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Comparative Study between Two Fractions of 9Gy & Three Fractions of 7Gy High Dose Rate Brachytherapy Following Concurrent Chemo Radiotherapy in Patients with Locally Advanced Carcinoma of Uterine Cervix

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Abstract:

Introduction: ***Traditionally, a judicious combination of external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) is the widely accepted primary modality of treatment for locally advanced carcinoma of the cervix. Although the recommendation ofAmerican Brachytherapy Society is <7.5 Gyfor individual fraction and four to eight should be the range of fractions; however, literature showed high dose rate (HDR) brachytherapy of two fractions of 9Gyresults in acceptable toxicity without compromising the local control.***

Methods: This was a Prospective Quasi-Experimental study, conducted in Department of Radiation Oncology, National Institute of Cancer Research and Hospital, Mohakhali, Dhaka from July 2018 to June 2019. Patients with Clinically diagnosed and histopathologically proven squamous cell carcinoma of uterine cervix in locally advanced stage (FIGO stage IIB to IVA) were selected. Total 60 patients were enrolled according to selection criteria and allocated in to group. Both arm was received 50Gy EBRT in 25 fractions with concurrent inj.Cisplatin 40 mg/m^2 weekly. Then Arm A was given HDR Brachytherapy 9Gy in each fraction for 2 fractions and Arm B was given HDR Brachytherapy 7Gy in each fraction for 3 fractions. Then treatment responses, locoregional control of disease and acute toxicities were compared between groups.

Result:Follow up at 6 months after completion of treatment, complete remission was 90% and 86% respectively for arm A and arm B. The overall complete response was 88%. The common toxicities associated with treatment were bladder and rectal toxicities, skin reaction, small bowel toxicity and haematologic complications which were managed well. During follow up after 6 months, 3 patients in arm A and 2 patients in arm B developed grade II bladder toxicities and only 2 patients in arm A developed rectal grade II toxicities, but there was no rectal toxicity in arm B.

Conclusions: Present study showed that a total dose of 18 Gy ICRT in two fractions of 9 Gy over 2 weeks is equally effective in short term local control with acceptable toxicities in comparison with a total dose of 21 Gy in three fractions of 7 Gy ICRT.

Key words: Comparative, high dose rate brachytherapy, locally advanced, carcinoma of uterine cervix

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Introduction:

Locally advanced carcinoma of the uterine cervix is a major public health problem in developing countries. In spite of advancement in chemoradiation therapy, the outcome of locally advanced disease remains suboptimal. Newer diagnostic methods, treatment approaches and technology to evaluate the response needs to be evaluated in this condition[1].Survival of cervical cancer patients is strongly determined by stage at diagnosis. Due to the late stage at diagnosis and inadequate management facilities, mortality rates from cancer cervix are very high in Bangladesh. The overall 5-year relative survival for early and localized cancers is 73.2%, but can be as low as 7.4% for advanced stage disease[2]. The standard radiation therapy for locally advanced cervical cancer is a combination of external beam radiation therapy and brachytherapy[3]. The

curative potential of RT in the management of carcinoma of the cervix is enhanced by the use of intracavitary brachytherapy, which delivers a high radiation dose directly to the tumor while sparing (to an extent) the surrounding normal tissues. High-dose-rate (HDR) intracavitary RT for carcinoma of the cervix is widely used because of its advantages of a short treatment time, rigid immobilization, patient convenience, and out-patient treatment[4].

There has been increasing use of the high-dose-rate technique in the recent years which reduces hospitalization, takes advantage of continuous reduction in size of the tumor target, allows variation in dosimetry, and reduces radiation exposure to treating personnel[5, 6].

The number of fractions in high-dose-rate brachytherapy should be ranged from 4 to 8 as per American Brachytherapy Society (ABS) recommendations[5].But none of the recommended fractionation schedules had been tested clinically in a large prospective randomized clinical trial against the "gold standard" of low-dose-rate brachytherapy and found to be at least as safe and effective[7]. Wong et al. (2003) stated 5 year failure free survival and cancer specific survival were 87.7% and 86.6%, 85% and 85%, 67.8% and 74%, 46.9% and 54.7%, 44.8% and 50.4%, 0% and 25% in teir retrospective review of 226 patients of squamous cell carcinoma cervix from stage IB-c!A with two regimens of HDR intracavitary brachytherapy (7 Gy in 3 fraction weekly & 6 Gy in 4 fractions weekly) with concurrent chemoradiotherapy. 93.4% patients had achived complete resolution of primary disease[8]. In a study of Patel et al. (2005), 121 patients of cervical cancer stage I–III were treated with HDR brachytherapy of 9Gy in 2 fractions at 1 week apart. 5 year local control and disease free survival was 74.5% and 62.0%. Only 2 patients developed G-3 bladder toxicity, no G-3 rectal toxicity was found that suggested this regimen was both safe and effective[9]. Ghosh & Rao. (2016) compared 7 Gy in 3 fractions vs 9 Gy in 2 fractions at 1 week apart in 124 patients of locally advanced carcinoma cervix with 62 patients in each group and found compareable local control, disease free survival and overall survival[10].

