Research Article

A comparative study between conventional high-dose-rate brachytherapy and once a week and twice a week concurrent brachytherapy in treatment of carcinoma of uterine cervix with external beam radiation therapy

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Abstract

Background: Carcinoma of uterine cervix is the most common cancer in women in many developing countries such as India and is a significant health-care problem worldwide.

Objectives: To compare effectiveness, safety, and toxicity profile of conventional high-dose-rate brachytherapy (HDR-BT) and once a week and twice a week HDR-BT study concurrent with external beam radiation therapy (EBRT), that is, 7 Gy/3 fraction of concurrent EBRT and 4.5 Gy/6 fractions of concurrent EBRT to be compared with conventional HDR-BT schedule.

Materials and Methods: In this open prospective randomized pilot comparative study, total 82 patients of cancer cervix were categorized into three treatment groups. (1) Group A (n = 27): Those received 3 weeks EBRT followed by concurrent once a week high-dose-rate brachytherapy (HDR-BT) along with EBRT from 4th week onward. The total dose of HDR-BT was 21 Gy in 3 fractions. (2) Group B (n = 28): Those received 3 weeks EBRT followed by concurrent twice a week HDR-BT and EBRT from 4th week onward. The total dose of HDR-BT was 27 Gy in 6 fractions (4.5 Gy in each fraction). (3) Group C (n = 27): Those received conventional brachytherapy, which was started 2 weeks after the completion of EBRT.

Results: It was observed that the fractionation schedule and dose in study Group B (4.5 Gy/6 fraction of concurrent EBRT) had produced most satisfactory results regarding response rate, local control, failure rate, and less acute and late toxicities of bladder, rectum, vagina, and skin compared to study Group A and control Group C.

Conclusion: HDR intracavitary brachytherapy using 4.5 Gy/6 fraction of concurrent EBRT twice in a week in locally advanced carcinoma cervix may be a good option as it has better local control and less toxicity. Continuing this study for prolonged period and recruiting more patients will help in arriving at more conclusive results.

KEY WORDS: Carcinoma cervix, external beam radiation therapy, high-dose-rate brachytherapy, different brachytherapy fractionations

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Introduction

Carcinoma of uterine cervix is the most common form of cancer in women in many developing countries like India and is a significant health-care problem worldwide.[1–3] Sixty percent of patients attending hospital are in the locally advanced stage. A combination of external beam radiotherapy (EBRT) and brachytherapy (BT) is an effective

treatment modality in advanced stages of cancer cervix. Fractionation and dose adjustments of the total dose are crucial factors in lowering the frequency of complications without compromising the treatment results.

Nearly 65% of the patients of carcinoma cervix seen at the center belong to Stage III and majority of them come from remote places and low socio-economic background. Radical radiotherapy plays an important role in these cases, and a combination of mega voltage external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) is the accepted definitive mode of treatment. Fractionation and dose adjustments of the total dose are very important factors in lowering the frequency of complications without compromising the treatment results.

The purpose of the study is to compare effectiveness, safety, and toxicity profile of conventional HDR-BT and once a week and twice a week HDR-BT study concurrent with EBRT.

Materials and Methods

A total of 82 patients who attended Department of Radiotherapy, IPGME&R and SSKM Hospital Kolkata, between July 1, 2008 and August 31, 2009, were divided into three groups for comparative analysis. The patients were randomly grouped under each treatment modality as (1) Group A (n = 27): those received 3 weeks external beam radiation therapy (EBRT) followed by concurrent once a week HDR-BT, (2) Group B (n = 28): those received 3 weeks EBRT followed by concurrent twice a week HDR-BT and EBRT from 4th week. The total dose of HDR-BT was 27 Gy in 6 fractions (4.5 Gy in each fraction, and (3) Group C (n = 27): those received conventional brachytherapy, which started 2 weeks after the completion of EBRT–BT. The total dose of EBRT was 50 Gy to radiate the whole pelvis with central shielding provided after 30 Gy of EBRT. During treatment, patients were evaluated weekly for clinical response, any complications, biochemical, and hematological abnormalities. Following the completion of treatment, the patients were followed up monthly for 6 months and thereafter in 2 months interval to see clinical, hematological, and radiological response and complications. Inclusion criteria were: age between 20 and 70 years, Karnofsky performance status above 70 (KPS > 70), hematological, renal, and liver function tests within normal limits, no evidence of distant metastases (clinically or radiologically), no history of prior radiotherapy or chemotherapy, non-pregnant and non-lactating women, and no associated medical or surgical diseases. Informed consent of the patient and consent of hospital ethics committee were taken.

