RESEARCH ARTICLE

Editorial Process: Submission:04/06/2023 Acceptance:10/16/2023

External Beam Radiotherapy Interdigitated with High Dose Rate(HDR) Intracavitary Brachytherapy versus External Beam Radiotherapy followed by Sequential HDR Intracavitary Brachytherapy for Locally Advanced Carcinoma Cervix–Randomized Control Study

Indra Jeet Gupta[1], Arunima Ghosh[1]*, Jagrati Yadav[2], Jasmeet Singh Tuteja[1], Rajeev Gupta[1], Kirti Srivastava[1], Mrinalini Verma[1], Seema Gupta[1], Shraddha Srivastava[1], Madan Lal Brahma Bhatt[1]

Abstract

Background: In cervical cancer treatment, overall treatment time (OTT) is an important prognostic factor. This study compares the clinical outcomes when High-Dose-Rate Intracavitary-Brachytherapy(HDR-ICRT) is interdigitated with external beam radiotherapy(EBRT) versus sequential HDR-ICRT after EBRT in the treatment of locally advanced carcinoma cervix. **Methods:** Histologically confirmed carcinoma cervix patients [FIGO Stage IIB–IVA (except IIIC-2)] were included and randomized into two groups. The study group received EBRT 50Gy in 25 fractions with interdigitated HDR-ICRT 7Gy per fraction weekly for three fractions starting after completion of 3 weeks of EBRT or as soon as cervical os became negotiable thereafter. Patients in the control group received EBRT 50Gy in 25 fractions with sequential HDR-ICRT 7Gy per fraction weekly for three fractions starting one week after completion of EBRT. All patients were regularly followed up during and after radiotherapy for local toxicity and disease control. **Results:** This study enrolled 102 patients; 51 in each arm. Median OTT in study and control arm were 46 and 60 days, respectively. Median follow-up duration was 24 months (two years). Loco-regional control after two years of follow-up was 84.31 % and 72.54% of patients in study arm control arm respectively (p-value 0.148). Two (3.92%) patients from study arm and eight (15.68%) from control arm had residual disease. Two patients in study arm and one from control arm had local recurrence. Two patients from study arm three patients from control arm developed distant metastases. RTOG mucosal grade <II toxicities were seen in 31(60.8 %) and 9(17.6 %) patients of study and control arms (p-value 0.00001) respectively. No patient developed grade >III acute mucosal toxicity in either arm. Cervical-os negotiability was limiting factor for interdigitated HDR-ICRT. **Conclusions:** Interdigitated HDR-ICRT with EBRT may give local control with manageable toxicities as compared to sequential HDR-ICRT, with the advantage of significant reduction in OTT.

Keywords: Cervical cancer- concurrent chemoradiotherapy- interdigitation- overall treatment Time

Asian Pac J Cancer Prev, **24 (10)**, 3441-3445

Introduction

Cervical cancer is the second most common cancer to affect females in India, next only to breast cancer (Mathur et al., 2020). It accounts for around 77,348 (9.1%) of all cancer deaths annually occurring in India. Worldwide, this disease ranks as the fourth most frequently diagnosed cancer and is the fourth leading cause of cancer death in women (Sung et al., 2021). Concomitant chemoradiotherapy (CCRT) is the recommended standard treatment for locally advanced cervical cancer (LACC) [i.e. International Federation of Gynaecology and Obstetrics (FIGO) stages IIB, III, IVA] and has improved survival outcomes compared to radiation therapy alone (Keys et al., 1999; Rose et al., 1999; Whitney et al., 1999; Peters et al., 2000).

