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Original Research

Comparative Analysis of Dosimetry and Treatment Outcomes of Two Different Dose Fractionation Schedules of HDR Brachytherapy in Carcinoma Cervix Amid Covid-19 Pandemic

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Background: Cervical carcinoma is the fourth most common cancer and leading cause of cancer related deaths in women worldwide. Brachytherapy is an important part in the treatment of cervical cancer. Delivering HDR Intracavitary Brachytherapy in the Covid-19 era is challenging.
Objective: To compare the dosimetry and treatment outcomes between two fractionation schedules of 9Gy in 2 fractions v/s 7Gy in 3 fractions of high dose rate Brachytherapy in patients with locally advanced carcinoma cervix.
Methods: A randomized observational study was carried out on 80 histopathologically proven squamous cell carcinoma patients of cervix. All patients were treated with EBRT 50Gy in 25 fractions over a period of 5 weeks (2Gy/#) with concurrent weekly cisplatin 30mg/m^2. After assessing fitness for brachytherapy, patients in the study arm received HDR intracavitary brachytherapy in 9Gy for 2 fractions v/s 7Gy for 3 fractions in the control arm.
Results: The median time of follow-up was 14 months for the study (range 7 – 20 months). Local control rate was 89.75% for study arm and 92.30% for control arm. One year disease free survival in the study arm was 76.92% as compared to 74.35% in the control arm. Median disease-free survival was better in the study arm (14 months v/s 12 months) with a trend of significant benefit. Rectal and bladder toxicities were comparable in both the arms. Median dose to ICRU bladder and rectal point, and EQD2 dose in both arms were not found to be statistically significant.
Conclusion: Both the regimes were found to be safe. Disease response and toxicities were also similar in both the arms. There was a better patient compliance with 9Gy for 2 fractions schedule in view of lesser number of fractions resulting in less hospital visit in the Covid-19 pandemic.

Introduction

Carcinoma of uterine cervix is the second most common gynecological malignancy among females in India accounting for 18.3% of all cases [1]. In developing countries like India, majority of patients present in a locally advanced stage. Radiotherapy has a proven role in the management of cervical cancer. External Beam Radiation Therapy along with concurrent chemotherapy followed by HDR intracavitary brachytherapy is the treatment of choice [2-4]. Intracavitary brachytherapy is most commonly practiced form of brachytherapy for cervical cancer. Brachytherapy is the application of radioactive source in close proximity to the tumor. It enables to deliver a very high dose to the tumor with relative sparing of the normal surrounding structures. This results in low recurrence

rates and improved survival [5]. Dose escalation with Intensity Modulated Radiation Therapy has been associated with an inferior outcome compared to brachytherapy. Overall treatment time has a major role in pelvic control of tumor. There is no uniform consensus about optimal fractionation schedule of brachytherapy to be followed in the treatment of cervical cancer.

Many studies have reported that prolongation of overall treatment time is associated with lower tumor control and survival rate. So, reducing the treatment time by giving large dose per fraction of intracavitary brachytherapy can maximize the overall disease-free survival. We conducted an observational study in 80 patients diagnosed with carcinoma cervix to compare the dosimetry and treatment outcomes between two different dose fractionation HDR brachytherapy schedules of 9Gy for 2 fractions and 7Gy for 3 fractions in terms of local disease control, disease free survival, early and late toxicity of bladder and rectum during the Covid 19 pandemic.

Materials and Methods

This is a prospective randomized study conducted in the Department of Radiotherapy from April 2020 to March 2021. Total 80 women aged 18 to 70 years with newly diagnosed histopathologically confirmed squamous cell carcinoma of cervix having FIGO stage IIA–IIIC (FIGO Staging 2018) were included in the study after obtaining informed consent. Eastern Cooperative Oncology Group performance status was 0-2 with adequate baseline organ function (hematological examination, RFT and LFT) of all patients. Patients with previous history of radiotherapy and those with severe comorbidity and having distant metastasis were excluded from the study.

The pre-treatment evaluation included detailed history, complete physical examination including gynecological examination, hematological and biochemistry studies, chest radiography, ultrasound of abdomen and pelvis, CECT abdomen and pelvis. MRI pelvis was done when required. All patients underwent biopsy to obtain histopathological proof of malignancy. Staging was done according to the FIGO 2018 staging system.

All 80 patients were treated with EBRT on BHABHATRON – 2 Cobalt-60 machine in supine position with immobilization using AP/PA field and given a dose of 50Gy in 25 fractions at the rate of 200cGy per fraction along with concurrent chemotherapy with Cisplatin in a dose of 30mg/m^2 as per institutional protocol.