Exclusion criteria were: age >70 years or <20 years, pregnancy and lactation, KPS below 70, patients with any benign rectal disorders or bladder disorders, with genital prolapse, with willingness to have anesthesia, or with deformities of the knee or hip, and participation in other clinical studies. Acute toxicities were graded according to RTOG acute radiation morbidity scoring criteria, and late toxicities were evaluated using RTOG/EORTC late radiation morbidity scoring schema.[6]

Result

Out of the total 82 patients of carcinoma cervix, 27 patients were in Group A; 28 patients were in Group B were compared with the Group C patients (n = 27).

Table 1: The incidence of cancer cervix patients who attended Radiotherapy Department of IPGMER& SSKM Hospital, Kolkata, West Bengal, India between year 2003 and 2009

Year	Total no. of all cases of malignancies	No. of cases of carcinoma cervix	Percentage
2003	2452	360	14.6
2004	2552	335	13.1
2005	2702	372	13.8
2006	2846	390	13.7
2007	2426	270	11.1
2008	2511	283	13.3
2009	2492	292	11.7

Table 2: Stage-wise incidence of carcinoma cervix in the year 2009 (n = 292)

Stage	No. of carcinoma cervix cases	Percentage
Carcinoma in institute	2	0.68
I	1	0.34
IIA	11	3.77
IIB	76	26.0
IIIA	7	2.40
IIIB	149	51.03
IVA	27	9.25
IVB	19	6.51

Table 3: Age distribution of the total cohort of patients

Age group (years)	No. of cases (percentage)		
	Group A	Group B	Group C
21–30	01 (3.70%)	01 (3.57%)	01 (3.70%)
31–40	02 (7.41%)	04 (14.28%)	04 (14.81%)
41–50	12 (44.44%)	11 (39.29%)	12 (44.44%)
51–60	08 (29.63%)	09 (32.14%)	08 (29.63%)
61–70	04 (14.81%)	03 (10.71%)	02 (7.41%)
Total	27	28	27

Table 4: Stage-wise distribution of the total study group patients

Stage	No. of cases (percentage)		
	Group A	Group B	Group C
IIB	08 (29.63%)	10 (35.71%)	08 (29.63%)
IIIA	03 (11.11%)	02 (7.14%)	05 (18.51%)
IIIB	16 (59.26%)	16 (57.14%)	14 (51.85%)
IVA	00 (0.0%)	00 (0.0%)	00 (0.0%)
Total	27	28	27

