., 1993; Perez et al., 1995; Chen et al., 2003). A study from France (Krebs et al., 2015) showed that overall treatment duration is as important as dose to the high risk clinical target volume to achieve complete response in cervical cancer. However Song et al. (2013) showed a paradoxical result. The authors observed prolonged brachytherapy duration correlated with higher pelvic failure though it did not show any impact on distant failure or disease specific mortality. Higher incidence of treatment related toxicities and delay in start of brachytherapy was attributed as potential reasons for prolongation of treatment duration. Interspacing brachytherapy with EBRT may be an option to avoid this problem.

The effect of overall treatment time on survival and toxicity was studied for patients receiving radical radiotherapy for cervical cancer (Erridge et al., 2002). The authors observed higher late morbidity and no impact of treatment prolongation as all patients completed treatment within 7 weeks. Our study did not observe increased morbidity in the shorter treatment arm. Recent guidelines by American brachytherapy society (Vishwanathan et al., 2012) recommend to limit the overall treatment duration below 8 weeks. They recommend HDR brachytherapy to commence after 39.6 Gy or 45 Gy with up to 2 fractions being given per week during the conclusion of external beam and the parametrial boost.

The present study observed a comparable compliance with, a superior response rate in the study arm at 6 months of follow-up. The grade 3 or higher toxicities was also comparable to the conventional treatment arm inspite of significantly shorter overall treatment duration. The rate of grade ≥ 3 toxicity in our study arm is less when compared to other series from our country 25% vs 16% (Kumaran et al., 2014) and equivalent to other contemporary series (Song et al., 2013). Shorter duration of treatment did not result in higher toxicity which is in contrary to the finding by other study (Erridge et al., 2002).The possible explanation of our finding could be due to conventional fraction size practiced in the study. The current study aimed comparative evaluation of two treatment regimen using conventional fractionation and concurrent chemotherapy and thus differs from most of the above studies which evaluated its efficacy with altered fractionation (Erridge et al., 2002; Krebs et al., 2015). The homogenous study population, randomized treatment allocation and prospective evaluation are the strengths of the study when compared to some other contemporary studies, which are mostly retrospective in nature (Erridge et al., 2002; Song et al., 2013), with a heterogeneous study population and varied treatment techniques. Our study practiced a uniform dose fractionation schedule and radiation techniques for all the patients.

In the current randomized study interspacing brachy, therapy with EBRT and concurrent chemotherapy resulted in significantly shorter treatment duration with a superior response rate and comparable toxicity as compared to the standard practice. The schedule improves the overall output and reduces the waiting period in a high burden cancer centre.

Interspacing brachytherapy with concurrent chemo-radiation is feasible and reduces the overall treatment time and completes the treatment in the recommended 8 weeks time. In the current study a trend for higher response was observed in the arm with shorter overall treatment time with acceptable morbidity. The study also emphasizes that a shorter and effective treatment regimen will be of

immense benefit for cost effective treatment of cervical cancer in a developing nation.

The small sample size and short follow-up limits the power of the study. Therefore the results of the present study need to be interpreted with caution and larger study will be worthwhile for a resource appropriate practice.

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