A Comparative Study to Evaluate the Efficacy and Toxicities of Hypofractionated Radiotherapy Vs Conventional Radiotherapy in Advanced Carcinoma Cervix

Abstract:

Background: In Bangladesh among women, cervical cancer is one of the most prevalent cancers. The current study was conducted to compare the short term effectiveness and acute toxicities of hypofractionated radiotherapy (45 Gy in 18 fractions) with conventional fractionated radiotherapy (50 Gy in 25 fractions) in EBRT in inoperable locally advanced cervical cancer. **Methods:** It was a quasi-experimental study conducted in the department of Radiation Oncology of National Institute of Cancer Research & Hospital, Dhaka, Bangladesh. Sixty patients of locally advanced carcinoma of cervix were included in the study. They were enrolled in either arm A or arm B to receive 45 Gy in 18 fractions or 50 Gy 25 fractions respectively. **Result:** The mean age of the arm A patients was 56.53 (SD ± 8.61) years and that of the arm B patients was 52.97 (SD ± 9.62) years. Various symptoms including abnormal bleeding, unusual discharge from cervix, pelvic pain and weight loss were compared between two groups before and after giving hypofractionated radiotherapy. No statistically significant differences were noted between arms in case of urinary and skin toxicities. **Conclusion:** In resource challenged setting where radiotherapy treatment facilities are limited this hypofractionated therapy could be a reasonable choice. **Keywords:** Carcinoma, cervix, conventional, hyperfractionated, radiotherapy.

Introduction:

Bangladesh, at about 170 million people, is the 9th most populous country in the world. According to Globocan 2018 report, 5-year cancer prevalence in the country is 242731 cases & about 151000 patients are newly diagnosed with cancer each year. Oesophageal cancer, cancer of the lip and oral cavity, breast, lung and cervical cancers were the five leading cancer irrespective of sex. In women, breast cancer and

cervical cancer were most prevalent [1]. Cervical cancer has a low incidence in Western Europe and North America but still a high incidence in developing countries like Bangladesh [2].

Cervical cancer has a low incidence in Western Europe and North America but still a high incidence in developing countries like Bangladesh [3]. Human papilloma virus (HPV 16, 18, 31, 33) plays an important role in genesis of cervical cancer, observed in 90% of all women with cervical cancer [4]. Radiation therapy plays important role in carcinoma cervix stage II, III and IV [5]. As per NICRH cancer registry 88% of the patients receive radiation therapy as the single modality treatment.

Treatment for carcinoma cervix in advanced stage is a combination of external beam radiation and brachytherapy. Conventional external beam radiation delivers a dose of 2 Gy per fraction with standard pelvic portals with antero-posterior or box field technique. Time, dose and fractionation schedules have been altered in an attempt to improve the probability of local control. Various altered fractionation schedules include hypofractionation, rapid fractionation, split course regimen, hyperfractionation and accelerated hyperfractionation [6].

Hypofractionated radiotherapy delivers high dose per fraction (>2-2.5Gy). Reduction in the total dose is needed taking into consideration high dose per fraction so as to reduce the normal tissue effects. The treatment time and number of fractions is hence reduced. At few centers hypofractionated radiotherapy has been delivered twice weekly or four days a week. Hypofractionated radiotherapy has been considered at a few centers for palliation. Various studies with split course radiation therapy have also practiced hypofractionation [7]. Overall treatment time has considerable effect on local control and survival. In hypofractionated treatment the overall treatment time is reduced. But the beneficial effect of reduction in overall treatment time is counteracted by high dose per fraction. The chances of late complication increase with increasing dose per fractionation.Alteration in the fractionation has been attempted mainly to improve the local control at the same time decreasing the normal tissue complications. Carcinoma cervix stage IIB to IVA includes a heterogeneous group of patients of small volume disease to extensive disease with bilateral parametrial involvement up to lateral pelvic wall. Some of these patients do not have good general condition and hence are not suitable for 4-5 weeks of external radiation. These patients will be considered for hypofractionated radiotherapy in this study. Experience with hypofractionated radiotherapy will be reviewed [8].

An analysis of all the patients of carcinoma cervix stage IIB to IVA who will receive hypofractionated external beam radiation therapy will be carried out with aims to assess the short term efficacy of hypofractionated radiotherapy, to assess the early complications related to the treatment.