Table 5: Tumor response at 6 weeks, 3 months, 6 months, 9 months, and 1 year

Group	Time	CR (%)	PR (%)	SD (%)	PD (%)	Total
Group A	6 weeks	11 (40.74)	06 (22.22)	10 (37.04)	00 (0.0)	27
	3 month	22 (81.48)	04 (14.81)	01 (3.70)	00 (0.0)	27
	6 month	21 (77.78)	05 (18.52)	01 (3.70)	00 (0.0)	27
	9 month	20 (74.07)	04 (14.81)	01 (3.70)	02 (7.41)	27
	1 year	19 (70.37)	03 (11.11)	01 (3.70)	04 (14.81)	27
Group B	6 weeks	12 (42.86)	07 (25.0)	09 (32.14)	00 (0.0)	28
	3 month	24 (85.71)	03 (10.71)	01 (3.57)	00 (0.0)	28
	6 month	23 (82.14)	04 (14.29)	01 (3.57)	00 (0.0)	28
	9 month	21 (75.0)	03 (10.71)	02 (7.14)	02 (7.14)	28
	1 year	20 (71.43)	03 (10.71)	02 (7.14)	03 (10.71)	28
Group C	6 weeks	08 (29.62)	09 (33.33)	10 (37.03)	00 (0.0)	27
	3 month	18 (66.66)	07 (25.92)	02 (7.40)	00 (0.0)	27
	6 month	18 (66.66)	07 (25.92)	02 (7.40)	00 (0.0)	27
	9 month	16 (59.25)	06 (22.22)	03 (11.11)	02 (7.41)	27
	1 year	16 (59.25)	03 (11.11)	02 (7.41)	06 (22.22)	27

Table 6: Local control as in August 2009

Group	No. of patients	Local control
Group A	27	19 (70.37%)
Group B	28	20 (71.43%)
Group C	27	17 (62.96%)

Table 7: Acute toxicities

Type of acute toxicity	Grade	Week 12		
		Group A	Group B	Group C
Acute bladder toxicity	0	14	15	16
	1	10	9	8
	2	3	4	3
	3	0	0	0
	4	0	0	0
Acute rectal toxicity	0	16	18	14
	1	9	7	9
	2	4	3	4
	3	0	0	0
	4	0	0	0
Acute vaginal toxicity	0	20	23	2
	1	6	4	3
	2	1	1	0
	3	0	0	0
	4	0	0	0
Acute skin toxicity	0	21	23	25
	1	6	5	2
	2	0	0	0
	3	0	0	0
	4	0	0	0

Table 1 shows that the incidence of cancer cervix is about 12%–14% of patients presenting in outpatients department. The incidence of cancer cervix has slightly gone down (~11%) in the last 3 years.

Table 2 shows that 77.06% (225 out of 292 patients) of cases of cancer cervix in our institute belong to Stages IIB and IIIB only.

Table 3 shows that 74.03% of Group A and 71.43% (20 of 28 patients) of Group B cases are between 41 and 60 years of age and 74.07% (20 of 27 patients) of control group (Group C) are between 41 and 60 years of age.

Table 4 shows that 88.89% in Group A, 92.85% in Group B, and 81.48% in Group C are in Stage IIB and IIIB cases of cancer cervix, which constitute the maximum number of patients.

Table 5 shows that complete response is slightly higher in Groups A and B than Group C at 6 weeks, complete response is slightly higher in Groups A and B than Group C at 3 months, complete response is slightly higher in Groups A and B than Group C at 6 months, complete response is slightly higher in Groups A and B than Group C, and complete response is slightly higher in Groups A and B than Group C at 1 year.

Table 6 shows that it has been observed that 19 patients (70.37%) out of 27 in study Group A and 20 patients (71.43%) out of 28 in study Group B as compared to 17 patients (62.96%) out of 27 in control Group C are under local control. The patterns of failure were studied for all the patients in all the groups. Out of 28 patients in Group B, 3 patients (10.71%) developed local failure in the pelvis only and 1 patient (3.57%) in both pelvis and distant sites. The local disease was under control in 3 patients (10.71%), but they developed failure in the distant sites. The most common site of distant metastases was lung, followed by bones.

