Original Research Article

A comparative study between two different fractionation of High Dose Rate Brachytherapy in locally advanced carcinoma of Uterine Cervix after pelvic concurrent Chemoradiotherapy

ABSTRACT:

Background: Uterine cervical cancer is the commonest form of gynecologic malignancy in Bangladesh. In locally advanced cases radiotherapy with a combination of external beam radiotherapy (EBRT) with concurrent chemotherapy and intracavitary brachytherapy (ICRT) is the mainstay of treatment. The aim of this study is to compare the treatment outcome and acute complications following treatment with 9 Gy (gray) in two fractions of ICRT with EBRT.

Methodology: A prospective study was carried out in the Department of Oncology, Bangabandhu Sheikh Mujib Medical University, Department of Radiation Oncology, National Institute of Cancer Research and Hospital, Dhaka during the period of 2017 to 2018.

Results:The mean age of patient at diagnosis was 50 years. During follow up at 6 month 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 and hematologic complications which were managed conservatively. During follow up after 6 months, rectal and bladder toxicities were similar in both arms.

Conclusion:This 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: Brachytherapy, Gray, Carcinoma cervix, Treatment response, Toxicity

INTRODUCTION

Uterine cervical cancer is the fourth most common cancer in women worldwide, and the seventh overall,[1-6] there is an estimated 604,127new cases in 2020.[7] A large majority (around 85%) of the global burden occurs in the less developed regions, where it accounts for almost 12% of all female cancers.[7-11] There were an estimated 341,831deaths from cervical cancer worldwide in 2020, accounting for 7.5% of all female cancer deaths. Almost nine out of ten (87%) cervical cancer deaths occur in the less developed regions .[7]

In Bangladesh and many other developing countries, unfortunately the incidence and mortality rates of carcinoma uterine cervix remains high, predominantly due to late detection.[12-16] There is no nationwide data of cancer in Bangladesh, but according to the cancer registry report of National Institute of Cancer Research and Hospital (2014) carcinoma cervix is the second leading cancer among women.[17] More than 80% cases usually present at an advanced stage with a high mortality rate. According to WHO report, age standardized incidence of cervical cancer in Bangladesh is 29.4 per lac women. Mortality from this disease is 17.9 per lac women. One third cervical cancer cases of world are found in South-Asian region, especially in India, Bangladesh and Pakistan.[3]In Bangladesh this is the commonest gynecological cancer, about 70% of the hospital cases of gynecological cancer are cervical cancer.About 11,956 new cervical cancer cases are diagnosed annually in Bangladesh. Cervical cancer is the 2nd most common female cancer in women aged 15 to 44 years in Bangladesh.[18]

A number of factors may influence the choice of treatment for carcinoma cervix, including tumor size, histology, stage, evidence of lymph node metastasis, risk factors for complications of surgery or radiotherapy and preference of patient.[19-23] Depending on stage, primary treatment consists of surgery, radiotherapy (RT) or a combination of radiotherapy and chemotherapy.[24-27] Concurrent chemoradiotherapy is the cornerstone of choice for FIGO stage IIB, IIIA, IIIB and IVA carcinoma of the cervix and is an excellent alternative to surgery to selected patients with stage IA, IB, or IIA diseases. Radiotherapy for primary cervical cancer consists of a combination of external beam radiotherapy (EBRT) and intracavitary radiotherapy(ICRT), except stage IA disease where ICRT alone may be used.[28] Primary radiotherapy is the treatment of choice for locoregionally advanced disease with a careful balance of pelvic EBRT with high energy photons andICRT, and must be administered at high doses (>80 -90Gy) and in a short time (<55 days) with the best technological resources available.[29]

Intracavitary brachytherapy delivers a high radiation dose directly to the tumor while sparing the surrounding normal tissues. HDR brachytherapy 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.[30]

Treatment duration of cervical carcinoma with radiotherapy (EBRT and ICRT) should be as short as possible (within 8 weeks), and any planned or unplanned interruptions or delays should be avoided. Overall treatment time should not exceed 56 days including brachytherapy and should ideally be 49 days or less. Lower pelvic tumor control and survival rates are observed in invasive carcinoma of the uterine cervix when the overall treatment time in a course of irradiation is prolonged.[31]

Bangladesh is a developing country with a dense population. In Bangladesh 80% of carcinoma of uterine cervix presents at a fairly advanced stage with a high mortality rate. We have a variety of problems in managing cervical cancer including patient load, which is very high due to inadequate number of radiotherapy centre. So decreasing the insertion of HDR brachytherapy from 3 to 2 fractions gives similar result, then it will help patients by reducing treatment cost and decreasing repeated attendance in hospital, as well as reduction in patient load in radiotherapy centres to some extent and more patients will get chance of treatment.

So, the objective of this study was to observe and compare the local control of disease and complications following treatment of locally advanced carcinoma cervix with two fractions of HDR brachytherapy after standard concurrent chemoradiation.