Radiotherapy is delivered as a combination of external beam radiotherapy (EBRT) and intracavitary radiotherapy (ICRT). The objective of EBRT is to deliver radiation dose to the whole pelvis to treat the primary disease, parametrium and pelvic lymph nodes. The objective of ICRT is to deliver radiation dose directly to the tumor while sparing the adjacent normal tissues. Overall treatment time (OTT) for radiotherapy (including EBRT

*[1]Department of Radiotherapy, King George's Medical College, Lucknow, Uttar Pradesh, India. [2]Kalyan Singh Super speciality Cancer Institute, Lucknow, India. *For Correspondence: arunima2090@gmail.com*

and ICRT) correlates with local disease control and survival (Fowler and Lindstorm, 1992). The American Brachytherapy Society (ABS) has recommended that the total treatment duration including EBRT and ICRT should be less than 8 weeks (Viswanathan et al., 2000). Some studies have suggested that there may be as much as 1% decrease in survival and local control for each extra day of treatment beyond a total treatment time of 55–60 days for all stages of disease due to accelerated repopulation. (Lanciano et al., 1991; Fyles et al., 1992).

According to Lanciano (1991), in field recurrence increased from 6% to 20% when overall treatment time increased from 6 weeks or fewer to 10 weeks ($p = .0001$); which translated into significantly decreased survival. In a study conducted by Perez (1995) in which 1,224 patients were treated with definitive irradiation, they noted a major impact of prolongation of treatment time on pelvic tumor control in FIGO stages IB, IIA, and IIB. In FIGO stage III, although the rate of pelvic failure was higher with prolongation of treatment time, the difference was not statistically significant.

HDR-ICRT can be interdigitated with EBRT if vaginal geometry is suitable for brachytherapy application to decrease the OTT (Fyles et al., 1992; Fowler and Lindstorm, 1992; Patidar et al., 2012; Viswanathan et al., 2000). The overall treatment time (OTT) amounted to 56 days for sequential radiotherapy and 35 days for continuous (interdigitated) radiotherapy in a study by Mayer (2004). The median OTT for patients in interdigitated arm in our study was 46 days as well, although OTT for control arm was higher compared to that seen in Mayer (2004). With a median follow-up time of 3.4 years, progression free 5-year survival (PFS) was 71 % in continuous (interdigitated) radiotherapy and 56 % in sequential radiotherapy.

Our aim in this study was to assess the feasibility and locoregional control in patients of locally advanced cervical cancer undergoing interdigitated EBRT and HDR-ICRT compared to those undergoing sequential EBRT followed by HDR-ICRT.

Materials and Methods

Study design

This study was designed as a prospective randomized study approved by the Institutional Ethics Committee, Research Cell, King George's Medical University (KGMU), Lucknow, Uttar Pradesh, India. Study was conducted in the Department of Radiotherapy, KGMU, Lucknow from August 2019 to April 2020. Patients with carcinoma of the uterine cervix were enrolled in the study. With the help of computer-generated random numbers, the principal investigator allocated the participants to either arms after simple randomisation. Patients in the study arm received HDR-ICRT interdigitated with pelvic EBRT and those in the control arm received HDR-ICRT after completion of EBRT. This study was done as per the principles laid out in the Declaration of Helsinki, and in accordance with the international guidelines on Good Clinical Practice.

Study population

Eligible patients had FIGO stage IIB, IIIA, IIIB, IIIC1 or IVA biopsy-proven invasive squamous cell carcinoma of the uterine cervix and a performance status of Eastern Cooperative Oncology Group (ECOG) index of 0-2. Patients had adequate hepatic, renal, and cardiopulmonary functions and no history of previous malignancy. Pre-treatment evaluation included a complete medical history taking and physical examination, baseline blood tests, chest radiography, ultrasound abdomen and magnetic resonance imaging (MRI) of the pelvis. Eligible patients had to be free of clinically significant infection, have no prior exposure to pelvic irradiation or cytotoxic chemotherapy.