Table 7 shows that at the end of 3 months, acute bladder toxicity is found; in Group A, 14 patients are in Grade 0 toxicity, 10 patients are in Grade 1 toxicity, and 3 patients in Grade 3 toxicity, whereas in Group B, bladder toxicity is found in 15 patients in Grade 0, 9 patients in Grade 1 and 3

Table 8: Late toxicities

Type of late toxicity	Grade	6 month			12 month		
		Group A	Group B	Group C	Group A	Group B	Group C
Late bladder toxicity	0	23	24	26	20	24	24
	1	4	4	1	4	2	2
	2	0	0	0	2	2	1
	3	0	0	0	1	0	0
	4	0	0	0	0	0	0
Late rectal toxicity	0	23	25	26	18	23	23
	1	4	3	1	4	4	2
	2	0	0	0	4	1	2
	3	0	0	0	1	0	0
	4	0	0	0	0	0	0
Late vaginal toxicity	0	20	20	23	23	24	27
	1	6	8	4	4	4	0
	2	1	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
Late skin toxicity	0	22	23	26	26	27	27
	1	5	5	1	1	1	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0

patients in Grade 2. But, in control Group C, bladder toxicity is much less.

Acute rectal toxicity at the end of 3 month in Group A shows Grade 0 toxicity in 16 patients, Grade 1 toxicity in 9 patients, and Grade 2 toxicity in 4 patients. Group B shows Grade 0 toxicity in 18 patients, Grade 1 toxicity in 7 patients, and Grade 2 toxicity in 3 patients. In control Group C, these are 14, 9, and 4, respectively.

Acute vaginal toxicity at 12 weeks,8 pt in Group A, 5 pts in Group B, 2 pts in Group C had Grade 2 vaginal mucositis at the end of 8 weeks. At 3 months, 1 patient in each study group (A and B) had Grade 2 vaginal stenosis, for which regular vaginal dilatation was advised.

At 3 months follow-up for acute skin toxicity it showed that 6 patients in Group A had dry desquamation over the radiation field compared to 5 patients in Group B.

As shown in Table 8, at 6 months follow-up for late bladder toxicity, it was found that 4 patients in Groups A and B and 1 patient in Group C had mild frequency and dysuria and on urine analysis it revealed that they suffered microscopic hematuria. At the end of 1 year, 2 patients in Group A and 2 patients in Group B had Grade 2 bladder toxicity and presented with intermittent macroscopic hematuria. One patient in each group suffered from severe frequency and dysuria and frequent hematuria at the end of 12 months.

At the end of 6 months follow-up for late rectal toxicity, it was found that 4 patients in Group A, 3 patients in Group B, 1 patient in Group C had Grade 1 rectal toxicity with mild diarrhea or slight rectal bleeding. They were effectively managed with medicines and steroids. After a follow-up of 12 months, 4 patients in Group A and 1 patients in Group B and 2 patients in Group C had moderate diarrhea and bowel movement >5 times/day or excessive rectal mucus or intermittent bleeding. One patient in Group A had severe rectal bleeding and was planned to undergo colostomy, and other patient developed recto-vaginal fistula at the end of 1 year.

At the end of 6 months follow-up for late vaginal toxicity, it was found that 6 patients in Group A had developed Grade 1 vaginal toxicity compared to 5 patients in Group B. One patient in Group A had Grade 2 vaginal toxicity. At the end of 1 year, 4 patients in each group had been suffering from Grade 1 vaginal toxicity.

At the end of 6 months follow-up for late skin toxicity, 5 patients in Group A and 5 patients in Group B were suffering from Grade 1 skin toxicity. At the end of 12 months, one patient in each study group had Grade 1 skin toxicity.

Discussion

Carcinoma cervix is one of the leading causes of malignancy among Indian women. In our tertiary cancer institute, about 12%–14% of patients presenting in the outpatients department each year comprise of cancer cervix.

Radiotherapy plays an important role in the treatment of carcinoma cervix, and a combination of megavoltage external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICRT) is the accepted definitive mode of treatment.[7] The curative potential of radiotherapy 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 the surrounding normal tissues.[8] The goals are to treat point A to at least a total LDR equivalent of 80–85 Gy for early stage disease and 85–90 Gy for advanced-stage disease. The pelvic sidewall dose recommendations are 50–55 Gy for early lesions and 55–65 Gy for advanced ones. Every attempt should be made to keep the bladder and rectal doses below 80 Gy and 75 Gy LDR-equivalent doses, respectively. Interstitial brachytherapy should be considered when the tumor cannot be optimally encompassed by intracavitary brachytherapy. Some suggested dose and fractionation schemes for combining the external beam radiation therapy with HDR brachytherapy for each stage of disease were presented, although they have not been thoroughly tested. It was emphasized that the responsibility for the medical decisions ultimately rests with the treating radiation oncologist.[5]

The main objective of our study is to achieve a suitable HDR brachytherapy fractionation protocol for safety regarding both complication and efficiency in respect of tumor control and disease-free survival for the patients and also convenient to comply with by the patients.