Methods:

This quasi-experimental study conducted in National Institute of Cancer Research and Hospital, Mohakhali, Dhaka was started January 2018 to December 2018. 60 Patients with histopathology report proven carcinoma of cervix, FIGO stage IIB-IVA (locally advanced). Arm A patients were treated with 45 Gy in 18 fractions (2.5 Gy/fraction), 5 days in a week for 3.5 weeks whereas arm B patients received 50 Gy 25 fractions (2 Gy/fraction) 5 days in a week for 5 weeks. Both arms were treated by intracavitary brachytherapy accordingly (21-28 Gy in 3-4 fractions). Responses were evaluated according to RECIST criteria version 1.1. Toxicities were observed according to common terminology criteria for adverse effects (CTCAE) version 4.0. (2010) and WHO reporting results of cancer treatment recommendation for grading of acute and sub- acute toxicity. Data analysis was done according to the objectives of the study by using the SPSS (Statistical Package for Social Science) software program for windows, version 25.0 available in the institute. The results were presented in tables, figures, diagrams. All reported p values were two sided and $p < 0.05$ was considered statistically significant.

Result:

Table 1: Age group distribution of the patients (n=60)

Table 1 illustrates age group distrivution of the patients. A total of 60 patients of locally advanced cervical carcinoma were included in arm A and arm B in the study. They were divided into three age groups and their age ranged from 34 to 72 years. Maximum numbers (22, 73.3%) in arm A and (17, 56.7%) in arm B were found in the age group of >50 years. Second leading numbers of patients were found in 41-50 years age group.

Age groups (years)	Arm A	Arm B	*Range (years)*
<=40	1 (3.3)	3 (10.0)	
41-50	7 (23.3)	10 (33.3)	34-72
>50	22 (73.3)	17 (56.7)	

Table 2: Distribution of the patients by some risk factors (n=60)

Distribution of the patients by some risk factors is shown in the above table. Most of the mothers were multipara. One patient in arm A and three patients in arm B had family history of cervical cancer. Negligible number of patients had multi-sex partners. Most of the patients in both arms were used to taking OCP (arm A 86.7% and arm B 76.7%). Most of the patients in both arms were exposed to passive tobacco smoking (arm A 90% and arm B 93.3%). However, no differences were statistically significant (p-value>0.05).

Risk factors	Category of treatment		Fisher's Exact Test	*p*-value
	Arm A (45 Gy in 18 fractions)	Arm B (50 Gy 25 fractions)		
Multiparty	27 (90.0)	28 (93.3)	0.218	1.00
Multiple sex partners	01 (3.3)	02 (6.7)	0.351	0.554
H/O taking OCP	26 (86.7)	23 (76.7)	1.390	0.731

Passive smoking	27 (90.0)	25 (83.3)	0.576	0.447

Table 3: Distribution of the patients according to the clinical manifestation:

Table 3 resembles distribution of the patients according to the clinical manifestation. Twenty-six patients in arm A and 23 patients in arm B were suffering from moderate anaemia while severe anaemia was noted in three and six patients in arm A and in arm B respectively. Most of the patients experienced P/V bleeding before starting of treatment. In 2nd follow up onward cent percent complete responses were noted in both arms. However, no differences were statistically significant (p-value>0.05). At 1st follow up only three and two patients in arm A and arm B respectively had mild unusual P/V discharge and at 2nd & 3rd follow up two patients had experienced mild unusual P/V discharge.

Anaemia (n=60)	**Category of treatment**		**Fisher's Exact Test**	***p*-value**
	Arm A (45 Gy in 18 fractions)	**Arm B (50 Gy 25 fractions)**		
Mild	01 (3.3)	01 (3.3)		
Moderate	26 (86.7)	23 (76.7)	1.390	0.731
Severe	03 (10.0)	06 (20.0)		
Weight loss	**Category of treatment**		**Fisher's Exact Test**	***p*-value**
	Arm A (45 Gy in 18 fractions)	**Arm B (50 Gy 25 fractions)**		
Pre-treatment (n=60)				