The patients were assessed for ICRT fitness and randomized into two arms - Arm A and Arm B. 40 study subjects in Arm A received 9 Gy per fraction of HDR ICBT weekly for 2 fractions and 40 study subjects in Arm B received 7Gy per fraction of HDR ICBT weekly for 3 fractions. The procedure was done under strict aseptic precautions and conscious sedation. Patient was taken in lithotomy position and Foleys catheter was inserted with balloon inflated with 7ml of 1:2 diluted urograffin to identify bladder point. Cervical os was identified, length of uterine canal measured with uterine sound and Modified Fletcher Suit applicator – intrauterine tandem and paired ovoids were inserted. Anterior and posterior packing done by betadine-soaked gauze packs to push bladder and rectum away from the source and also to stabilize the applicator. Rectal marker inserted into rectum and rectal point was calculated 5mm behind posterior vaginal wall. The dose was calculated using a 3D computerized treatment planning system and two orthogonal radiographs of the pelvis. The plan of treatment was to prescribe a total dose of 85-90 Gy at point A. Dose calculations for rectum and bladder were made according to ICRU-38 recommendations.

Follow up

Patients were examined for tumor response and toxicity after completion of brachytherapy, at 1 month, 3 months, 6 months and 1 year. Tumor response evaluation was done based on RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria and toxicities were assessed as per RTOG/ EORTC Radiation Morbidity Scoring System and Common Terminology Criteria for Adverse Events.

Statistical Analysis

Qualitative data is expressed in terms of percentage and proportion. Quantitative data is expressed as median, geometric mean, arithmetic mean and standard deviation. Student-t test has been used to ascertain the significance of differences between mean values of two continuous variables. Chi-square tests were performed to analyze differences in proportions of categorical variables between two or more groups. The level $p < 0.05$ was considered as the cut-off value for significance. All analysis were performed using IBM SPSS statistics, version 20 for windows.

Results

From April 2020 to 31 March 2021, total 80 patients of carcinoma cervix were included in the study. Two patients from each arm were lost to follow-up, hence 78 patients were available for final analysis. The median time of follow-up was14months (range7–20 months).

At the end of 12 months, 59 patients (75.64%) had attained complete response (CR). CR rates were 76.92% for Arm A and 74.35% for Arm B ($p = 0.9$). Overall, 19 patients (24.35%) did not achieve complete response and had either partial response (PR), stable disease (SD) or progressive disease (PD). The non-CR rate was 28.20% for Arm A and 25.64% for Arm B. Among 19 patients of non-CR group 16 had loco-regional residual disease and 3 had failure at a distant site (Table 1).

			Arm-A					Arm-B		
	At end of RT	1 month	3 month	6 month	12 months	At end of RT	1 month	3 month	6 month	12 months
Complete Response (CR)	25(64.1%)	27(69.2%)	30(76.9%)	31(79.5%)	30(76.92 %)	22(56.4%)	25(64.1%)	29(74.4%)	30(76.9%)	29(74.35 %)
Partial Response (PR)	14(35.90 %)	12(30.80 %)	8(20.50%)	7(17.90%)	5(12.80%)	17(43.60 %)	14(35.90 %)	9(23.10%)	8(20.50%)	7(17.90%)
Stable Disease (SD)	0	0	0	0	0	0	0	0	0	0
Progressive Disease (PD)	0	0	1(2.6%)	1(2.6%)	4(10.25%)	0	0	1(2.6%)	1(2.6%)	3(7.69%)

Table 1. Comparison of Local Disease.

Residual disease was seen in 5 (12.8%) patients in Arm A and 7 (17.9%) patients in Arm B (Table 1).

Similarly, distant failures were seen in 2 (5.12%) patients in Arm A and 1 (2.6%) patient in Arm B. Cases with progressive disease or distant metastasis were treated with further chemotherapy. One-year actuarial DFS in the study arm was 76.92% as compared to74.35 % in the control arm. Median period of DFS was better in the study arm (14 months v/s 12 months) with a trend of significant benefit. Improved DFS in the study arm was probably explained by reduction of overall treatment time.

14 patients reported grade I rectal toxicity, 24 had grade II and 1 patient reported grade III rectal toxicity in Arm A. While in Arm B, 17patients had grade I, and 22 patients had grade II rectal toxicity (Table 2).

		Arm-A				Arm-B		
Grade	I	II	III	IV	I	II	III	IV
Rectal toxicity	14(35.90%)	24(61.50%)	1(2.60%)	0	17(43.60%)	22(56.40%)	0	0

Bladder toxicity	13(33.3%)	25(64.1%)	1(2.6%)	0	16(41%)	23(59%)	0	0

Table 2. Comparison of Late Toxicities.