External Beam Radiotherapy

Radiotherapy planning (RTP) computed tomography scan was taken with the patient scanned in the supine position. Intravenous contrast was given to aid in nodal delineation. A bladder and bowel protocol was used to maintain a constant bladder filling – 'comfortably full'. The patients were asked to empty their bladder and drink 500 ml water 30 minutes before the scan and treatment each day. Clinical target volume primary (CTV-P) included the gross tumor of the uterine cervix, uterine corpus, parametrium, vagina and ovaries. Clinical Target Volume Nodal (CTV-N) was delineated by using pelvic blood vessels as a surrogate target. Planning target volume (PTV) delineation was done by the addition of 7 mm margin to the CTV as per departmental protocol.

All patients were treated on linear accelerator (Elekta Synergy) by using 6 and 15-MV photon beams with 3DCRT technique. Patients received pelvic EBRT 50 Gy, 2 Gy per fraction, 5 fraction per week over 5 weeks. ICRT HDR-ICRT was delivered by remote after loading Micro-selectron Ir-192 HDR unit. HDR-ICRT was delivered once a week with a per fraction dose of 7 Gy at point A once for 3 weeks. Patients were evaluated weekly for local mucosal toxicity and for cervical os negotiability weekly after three weeks from starting of EBRT. In the study arm, after completing 3 weeks of EBRT, ultrasonography of pelvis was done. If vaginal geometry was found to be suitable i.e., whence disease regressed to 4 cm or less in size then the 1st fraction of HDR-ICRT was delivered, otherwise patient was assessed at weekly intervals for suitability for brachytherapy and HDR ICRT was delivered when suitable for the same. For patients in control arm, ICRT was started one week after completion of EBRT as per institutional protocol.

Concurrent chemotherapy

Cisplatin (40 mg/m^2) intravenous infusion with adequate hydration was given concurrently with EBRT on a weekly basis. Neither EBRT nor chemotherapy was given on the day of ICRT in the study arm. All patients were assessed weekly during radiotherapy and 3 monthly after completion of radiotherapy for toxicities of treatment as per RTOG criteria and disease response as per RECIST criteria.

Patient and care providers assessing outcomes were blinded as to group allocation of patients.

Statistical Analysis

The evaluation of data was done using SPSS software version 25. The age number of cases summaries are listed as mean and standard error. The comparison between different groups and categorical data were done by using Pearson's chi square method. Percentage and modes were calculated wherever needed.

Results

This prospective comparative study enrolled 102 patients from August 2019 to April 2020. There were 51 patients in study arm (Arm A) and 51 patients in control arm (Arm B). The mean age of patients in study arm was 52.13 ±8.4 years and that in control arm was 51.88±8.2 years. Patient demographic and tumor characteristics details are given in Table 1.

In the study arm, we found that external cervical os i.e. opening of cervix at vaginal end of endocervical canal was negotiable in 36 out of 51 patients (70.58%) after 30 Gray of EBRT i.e., three weeks, in 8 out of 51 patients (15.68%) after 40 Gray of EBRT (4 weeks) and 7 out of 51 patients (13.72%) after completion of EBRT (50 Gray i.e., 5 weeks).

The median OTT in study arm and control arm were 46 and 60 days, respectively. In study arm, 10 patients (19.60%) had OTT more than 52 days compared to 47 patients (92.15%) in control arm. The median follow-up period was two years.

According to RTOG (Radiation Therapy Oncology Group) the acute grade I, II and grade III gastrointestinal toxicities were significantly higher in study arm than in control arm (68.6 % vs 58.8 %; p- value 0.0482). No patient had grade IV acute gastrointestinal toxicity. The acute genitourinary grades I and grade II toxicities were seen in 33 patients (64.7 %) of study arm and 13 patients (25.5 %) of control arm; p value 0.00006. There was no grade III and grade IV acute genitourinary toxicities in either arm.