Mild	24 (80.0)	22 (73.3)	0.373	0.542
At 1st follow-up (n=53)				
Mild	24 (88.9)	20 (76.9)	1.345	0.246
At 2nd follow-up (n=53)				
Mild	21 (77.8)	21 (80.8)	0.072	1.00
Bleeding	**Category of treatment**		**Fisher's Exact Test**	***p*-value**
	Arm A (45 Gy in 18 fractions)	**Arm B (50 Gy 25 fractions)**		
Pre treatment (n=60)	21	10	3.321	0.281
At 1st follow-up	1 (2.1)	3 (33.0)	1.165	0.351
2nd follow up				
Complete response	21 (100.0)	10 (100.0)	-	-
Unusual P/V discharge	**Category of treatment**		**Fisher's Exact Test**	***p*-value**
	Arm A (45 Gy in 18 fractions)	**Arm B (50 Gy 25 fractions)**		
Pre-treatment (n=60)				
Mild	9 (30.0)	8 (26.7)	0.181	1.00
Moderate	4 (13.7)	4 (13.7)		
At 1st follow-up				

Mild	03 (11.1)	02 (7.7)	0.179	1.00
At 2nd & 3rd follow-up				
Mild	2 (8.5)	2 (7.7)	0.002	1.00

Parametrium	**Category of treatment**		**Fisher's Exact Test**	***p*-value**
	Arm A (45 Gy in 18 fractions)	**Arm B (50 Gy 25 fractions)**		
1st follow up				
Free	3 (11.1)	1 (3.8)	1.002	0.610
Involved	24 (88.9)	25 (96.2)		
2nd follow up				
Partial response	5 (29.6)	4 (15.4)	1.535	0.215
Complete response	19 (70.4)	21 (84.6)		
3rd follow up				
Partial response	4 (25.9)	4 (15.4)	0.895	0.344
Complete response	20 (74.1)	21 (84.6)		

Table 4: Distribution of the patients according to the urological toxicity (n=60):

Table 4 illustrated distribution of the patients according to the urological toxicity. In 1st follow up most of the patients in both arms exhibited Grade 2 urinary toxicities. In 2nd follow up most of the patients exhibited Grade 1 toxicity while in 3rd follow up most of the patients were normal regarding urinary toxicity. However, no differences were statistically significant.

Urinary toxicity	**Category of treatment**		**Fisher's Exact Test**	***p*-value**
	Arm A (45 Gy in 18 fractions)	**Arm B (50 Gy 25 fractions)**		
1st follow up				
Grade 1	14 (51.8)	12 (46.2)		
Grade 2	10 (37.1)	9 (34.6)	0.120	1.00
Grade 3	3 (11.1)	5 (19.2)		
2nd follow up				
Grade 1	21 (77.8)	22 (84.6)		
			0.405	0.728
Grade 2	6 (22.2)	4 (15.4)		
3rd follow up				
Normal	19 (70.4)	22 (84.6)		
			1.535	0.215
Grade 1	8 (29.6)	4 (15.4)		
Hematological toxicity (WBC)	**Category of treatment**		**Fisher's Exact Test**	***p*-value**
	Arm A (45 Gy in 18 fractions)	**Arm B (50 Gy 25 fractions)**		
1st follow up				

Normal	24 (88.9)	23 (88.5)		
			3.195	0.74
Grade 1	3 (11.1)	3 (11.5)		
2nd follow up				
Normal	24 (88.9)	26 (100.0)		
			0.002	1.00
Grade 1	3 (11.1)	0 (0.0)		
3rd follow up				
Normal	27 (100.0)	25 (96.2)		
			1.058	0.491
Grade 1	0 (0.0)	1 (3.8)		

Table 5: Distribution of the patients by skin toxicities

Table 5 reveales distribution of the patients by skin toxicities. In 1st follow up most of the patients in both arms exhibited Grade 1 skin toxicities. In 2nd follow up number of patients with Grade 1 and Grade 2 toxicities reduced and at 3rd follow up there were no Grade 2 toxicities; only two patients in arm A and three patients in arm B showed Grade 1 toxicities.