In spite of implementing HDR brachytherapy strategy for the treatment of cervical cancer for more than four decades, wide variations in treatment modalities including different fractionations, applicators and planning modalities still exist and subsequently the optimum treatment scheme still remains controversial. This study was conducted to find out the suitable HDR brachytherapy treatment in our context for patients with locally advanced cervical carcinoma.

Material and methods:

This was a Prospective Quasi-Experimental study, conducted in Department of Radiation Oncology, National Institute of Cancer Research and Hospital, Mohakhali, Dhaka from July 2018 to June 2019. Patients with newly diagnosed and histopathologically proven squamous cell carcinoma of uterine cervix in locally advanced stage (FIGO stage IIB to IVA) who had ECOG PS 0-2 without any medical co-morbidities or uncontrolled infection were selected. Total 60 patients were enrolled and allocated in two groups. Both arm was received 50Gy EBRT in 25 fractions with concurrent inj. Cisplatin 40 mg/m^2 weekly. Then Arm A was given HDR Brachytherapy 9Gy in each fraction for 2 fractions and Arm B was given HDR Brachytherapy 7Gy in each fraction for 3 fractions. Then treatment responses, locoregional control of disease and acute toxicities were compared between groups.

External beam radiotherapy:

All patients received external beam radiotherapy by 2D radiotherapy technique using AP-PA field.Conventional simulation was done with comfortably full bladder protocol. Superior border was delineated at the level between L4 and L5 vertebrae, inferior border at the level of lowest extent of the obturator foramen or 3 cm below the most distal vaginal disease (whichever the most inferior) and lateral border at 2 cm lateral to widest true bony pelvic diameter. All Patients had received 50Gy EBRT in 25 fractions within 5 weeks with inj. Cisplatin 40mg/m^2 weekly.

Brachytherapy:

After completion of CCRT, all the patients of both arms were treated with HDR ICRT. A dose of 9 Gy per fraction, 2 fractions in 2 weeks for arm A and 7 Gy per fraction, a total of 3 fractions over 3 weeks for arm B to the point-A were given. A total ICRT dose of 18 Gy and 21 Gy were delivered for arm A and B respectively. Tandem and two ovoids were placed with proper sterile procedure and adequate bowel preparation. Anterior and posterior

vaginal packs were given to push the urinary bladder anteriorly and rectal wall posteriorly. A rectal probe was placed. Orthogonal films were used to check the position of the applicator and delineation of point-A, point-B, bladder point, rectal point was done according to Manchaster system. The treatment was delivered by after loading Ir-192 HDR machine.

Patient assessment & Follow up

After completion of treatment patients were assessed at week 6, 3 months and 6 months following treatment. At each follow up clinical examination, associated laboratory investigations and imaging were done and effects of RT (treatment response), quality of life and toxicities due to radiotherapy were assessed. Treatment response was assessed according to both subjective and objective manner through symptomatic improvement and RECIST (response evaluation criteria for solid tumors) criteria. Toxicities were assessed by RTOG (Toxicity criteria of the Radiation Therapy Oncology Group) toxicity grading.

Results

Symptomatic improvement

Post coital bleeding, intermenstrual/post-menopausal bleeding and per vaginal discharge was most commonly presented features of the patients in both treatment group. Symptomatic improvement was seen with both treatment regimens equivalently. PV bleeding was the symptoms in both groups which relieved in every patient after therapy in each groups.

Response rate

Treatment response was similar in both treatment groups. At the end of 6 months 27 (90%) patients of Arm-A and 26 (86.7%) patients of Arm-B achieved complete response. No patients experienced stable or progressive disease in both Arms.

Toxicity

Overall frequency of radiotherapy related acute toxicities (Table-5) were more in Arm A than that of Arm B but there were no statistically significant differences. All the toxicities were managed by conservative treatment. Treatment discontinuation or hospitalization for toxicity management was not needed during treatment and follow-up period. Rectal and bladder toxicities were most common.