In Arm A, 13 patients had grade I bladder toxicity, 25 had grade II and 1 patient had grade III bladder toxicity and in Arm B, 16 patients had grade I and 23 patients had grade II bladder toxicity (Table 2). There was no statistically significant difference between both the arms in terms of toxicities. Median dose to ICRU Bladder Point is 6.1Gy in Study Arm while 5.6Gy in Control Arm (p-value:0.23). Median dose to ICRU Rectal Point is 5.9Gy in Study Arm while 5.4Gy in Control Arm (p-value:0.21). Median EQD2 Tumor dose due to EBRT and HDR brachytherapy being 77.23Gy and 79.7Gy in Study and Control Arms respectively (Table 3).

	Arm A (Study Group)		Arm B (Control Group)	
Ca Cervix (stage I to stage III)	Median	Range	Median	Range
EBRT (whole pelvis)	50Gy	45 – 50Gy	50	45 - 50Gy
HDR	18/2#	-	21/3#	-
Point A	8.9Gy	8.5 - 9.2Gy	7Gy	7 - 7.5Gy
ICRU Bladder point	6.1Gy	5.2 - 6.3Gy	5.6Gy	4.2 - 7.3Gy
ICRU Rectum point	5.9Gy	5.4 - 7.2Gy	5.4Gy	5.2 - 5.6Gy
EQD2 Tumor (EBRT + HDR)	77.23Gy	-	79.7Gy	-

Table 3. Comparison between Dosimetry of Study and Control Arm.

Discussion

Role of radiotherapy in cervical cancer management is well documented. Combining External Beam Radiation Therapy (EBRT) with Brachytherapy is the standard of care in the management of cervical cancer. Brachytherapy enhances curative potential by dose escalation at the tumor site while sparing normal surrounding structures which results in lower recurrence rate and improved overall survival [3].

A study by Subhendu Gangopadhyay et. al. [6] reported that median disease-free survival was significantly better with 9 Gy per fraction HDR intracavitary brachytherapy as compared with 7 Gy per fraction and equivocal tumor control rates. Patel et.al. [7] demonstrated that two application of HDR intracavitary brachytherapy with 9 Gy per fraction was safe and effective in terms of good local control of tumor and minimal toxicities. The 3-year local tumor control and actuarial disease-free survival were 81.35% and 64.97% respectively. Ghosh et. al. [8] demonstrated that HDR brachytherapy with 9 Gy per fraction for two fractions is an effective dose fractionation for the treatment of cervical cancer with acceptable toxicity. The 2-year actuarial local control rate, disease free survival and overall survival rate were 88.1%, 84.2% & 81.8% respectively.

An American study found that two fractions of HDR ICBT with 9 Gy per fraction or even with 9.4 Gy per fraction, were safe and effective in the management of cervical cancer [9]. Orton GC [10] found that individual fraction size in HDR brachytherapy may be between 4-9 Gy. Data demonstrated that late complication rates were significantly lesser with HDR fraction size <7 Gy as compared to >7 Gy, but effect on cure rates are equivocal. P Thakur et al [11] reported a retrospective analysis of cervical cancer patients who were treated with EBRT followed by intracavitary brachytherapy with 9 Gy per fraction in two fraction 7 days apart. Median follow up period was 19 months. The 2-year actuarial local control rate, disease free survival and overall survival rate were 91.5%, 82.6% & 100% respectively.

In the present study 1-year actuarial DFS was 60% and local tumor control rate was 80%. There was no significant difference between two fractionation schedules in terms of toxicities. Similar results were also reported with earlier studies. So, 9 Gy per fraction for 2 fractions is an effective and safe HDR intracavitary brachytherapy fractionation schedule with equivalent local tumor control response.

In conclusion, brachytherapy is an essential part of treatment of cervical cancer. Various dose and fractionation schedules are being practiced in different institutes. In the present study both the regimes were found to be safe and well tolerated by patients. Disease response and toxicities were also similar in both the arms. Literature also supports that fraction size does not influence the local disease control and late toxicity. Considering the increased hospital burden of locally advanced cancer cervix patients in developing countries like India and also amid Covid 19 pandemic, HDR brachytherapy schedule of 9 Gy per fraction for 2 fractions is the reasonable option as compared to 7 Gy per fraction for 3 fractions and should be preferred with regards to comparable locoregional control, toxicity and better patient compliance.

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Conflicts of interest

There are no conflicts of interest.

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