At the end of study (August 2009), it was seen that 19 patients (70.37%) out of 27 in study Group A and 20 patients (71.43%) out of 28 in study Group B as compared to 17 patients (62.96%) out of 27 in control Group C were under local control.

The patterns of failure were studied for all the patients in all the groups. Out of 28 patients in Group B, 3 patients (10.71%) developed local failure in the pelvis only and 1 patient (3.57%) in both pelvis and distant sites. In 3 patients (10.71%), the local disease was under control but they developed failure in the distant sites. The most common site of distant metastases was lung, followed by bones.

In Group A, 4 patients (14.81%) developed loco-regional failure and 1 patient (3.70%) developed both local and distant failure. Three patients (11.11%) had local disease under control, but developed distant metastases. In Group C, 5 patients (18.50%) developed loco-regional failure, 1 patient (3.70%) developed both local and distant failure. Three patients (11.11%) had local under control but developed distant metastasis.

When the final result tabulation was done, 2 patients (7.41%) in Group A, 1 patient (3.57%) in Group B and 2 patients in Group C had died. The cause of death in all the patients was due to distant metastases to the lungs.

The incidence of major late squeal of radiation therapy for Stage I and IIA carcinoma of the cervix ranges from 3% to 5%, and for Stage IIB and III, between 10% and 15%. Injury to the gastrointestinal tract usually appears within the first 2 years after radiation therapy, whereas complications of the urinary tract are seen more frequently 3–5 years after treatment.[16] Pedersen et al., in a review of morbidity of radiation therapy in 442 patients with cervical cancer Stages IIB, III, and IVA, recommended that actuarial estimates rather than frequency of squeal be reported to avoid underestimation of risks of late morbidity after radiation therapy in long-term survivors.[17]

Patients with gynecologic malignancies, including those receiving radiation therapies, are prone to development of urinary tract infections. Prasad et al. collected 216 urine samples from 36 patients receiving pelvic irradiation and found that 12 of them had urinary tract infection.[20]

In this study, at the end of 3 months, acute bladder toxicity was found in 10 patients in Grade 1 toxicity and 3 patients in Grade 3 toxicity in Group A, whereas it was in 9 patients in Grade 1 and 3 patients in Grade 2 in Group B. It was much less in control Group C.

Regarding rectal toxicity, at the end of 3 month, Group A showed Grade 1 toxicity in 9 patients and Grade 2 toxicity in 4 patients. Group B showed Grade 1 toxicity in 7 patients and Grade 2 toxicity in 3 patients. In control Group C, these are 9 and 4, respectively.

Genitourinary symptoms included dysuria, frequency and nocturia, secondary to cystourethritis. Microscopic intermittent hematuria occurred in some patients. These may be associated with urinary tract infection. Methenamine, phenazopyridine, tlavoxate, hyosciaminc, and tolterodine relieved these symptoms. Increased fluid intake was also recommended.

Acute gastrointestinal toxicities included abdominal cramps, diarrhea, rectal discomfort, and occasional rectal bleeding. Diarrhea and abdominal cramps were controlled by diphenoxylate hydrochloride, loperamide, atropine sulfate, and racecadotril. Proctitis and rectal discomfort was alleviated by hydrocortisone enemas and anti-inflammatory suppositories containing bismuth, benzyl benzoate, and zinc oxide. Low residue diet was advised.