Table 1. Patient Demography and Disease Characteristics

Characteristic	Study ARM (n=51) n (%)	Control ARM (n=51) n (%)
Age Groups (Years)		
30-40	5 (9.8)	5 (9.8)
41-50	18 (35.3)	20 (39.2)
51-60	22 (46.2)	21 (44.4)
61-70	6 (11.5)	5 (11.1)
FIGO Stage (2018)		
II B	37 (72.5)	38 (74.5)
III A	8 (15.7)	8 (15.7)
IIIC-1	5 (9.8)	6 (11.7)
IV-A	1 (1.9)	2 (3.9)
Histopathological differentiation		
Well Differentiated	21 (41.1)	18 (35.3)
Moderately Differentiated	25 (49.0)	32 (62.7)
Poorly Differentiated	5 (9.8)	1 (1.9)

FIGO, International Federation of Gynaecology and Obstetrics

Table 2. Acute Toxicities

Acute toxicities	RTOG Toxicity Grade	Study ARM n (%)	Control ARM n (%)	P value
Gastrointestinal	<III	41 (80.4)	32 (60.7)	0.0482
Genitourinary	<II	33 (64.7)	13 (25.5)	0.00006
Mucosal	<II	31 (60.8)	9 (17.6)	0.00001
Skin	I	14 (27.4)	12 (23.5)	0.649

RTOG, Radiation Therapy Oncology Group

Mucosal grades I and grade II toxicities were found in 31 patients of study arm and nine patients of control arm (60.8 % vs 17.6 %; p-value of 0.00001). There were neither grade III nor grade IV acute mucosal toxicities in either arm. Skin reactions of RTOG grade I were seen in 14 patients of study arm and 12 patients of control arm (27.4 % vs 23.5 %; p-value of 0.649). No patient had grade II or higher skin reaction (Table 2). Three patients developed radiation proctitis in study arm compared to none in control arm as chronic toxicity and no other chronic toxicities occurs in either arm.

The Pearson's chi square test between the toxicities and their association shows that acute genitourinary and acute mucosal toxicities were significantly increased in study arm compared to control arm. However, the other acute toxicities like gastrointestinal, haematological and skin toxicities were not significantly different in both arms. All acute toxicities could be managed conservatively and there were no treatment interruptions in either arm.

Forty-three patients (84.31 %) in study arm and 37 patients (72.54 %) in control arm had no local disease at two years of follow-up (p-value 0.148). LRC was higher in the study arm when compared with control arm. Two patients from study arm and eight from control arm had residual disease. Two patients in study arm and one in control arm had local recurrence. Two patients in study arm and three patients in control arm developed distant metastases. A total of four patients died, two in each arm, the cause of death was disease related for all (Table 3).

Discussion

Cervical cancer is a significant burden on the women and health systems of low-middle income countries. As growing evidence has emerged regarding the influence of OTT on oncological outcomes in case of cervical cancer,

Table 3. Disease Status after Two Years of Follow-Up

Disease Status	Study ARM n (%)	Control ARM n (%)	P value
No Residual Disease	43 (84.31)	37 (72.54)	0.148
Residual Disease	2 (3.92)	8 (15.68)	
Local Recurrence	2 (3.92)	1 (1.96)	
Distant Metastasis	2 (3.92)	3 (5.88)	
Death	2 (3.92) n	2 (3.92)	

it becomes imperative to find ways to reduce the OTT while treating such a patient.

Petereit (1995) found the 5-year pelvic control rates were 87% and 72% when treatment time was < 55 days vs. > 55 days (p = 0.006). In our study we found similar pelvic control rates. They also concluded that pelvic control was significantly dependent on total treatment time more so for Stage IB/IIA (96 and 84%) and Stage III (76 and 55%), but not for Stage IIB (74 and 80%, respectively). Girinsky (1993) observed a sharp decrease in the local control rate of about 20% when OTT increased from 52 days to 62 days (approximately 20%) and by a further 13% when treatment time was extended beyond 62 days. A plot of 10- year actuarial local control rate as a function of treatment duration showed a 1.1% loss of pelvic control per day with the slope of the regression line significantly different from zero (p = 0.03).