MATERIALS AND METHODS

It was a prospective analytical study and conducted in Department of Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka and Department of Radiation Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka. The duration was one year from 2017 to 2018.

A total 60 patients with clinically diagnosed and histologically proven locally advanced squamous cell carcinoma of the uterine cervix (Stage IIB- Stage IVA) was selected as sample and random sampling was done by computer generated method to divide them in both arms. The aim of this study was to see the effects of different fractionation of brachytherapy as the primary outcome and secondary outcome was to compare the toxicities.

Ethical approval was taken from the institutional review board (IRB) of BSMMU, informed consent was taken from each patient before enrolling in the study.

For radiotherapy the target volume was whole pelvis encompassing the extent of primary tumor and the pelvic lymph nodes. During EBRT whole pelvis was treated with 2 Gy per fraction, 5 days in a week with a total dose of 50 Gy for 5 weeks in a Cobalt 60 teletherapy machine with SSD of 100 cm,Inj. cisplatin 40 mg/m^2 was given weekly to the patients on days 1, 8, 15, 22 and 29. After EBRT, 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

Response evaluation criteria for solid tumorsRECISTcriteria was followed to assess the treatment response. Fortoxicityassessment, 'Toxicity criteria of the Radiation Therapy Oncology Group(RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) 1995'criteria was used.SPSS software (version 20) was used for data analysis. Chi square test was used for comparison of demographic variables and qualitative data.

OBSERVATIONS ANDRESULTS

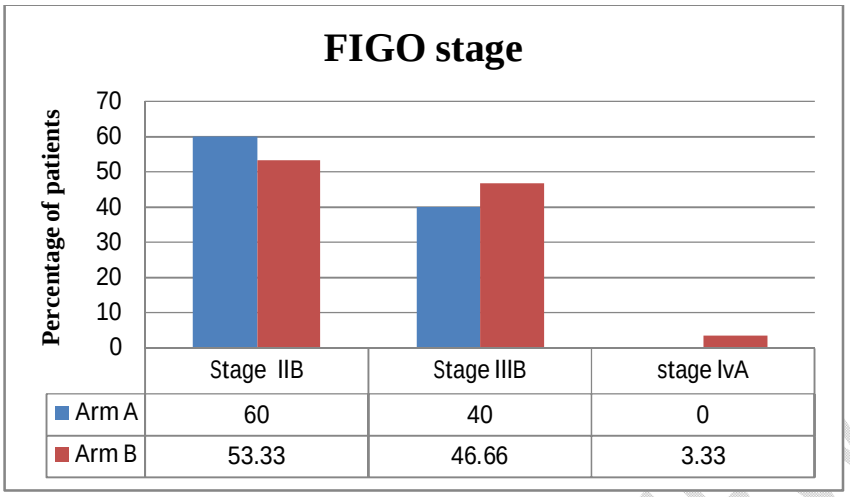
Patients with locally advanced carcinoma of uterine cervix were enrolled in this study and demographic and baseline characteristics were comparable in both groups (table I),

Table I: Patient characteristic (n=60)

Characteristics	**Arm A (n=30)**	**Arm B (n=30)**
Age at diagnosis		
31 to 60	26	25
Above 60	4	5
Early age of marriage (≤16 year)	25	24
Lower Economic condition	18	19
Grand multiparous	17	15
Sign and symptom		
Post Coital Bleeding	25	24
Inter-menstrual bleeding/ Postmenopausal bleeding	20	18
Excessive per vaginal Discharge	27	28
Pelvic Pain	10	12
Dysuria	6	7
Rectal Pain	0	0
Loss Of Appetite	19	18
Anemia	22	23

Most of the patients was diagnosed as stage IIB disease in both arms, 18(60%) and 16(53.33.0%) patients in Arm A and B respectively.12 patients(40.0%) in Arm-A & 13 patients(43.33%) in Arm-B were in Stage IIIB & there was only 1 patient from stage IVA in Arm-A (Figure 1).

Figure 1: Graphical presentation of clinical stage of disease in both arms



At 1st follow up, there were 18(60%) patients of Arm-A and 16 (53.33%) of Arm-B with stage IIB disease and complete response observed in 16 (53%) of Arm-A and 13 (43.3%) of Arm-B patients. There was no statistically significant difference in complete and partial response between two arms on the basis of staging (p>0.05).

Table II: Distribution of the patients on the basis of staging and response at 6 week after completion of treatment

Total Patients n= 30 (each arm)	No. of patients N (%)	Complete response N (%)	Partial Response N (%)	Progressive Disease N (%)	p value
Stage IIB					
00(0.0%)	18(60%)	16(53.33%)	02(6.7%)		0.530
00(0.0%)	16(53.33%)	13(43.33%)	03(10%)		
00(0.0%)	12(40%)	11(36.6%)	01(3.33%)		0.587
00(0.0%)	13(43.3%)	11(36.7%)	02(6.7%)		
00(0.0%)	0(0%)	00(0.0%)	00(0.0%)		
▪ Arm-B	01(3.33%)	00(0.0%)	01(0.0%)	00(0.0%)	

Then response evaluation was done at 2nd follow up which was at 12th week after completion of treatment. Response was similar like 1st follow up and there was no progression of disease

Final follow up was done at 6 month (24 weeks) after completion of treatment and it was observed that 90% of patients had complete response in Arm A. In Arm B 86% had complete response. The overall complete remission was 88%. Statistical analysis revealed there was no significant difference in terms of response in both arms.