During follow up at 6 months after completion of treatment 3 patients in arm A and 2 patients in arm B developed grade II bladder toxicities and only 2 patients in arm A developed rectal grade II toxicities (Table-6), there was no rectal toxicity in arm B. the late bladder and rectal toxicity was higher in arm A than arm B but it was not statistically significant (p value 0.2899).

Table-I

Patients characteristics

Patient characteristics		Arm A	Arm B	P value
Mean age		52.4±6.2	52.8±7.3	0.935
FIGO stage	IIB	15 (50.0)	22 (73.3)	0.161
	IIIA	3 (10.0)	0 (0.0)	
	IIIB	10 (33.3)	7 (23.3)	
	IVA	2 (6.7)	1 (3.3)	
ECOG PS	0	4	6	
	1	19	19	
	2	7	5	

Table-II

*Clinical manifestation amongst the respondents (n=60)**

Clinical presentation	Group		Chi square	P value value
	Arm-A (total= 30) n (%)	Arm-B (total= 30) n (%)		
Post Coital Bleeding	25 (83.3)	24 (80.0)		
Intermenstrual Bleeding/Post menopausal bleeding	20 (66.7)	18 (60.0)	0.397	0.982
Excessive per vaginal Discharge	27(90.0)	28(93.3)		
Pelvic Pain	10 (33.33)	12 (40.0)		
Dysuria	6 (20)	7 (23.33)		
Rectal Pain	0(0)	0(0)		
Loss Of Appetite	19 (63.3)	18 (60.0)		
Anemia	22 (73.3)	23 (76.7)		

Table-III

Symptomatic response of both group (at final week of CCRT) (n=60)

Total Patients n= 30 (each arm)	Pre-treatment n(%)	Post treatment n(%)	Response n(%)	Chi square value n(%)	p value
Per vaginal Bleeding					
• Arm-A	20 (66.7)	0 (0.0)	20 (100.0)	0.0053	0.942
• Arm-B	18 (60.0)	0 (0.0)	18 (100.0)		
Vaginal Discharge					
• Arm-A	27(90.0)	8 (26.7)	19 (70.3)	1.219	0.269
• Arm-B	28(93.3)	4 (23.3)	24 (85.7)		
Pelvic Pain					
• Arm-A	10 (33.33)	2(6.66)	8 (80)		0.824
• Arm-B	12 (40.0)	3(10)	9(75.0)	0.0491	
Dysuria					
• Arm-A	6 (20)	2 (6.66)	4(66.66)		0.155
• Arm-B	7(23.33)	0 (0.0)	7 (100.0)	0.410	
Loss Of Appetite					
• Arm-A	19 (63.3)	11 (36.7)	8 (42.1)		0.939
• Arm-B	18 (60.0)	10 (33.3)	8 (44.4)	0.0057	
Anemia					
• Arm-A	22 (73.3)	9 (30.0)	13 (59.0)	2.603	0.106
• Arm-B	23 (76.7)	3 (10.0)	20 (86.9)		

Table-IV

Treatment response at different follow up

Follow up	Response	Arm A (total=30) n%	Arm B (total =30) n%	*p*-value
First FU (6 weeks after completion)	Complete response Partial response	27 (90) 3(10)	24 (80) 6(20)	0.278
Second FU (3 months after completion)	Complete response Partial response	27 (90) 3 (10)	26 (86.7) 4 (13)	0.687
Third FU (6 months after completion)	Complete response Partial response	27 (90) 3 (10)	26 (86.7) 4 (13)	0.687

Table-V

Acute toxicity of both treatment groups

Variables	Groups		*p*-value
Skin Reaction			
Grade-0	12 (6.66)	14 (43.33)	
Grade 1	10(33.33)	9(30)	0.967
Grade 2	8(26.66)	7(23.33)	
Vaginal mucositis			
Grade 0	18(60)	20(66.66)	
Grade 1	8(26.66)	6(20)	0.746
Grade 2	4(13.33)	4(13.33)	
Bladder toxicity			
Grade-0	10 (33.3)	14 (46.6)	
Grade-1	12 (40.0)	10 (33.3)	0.878
Grade 2	8(26.66)	6(20)	
Small gut toxicity			
Grade 0	12(43.33)	15(50)	
Grade 1	7(23.33)	5(16.66)	0.741
Grade 2	11(36.66)	10(33.33)	
Rectal toxicity			
Grade-0	11 (36.66)	14 (46.66)	
Grade-1	9 (30)	10 (33.3)	0.370
Grade 2	10(33.33)	6(20)	
Haematologic toxicities			
Grade 1	10(33)	11(37)	0.473
Grade 2	5(17)	3(10)	