In another study Patidar et al., (2012) median OTTs were 38 and 61 days in the study (Concommitant EBRT and HDR-ICRT) and the control groups (EBRT followed by HDR-ICRT), respectively. At the completion of the study, there were 80% and 68 % complete responses, 16 and 20 % patients had partial responses, 0 and 8 % with stable diseases in the study group and the control group, respectively. Acute toxicities were evaluated at weekly intervals with higher proportion and greater severity in the study group as compared to those in the control group but not found to be statistically significant. We also found acute toxicities to be manageable without interruption of treatment.

Another Indian study to evaluate local disease control and early complications of concomitant HDR- ICRT with EBRT and thereby decrease the OTT in IB–III B stage carcinoma cervix, (Kumari et al., 2015) found the median OTTs were 42 and 63 days in the study (concomitant EBRT and HDR- ICRT) and the control (EBRT followed by HDR-ICRT) groups, respectively. Similar OTTs were observed in our study as well. It is recommended that radiation therapy for cervical cancer patients should be delivered in the shortest possible overall treatment time (Perez et al., 1995) as radiotherapy duration could be the most independent treatment related prognostic factor in cervical cancer (Viani et al., 2009).

Earlier, due to the long waiting list for hospitalization, many patients with cervix cancer had to wait for their treatment with LDR brachytherapy. HDR brachytherapy (Wright et al., 1994) permits treatment of a larger number of patients and attenuation of the social problems regarding their outcome (Meena et al., 2023). It has been suggested that the mechanism for patients with longer treatment durations exhibiting a greater risk of local relapse could be the accelerated repopulation of tumour clonogens surviving a course of radiotherapy (Withers et al., 1998).

In our setup, around 15-20 % of out-patients in Radiotherapy department are carcinoma cervix patients. Completing definitive treatment of a large number of patients within 8 weeks each is a challenging task.

Conventionally, carcinoma cervix patients first undergo EBRT which is given over 5-6 weeks, and then patients are called at least a week after completion of EBRT for ICRT given weekly over 2-3 weeks as per availability of slots resulting in OTT of around 10 weeks. Due to multiple visits for HDR-ICRT, patients sometimes do not complete treatment or further delay treatment due to socio-economic problems and other logistic reasons.

In our study, interdigitaion decreased the OTT from 10 to 6 weeks, a 30 % reduction in treatment time. Treating a patient in as short time as possible is beneficial to both the patient and hospital administration and radio-biologically more useful for better tumor control. Large randomized trials may be undertaken which will determine the benefit of reducing OTT on the financial burden to patients and hospitals. It is necessary to determine that tumor volume has regressed sufficiently with proper clinical examination and image guidance before starting brachytherapy such that residual disease can be encompassed in treating volumes during brachytherapy.

In this prospective randomized study, we conclude that decreasing the OTT improved the local control rate. Although the difference was statistically insignificant and number of patients included in the study was limited, the results found were encouraging. Clinical benefit of interdigitation of ICRT with EBRT may be verified with larger patient population in phase III randomised control studies with long term follow-up.

Author Contribution Statement

Indra Jeet Gupta: guarantor of integrity of the entire study, study concepts and design, literature research, clinical studies, experimental studies / data analysis, manuscript preparation. Arunima Ghosh: study concepts and design, manuscript preparation, manuscript editing. Jagrati Yadav: clinical studies, study concepts and design, experimental studies / data analysis, manuscript preparation. Jasmeet Singh Tuteja: clinical studies, study concepts and design, manuscript preparation. Rajeev Gupta: clinical studies, study concepts and design, manuscript editing. Kirti Srivastava: clinical studies, study concepts and design, manuscript editing. Mrinalini Verma: clinical studies, study concepts and design, manuscript editing. Seema Gupta: clinical studies, study concepts and design, manuscript editing. Shraddha Srivastava: clinical studies, study concepts and design, data analysis. Madan Lal Brahma Bhatt: study concepts and design, manuscript editing

Acknowledgements

This study was approved by the Institutional Ethics Committee, Research Cell, King George's Medical University (KGMU), Lucknow, Uttar Pradesh, India.