Skin toxicity	**Category of treatment**		**Fisher's Exact Test**	***p*-value**
	Arm A (45 Gy in 18 fractions)	**Arm B (50 Gy 25 fractions)**		
1st follow up				
Normal	13 (48.1)	8 (30.8)		
Grade 1	10 (37.1)	13 (50.0)	1.695	0.414
Grade 2	4 (14.8)	5 (19.2)		

2nd follow up				
Normal	17 (62.9)	17 (65.4)		
Grade 1	8 (29.6)	9 (34.6)	1.70	0.611
Grade 2	2 (7.4)	0 (0.0)		
3rd follow up				
Normal	25 (92.6)	23 (88.5)	0.265	0.669
Grade 1	2 (7.4)	3 (11.5)		

Table 6: Distribution of the patients according to the final outcome (n=60):

Table 6 showed distribution of the patients according to the final outcome. Almost equal numbers of patients in both arms experienced complete response (22 in arm A and 23 in arm B). Partial responses were in five patients in arm A and three patients in arm B. Few patients were excluded from final analysis due to drop out or death. This differences of outcome was not statistically significant (p-value>0.05)

Final outcome	**Category of treatment**		**Fisher's Exact Test**	***p*-value**
	Arm A (45 Gy in 18 fractions)	**Arm B (50 Gy 25 fractions)**		
Dropped out/Died	3 (10.0)	4 (13.3)		
Complete response	22 (73.3)	23 (76.7)	0.729	0.829
Partial response	5 (16.7)	3 (10.0)		

Discussion:

Conventional fractionation delivers 2Gy per fraction 5 days a week. This fractionation scheme was developed because of tolerable acute reactions, acceptable delayed effects and reasonable local controls. In an attempt to improve the therapeutic ratio various fractionation schedules have been attempted. Hypofractionated radiotherapy has been used in various head and neck, bladder and gynecological malignancies [9].

Lee et al. (1979) studied 23 patients with stage III and IV head and neck carcinomas treated with 44-52Gy/11-13 fractions. The actuarial survival rate at 2 years was 45% and local control was 59%. Fraction size is the dominant factor in deciding the late effects. Increase in the dose per fraction also causes increase in the late effects.

Carcinoma cervix is one of the most common gynecological malignancies in Bangladesh. Large number of patients present at late stages due to various reasons. Carcinoma cervix stage IIB to IVA forms a heterogeneous group of patients ranging from small volume disease with bilateral parametrial involvement up to lateral pelvic wall to extensive disease with bulky parametrial involvement.

In the current study 73.3% patients achieved complete response after completion of hypofractionated radiotherapy, which is comparable to that of conventional treatment. In an Indian study the complete response rate was 85% in hypofractionated radiotherapy.

In 1st follow up most of the patients in both arms exhibited Grade 2 GI & rectum toxicities (44.4% vs 42.3%, p-value=0.923). In 2nd follow up number of patients with Grade 1 (40.7% vs 46.1%, p-value=0.625) and Grade 2 (7.4% vs 0%, p-value=0.625) toxicities reduced and at 3rd follow up there were no Grade 2 toxicities; only seven patients in arm A (25.9%) and six patients in arm B (23.1%) showed Grade 1 toxicities whereas 27% of the patients developed late rectal reactions in Muckaden et al. (2002) study. Radiation proctitis is one of the troublesome complications after pelvic radiotherapy [10]. The clinical manifestations vary from rectal proctitis, stricture, bleeding ulcers and fistula formation. The rate of late rectal morbidity has been reported as between 2-25% of the patients [11].

In 1st follow up most of the patients in both arms exhibited Grade 1 urinary toxicities (51.8% vs 46.2%, p-value=1.0). In 2nd follow up most of the patients exhibited Grade 1 toxicity (77.8% vs 84.6%, P-value=0.728) while in 3rd follow up most of the patients were normal regarding urinary toxicity (70.4% vs 84.6%, p-value=0.215). Twenty percent patients had acute genitourinary toxicity in Muckaden et al. (2002) study.

In 1st follow up most of the patients in both arms exhibited Grade 1 skin toxicities (37.1% vs 50%, p-value=0.414). In 2nd follow up number of patients with Grade 1 and Grade 2 toxicities reduced and at 3rd follow up there were no Grade 2 toxicities. In an Indian study skin reactions were observed in 29% patients [12]. In their study 11 patients had grade III skin reaction and were treated symptomatically.

Conclusion:

the hypofractionated radiotherapy will reduce the treatment time for each patient thus more patients can be treated with the same facility. In resource challenged setting where radiotherapy treatment facilities are limited this hypofractionated therapy could be a reasonable choice.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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