Table-VI

Late toxicity of both treatment group at 6 months

Toxicity	Arm A (total=30) n(%)	Arm B (total=30) n(%)	Chi square value	p value
Bladder	3(10%)	2(6.66%)	0.035	0.850
Rectal	2(6.66%)	0		

Discussion:

One of the crucial components in the treatment of cervical cancer is intracavitary brachytherapy. Although HDR brachytherapy has radiobiologic disadvantages, it's still being popular currently in most of the country due to better geometric placement and shortened treatment time. As per American Brachytherapy Society the fraction size should be <7.5 Gy using four to eight fractions of HDR brachytherapy in cervical cancer[9]. However, there is still some controversy regarding the optimal time dose fractionation schedule[7].

This study had been conducted to evaluate the response rate and acute toxicity of HDR brachytherapy comparing two fractions of 9 Gy& three fractions of 7 Gy.After completion of treatment response evaluation was done periodically according to follow up schedule which was set earlier. There was no difference between HDR brachytherapy of two fractions of 9 Gy& three fractions of 7 Gy in terms of treatment response. At the end of 6 months 90% and 86.7% patients of both treatment group achieved complete response. Passi et al. in their study found 80% and 85% complete response using HDR brachytherapy of 9.5 Gy in two fractions and 7.5 Gy in three fractions[11]. No difference in local control, disease free survival and toxicities had been found in the study of Patel et al. (2011) where comparison done between 9 Gy per fraction in two fractions & 6.8 Gy per fraction in 3 fractions in 104 patients of stages IIB and IIIB of cervical carcinoma who were treated with EBRT and HDR ICBT[12]. Ghosh & Rao. (2016) had found comparable local control, disease free survival and overall survival in their study using 7 Gy in 3 fractions vs 9 Gy in 2 fractions at 1 week apart in 124 patients of locally advanced carcinoma cervix with 62 patients in each group.

Cisplatin-based chemotherapy was used in this study, as it has been an integral part of the management of cervix cancer[13-16], and literature suggests even in conjunction with concomitant cisplatin, two fractions of high-dose-rate brachytherapy are very safe and effective, which is reflected in this study also. Although tri-weekly cisplatin had been better in terms of safety and efficacy[17-19], but the optimal dose and schedule of concurrent cisplatin is not well defined and still widely accepted practice is the weekly schedule of 40 mg/m^2 for 5 weeks[20].

The most prevalent acute toxicities in both the arms were bladder and rectum related toxicies. No patient in both arms developed grade III or grade IV toxicity and there was no interruption of treatment due to toxicity. Although treatment related toxicities were slightly more in arm A and was managed well but it was not statistically significant (p value <0.05). As the study period was short and patients were followed up for 6 months only, late toxicities could not be evaluated properly. During follow up after 6 months, 3 patients in arm A and 2 patient in arm B developed grade II bladder toxicities and only 2 patients in arm A developed rectal grade II toxicities, but there was no rectal toxicity in arm B. These observation correlates with study of Sood et al and Patel et al where grade 2 or higher bladder toxicities were 2-4 % and rectal toxicities was 3-5%[8].

Due to short time follow-up, long term local control or overall survival rate could not be evaluated. But the existing data suggested a comparable long term control and overall survival with HDR brachytherapy of two fractions of 9 Gy.

After careful analysis, it is very much clear that locoregional control after two fractions of HDR brachytherapy is effective to three fractions of HDR brachytherapy with comparable toxicities. It is convenient for patient and improved their compliance. Reducing the risk of multiple exposures to anesthetic agents and minimizing the number of hospital attendance makes this schedule cost effective. This schedule also reduces the patient load in radiotherapy centres to some extent which is a major consideration in a developing country like ours where radiotherapy canters are overburdened with patients. So this treatment regimen should be studied in a multicentric, randomized trial for widely acceptance.

Conclusions:

Cervical cancer is the global burden of female health . Women with locally advanced cervical cancer have a higher rate of recurrence and worse survival than those with early stage disease. The addition of chemotherapy to RT have improved local tumor control, disease free survival rate and overall survival in advanced cervical tumors. Brachytherapy or local application of radiation represents an integral component of treatment for cervical cancer. Present study concluded that HDR brachytherapy 2 fractions of 9 Gy after concurrent

chemoradiotherapy is equally effective with the brachytherapy of 3 fractions of 7 Gy after concurrent chemoradiotherapy for the control of locally advanced carcinoma cervix but more convenient regarding time and cost.

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