Table III: Distribution of the patients according to treatment response at 6 month

Response	**Arm A(total=30) N (%)**	**Arm B(total =30) N (%)**	**Total**
Complete response	27(90)	26(86)	53(88)
Partial response	3(10)	4(13)	7(12)
Progressive disease	0	0	0

The frequencies of common toxicities related to treatment shown on table IV which are not statistically significant. Table shows that overall radiotherapy related toxicities were more in Arm A than that of Arm B but statistically it was not significant andall the toxicities were managed by conservative treatment. Treatment discontinuation or hospitalization for toxicity management was not neededduring treatment and follow-up period. Most of the patients suffered from rectal and bladder toxicities in both arms.

Table IV: Distribution of patients according to acute toxicity

Variables	**Group (Total=30)**		**p value**
	Arm-A [N (%)]	**Arm-B [N (%)]**	
Skin Reaction			
Grade 1	10(33)	9(30)	
Grade 2	8(27)	7(23)	0.967
Bladder toxicity			
Grade-1	12 (40)	10 (33)	
Grade 2	8(26.66)	6(20)	0.878
Haematologic toxicities			
Grade 1	10(33)	11(37)	0.473
Grade 2	5(17)	3(10)	
Rectal toxicity/ Rectal discomfort			
Grade-1	9 (30)	10 (33)	0.370
Grade 2	10(33.33)	6(20)	

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, 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 V: Distribution of patients according to toxicity at 3rd follow up

Toxicity	Arm A(total=30) N (%)	Arm B (total=30) N (%)	p value
Bladder	3(10)	2(7)	0.850
Rectal	2(7)	0	

DISCUSSION

Diagnosed patients of locally advanced carcinoma cervix (stage IIB to IVA) of squamous cell variety were enrolled in this study. Etiological factors of carcinoma cervix are early age of marriage, low socioeconomic condition, multiparity, illiteracy, long term oral contraceptive pill use and this study correlates with previous findings.

For locally advanced carcinoma cervix radiotherapy is the main modality of treatment and intracavitary brachytherapy is an essential part of it. In recent years, owing to the obvious physical advantages of shortened treatment time and better geometric placement HDR brachytherapy has gained popularity. No clear consensus of the appropriate number of fractions or appropriate dose per fraction has been reached. Various fractionation schemes have been used experimentally in search of the optimal technique. The number of fractions has varied from as low as 1 to as many as 16. The dose per fraction to point A has varied from 3 to 17 Gy/fraction.[32]

Our present study was done using the HDR Microselectron with an Iridium 192 source and the HDR MicroselectronNucleotron applicator. We used a dose of 9 Gy/fraction of 2 fractions

in Arm A and 3 fraction of 7 Gy/fraction in Arm B. The effects and toxicities were observed during and upto six months after completion of treatment. Both clinical examination and pap's smear test was done to see the presence of any microscopic residual disease. Complete remission was observed in 90% of patients in arm A and it was 86% in arm B, the overall complete response was 88%. Statistical analysis revealed there was no significant difference but arithmetically this is proven that Arm-A patients had better response than Arm-B.

The most prevalent acute toxicities in both the arms were bladder and rectum related toxicities, skin reaction, vaginalmucositis. 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).

During follow up after 6 months, only 10% of in arm A and 6% in arm B developed grade II bladder toxicities and only 6% in arm A developed rectal grade II toxicities, which is similar to findings of other studies.[33]

Differentstudies have effectively shown that in choosing the number of HDR fraction and consequently the dose per fraction, it is the prescribed dose received by the critical organs that is important. If the critical organs receive a smaller percentage of the point A dose, we can use larger dose per fraction without increasing morbidity.[34]The advantage of using fewer fractions is patient convenience and improved patient compliance. Two fractions of 9 Gy brachytherapy can be completed in 2 weeks whereas three fractions of 7 Gyneeds 3 weeks to complete the treatment.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 centers to some extent which is a major consideration in a developing country like ours where radiotherapy canters are overburdened with cancer patients.

CONCLUSION

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.

RECOMMENDATIONS

1. Brachytherapy 9 Gy of 2 fractions is an acceptable alternative to conventional fractionated brachytherapy in locally advanced carcinoma of cervix after CCRT
2. Further study with large sample size in multiple center of Bangladesh to see the long term effect.

CONSENT

Written informed consent was taken from all patient.

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