In this study, 8 pt in Group A, 5 pts in Group B, 2 pts in Group C had Grade 2 vaginal mucositis at the end of 8 weeks. At 3 months, 1 patient in each study group had Grade 2 vaginal stenosis, for which regular vaginal dilatation was advised. Vaginal dose was contributed from the ovoids and lower tandem dwell positions. Generally, the upper vagina can tolerate a higher dose (140–150 Gy) than the distal vagina.[21] Mostly, the difference is noted in the upper and mid-vagina in spite of the difference in their tolerance. This can be attributed to contributions both from the external radiation and HDR-ICBT to the apex and surrounding areas of the vagina; whereas the distal vagina received contributions only from the external radiation.

Regarding skin toxicity, it occurred mainly due to contributions from external beam radiotherapy. Hence, skin toxicity, which was found in this study solely due to external beam radiation. At 3 months follow-up, 6 patients in Group A had dry desquamation over the radiation field in contrast to 5 patients in Group B. They were treated with moisturizing lotions.

At 6 months, 4 patients in Groups A and B and 1 patient in Group C had mild frequency and dysuria, and on urine analysis it was found that they had microscopic hematuria. At the end of 1 year, 2 patients in Group A and 2 patients in Group B had Grade 2 bladder toxicity and presented with intermittent macroscopic hematuria. One patient in each group suffered from severe frequency and dysuria and frequent hematuria at the end of 12 months. They were planned for cystoscopy and fulguration.

All the patients were also assessed for late rectal toxicity. At the end of 6 months, 4 patients in Group A, 3 patients in Group B, and 1 patient in Group C had Grade 1 rectal toxicity and presented with mild diarrhea or slight rectal bleeding. They were effectively managed with medicines and steroids. After a follow-up of 12 months, 4 patients in Group A and 1 patients in Group B and 2 patients Group C had moderate diarrhea and bowel movement >5 times/day or excessive rectal mucus or intermittent bleeding. One patient in Group A had severe rectal bleeding and was planned to undergo colostomy, and other patient developed recto-vaginal fistula at the end of 1 year.

Similarly, the late vaginal and skin toxicity was also assessed. At the end of 6 months, 6 patients in Group A had developed Grade 1 vaginal toxicity in contrast to 5 patients in Group B. One patient in Group A had Grade 2 vaginal toxicity. At the end of 1 year, 4 patients in each group had been suffering from Grade 1 vaginal toxicity. At the end of 6 months, 5 patients in Group A and 5 patients in Group B were suffering from Grade 1 skin toxicity. At the end of 12 months, 1 patient in each study group had Grade 1 skin toxicity. Both late vaginal toxicity and late skin toxicity were less in the control group than in the two study groups.

There was 92.59% survival in patients treated with 7 Gy/fraction of HDR-ICBT compared to 96.43% in patients treated with 4.5 Gy/fraction of HDR-ICBT at the end of 1 year.

Conclusion

Carcinoma cervix is the most common cause of female malignancy in India with one of the most common causes of morbidity and mortality in perimenopausal and post-menopausal women. HDR brachytherapy has proved to be a standard treatment modality in carcinoma cervix.

In this study, the main objective is to observe the results using two study groups (7 Gy/3 fraction of concurrent EBRT and 4.5 Gy/6 fraction of concurrent EBRT) and a control group (conventional HDR brachytherapy) in locally advanced carcinoma of uterine cervix.

It is observed that fractionation schedule and dose in study Group B (4.5 Gy/6 fraction of concurrent EBRT) has produced satisfactory results in terms of response rate, local control, failure rate, and less acute and late toxicities of bladder rectum, vagina, and skin compared to the other study group and the control group. Hence, this study can be concluded with the assumption that HDR intracavitary brachytherapy using 4.5 Gy/fraction, twice in a week for 6 fractions concurrent with EBRT in locally advanced carcinoma cervix may be a good option as it has better local control and less toxicity. Continuing this study for prolonged period and recruiting more patients will help in arriving at more conclusive results.

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