Institutional Ethics Committee, Research Cell, King George's Medical University (KGMU), Lucknow, Uttar Pradesh, India.

Any conflict of interest

None.

References

Fowler JF, Lindstrom MJ (1999). Loss of local control with prolongation in radiotherapy. *Int J Radiat Oncol Biol Phys*, **23**, 457-7.

Fyles A, Keane TJ, Barton M, Simm J (1992). The effect of treatment duration in the local control of cervix cancer. *Radiother Oncol*, **25**, 273-9.

Girinsky T, Rey A, Roche B, et al (1993). Overall treatment time in advanced cervical carcinomas: a critical parameter in treatment outcome. *Int J Radiat Oncol Biol Phys*, **27**, 1051-6.

Keys HM, Bundy BN, Stehman FB, et al (1999). Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med*, **340**, 1154-1.

Kumari MPR, Reddy BN, Kumari CS, Krishna MR (2016). Comparison Between Concurrent EBRT and ICA with Conventional EBRT Followed by ICA in Cervical Cancer. *J Obstet Gynaecol India*, **66**, 263-3.

Lanciano RM, Martz K, Coia LR, Hanks GE (1991). Tumor and treatment factors improving outcome in stage III-B cervix cancer. *Int J Radiat Oncol Biol Phys*, **20**, 95.

Mathur P, Sathishkumar K, Chaturvedi M, et al (2020).. Cancer Statistics, 2020; Report from National Cancer Registry Programme, India. *JCO Glob Oncol*, **6**, 1063-5.

Mayer A, Nemeskéri C, Petneházi C, et al (2004). Primary radiotherapy of stage IIA/B-IIIB cervical carcinoma. A comparison of continuous versus sequential regimens. *Strahlenther Onkol*, **180**, 209-5.

Meena C, Saini NK, Mehta HN, et al (2023). Comparative Analysis of Dosimetry and Treatment Outcomes of Two Different Dose Fractionation Schedules of HDR Brachytherapy in Carcinoma Cervix Amid Covid-19 Pandemic. *Asian Pac J Cancer Care*, **8**, 73-6.

Patidar AK, Kumar HS, Walke RV, et al (2012). Evaluation of the response of concurrent high dose rate intracavitary brachytherapy with external beam radiotherapy in management of early-stage carcinoma cervix. *J Obstet Gynaecol India*, **62**, 562-5.

Perez CA, Grigsby PW, Castro-Vita H, Lockett MA (1995). Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys*, **32**, 1275-8.

Petereit DG, Sarkaria JN, Chappell R, et al (1995). The adverse effect of treatment prolongation in cervical carcinoma. *Int J Radiat Oncol Biol Phy*, **32**, 1301-7.

Peters WA, Liu PY, Barrett RJ, et al (2000). Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol*, **18**, 1606-13.

Rose PG, Bundy BN, Watkins EB, et al (1999). Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med*, **340**, 1144-3.

Sung H, Ferlay J, Siegel RL, et al (2021). Global Cancer Statistics 2020 (2021).: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*, **71**, 209-9.

Viani GA, Manta GB, Stefano EJ, de Fendi LI (2009). Brachytherapy for cervix cancer: low-dose rate or high- dose rate brachytherapy - a meta-analysis of clinical trials. *J Exp Clin Cancer Res*, **28**, 47.

Viswanathan AN, Beriwal S, De Los Santos JF, et al (2000). American Brachytherapy Society. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: high-dose-rate brachytherapy. *Brachytherapy*, **11**, 47-2.

Whitney CW, Sause W, Bundy BN, et al (1999). Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol*, **17**, 1339-8.

Withers HR, Taylor JM, Maciejewski B (1988). The hazard of accelerated tumor clonogen repopulation during radiotherapy. *Acta Oncol*, **27**, 131-6.

Wright J, Jones G, Whelan T, Lukka H (1994). Patient preference for high or low dose rate brachytherapy in carcinoma of the cervix. *Radiother Oncol*, **33**, 187-4.