Original research article

PROSPECTIVE RANDOMIZED STUDY ON TWO DOSE FRACTIONATION REGIMENS OF HIGH DOSE RATE BRACHYTHERAPY FOR CARCINOMA CERVIX: COMPARISON OF CLINICAL RESPONSE AND COMPLICATIONS IN ORGANS AT RISK

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Abstract

Introduction: Cancer Cervix is treated with a combination of external beam radiotherapy and intracavitary brachytherapy. With the recent American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix, atleast Equivalent Dose 2 > 80 Gy for patients with complete response or partial response with residual disease less than 4cm is recommended. For non responders or those with tumors larger than 4cm at the time of brachytherapy, tumor dose escalation to an Equivalent Dose 2 of 85-90 Gy is recommended to point A. Present study was designed to see the feasibility of these guidelines in terms of local tumor control and toxicities to rectum and bladder in our group of patients.

Material and Methods: Fifty patients of biopsy proven cancer cervix were enrolled. After pre-treatment evaluation all patients were delivered external beam radiotherapy 50 Gy in 25 fractions at 200 cGy/day with concurrent cisplatin on weekly basis. Patients were then randomized into three applications (Group A), four applications (Group B) of HDR Brachytherapy of 6 Gy each so that total treatment time does not exceed 8 weeks. BED and LQED were calculated and assessment of response and complications were assessed. Statistical analysis was done using Chi square test.

Results: Mean age of the patients was 50 years. No significant hematological toxicities and radiation reactions were seen during external beam radiotherapy. The mean BED of group A for tumor, rectum & bladder was 137.3 Gy, 112.53 Gy & 103.23 Gy respectively and of group B was 155.3 Gy, 120.98 Gy and 111.95 Gy respectively. The mean EQD2 in group A at tumor, rectum & bladder was 74 Gy, 54.08 Gy and 61.94 Gy respectively and in group B was 82 Gy, 59.18 Gy and 66.60 Gy respectively. There was no statistically significant difference in local response and early & late bladder reactions in both the groups.

Conclusion: In a follow up of six months we did not find any significant difference in toxicities of rectum and bladder. Long term follow up is needed to see for late rectal and bladder toxicities.

Keywords: Cancer cervix, high dose rate, Brachytherapy, fractionation regimens

INTRODUCTION

Radiotherapy is the cornerstone and the treatment of choice for Federation International de Gynaecologic et Obstetrique (FIGO) stage IIB, IIIA, IIIB or IVA carcinoma of the cervix and is an excellent alternative to surgery in selected patients with stage IA, IB, or IIA diseases.[1,2] Optimal treatment results require a combination of dedicated planned external beam RT (EBRT) and intracavitary brachytherapy (ICRT). The curative potential of RT in the management of carcinoma of the cervix is greatly enhanced by the use of ICRT.

Perez[3] showed that the most significant factor affecting the incidence of complications was the total dose of irradiation to the pelvic organs by both pelvic irradiation and the intracavitary insertion. The incidence of complications significantly increased when the dose exceeded 80 Gy. For the bladder, a dose below 80 Gy correlated with less than 3% probability of morbidity while this rate reached 5% with higher doses.[4] The incidence of morbidity from recto-sigmoid complications is significantly increased when the total dose exceeded 75 Gy: 4% with doses below 75 Gy and 9% with higher doses.

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With the recent American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix, atleast EQD2 > 80 Gy for patients with complete response or partial response with residual disease less than 4cm is recommended. For non responders or those with tumors larger than 4cm at the time of brachytherapy, tumor dose escalation to an EQD2 of 85-90 Gy is recommended to point A[5].

Present study was designed to look for dose escalation to point A as recommended by American Brachytherapy Society consensus guidelines for increasing the local tumor control and to judge whether our group of Indian patients can tolerate such dose escalation to point A without increase in toxicity to the organs at risk – rectum and bladder.

MATERIAL & METHODS

Fifty patients of biopsy proven cancer cervix with age > 18 years, Karnofsky Performance Scale above 70, Stage IA to IIIB, no history of previous malignancy with adequate hepatic, renal, and cardiopulmonary functions were enrolled into this study. Patients with carcinoma of the cervix FIGO stage IV patients, metastatic disease, any previous pelvic surgery, radiotherapy or chemotherapy were excluded.

Pretreatment Evaluation: Complete medical and physical examination including bimanual pelvic and rectal examination, cervical biopsy, baseline hematological tests (haemogram, renal function tests, liver function tests), chest radiography, ultrasound abdomen or CECT abdomen and pelvis (whichever was feasible) and cystoscopy & proctosigmoidoscopy (only if clinically indicated).

Radiotherapy Planning and Technique: All patients were planned and delivered by conventional and conformal 3DCRT using four field box technique. Radiotherapy dose delivered will be 50 Gy in 25 fractions at 200 cGy/day. Concurrent cisplatin based chemotherapy were delivered to these patients on weekly basis at dose of 35mg/m2 with adequate hydration.

Randomisation: Patients were randomized into two groups of 25 each by the simple randomization method after completion of external chemoradiation. Patients were planned for 3 applications (Group A) and 4 applications (Group B) of HDR brachytherapy of 6.0 Gy each with a gap of 4-7 days so that the current treatment time does not exceed 8 weeks

Calculation of Biological Effective Dose and Linear Quadratic Effective Dose (LQED): For each arm, the contribution of point A dose was calculated as per the linear quadratic model (LQM) from both external beam radiotherapy and intracavitary portions of the treatments. The total BED to the tumor was calculated by using and α/β ratio = 10 (Gy_{10}) and for late responding tissues like rectum and bladder $\alpha/\beta = 3$ (Gy_3).

Total biological effective dose delivered to point A, rectal and bladder points for each intracavitary application including external beam radiotherapy was calculated (Table-1).

Table-1: Formulas of calculating BED with Gy_{10} and Gy_3

Total A point BED (Gy_{10})
$= 2\times n1\times(1+2/10)+ICRA\times n2\times(1+ICRA/10)$

Total rectal point BED (Gy_3)
$= 2\times n1\times(1+2/3)+ICRR\times n2\times(1+ICRR/3)$

Total bladder point BED (Gy_3)
$= 2\times n1\times(1+2/3)+ICRB\times n2\times(1+ICRB/3)$

n1 : number of EBRT prior to midline shield
n2 : number of ICR fractions
ICRA : fraction size of A point in ICR
ICRR : fraction size of rectal reference point in ICR
ICRB : fraction size of bladder reference point in ICR

The BED Gy_{10} can be converted to a LQED for a 2 Gy fraction by dividing the BED dose by 1.2 (the relative effectiveness for a 2 Gy fraction is shown in Table 2 for two HDR fractionation schedules).

Table-2: BED Gy_{10} dose to point A for 2 HDR fractionation regimens

Group	EBRT Dose Gy/fx[3]	EBRT No. fx	HDR Dose Gy/fx	HDR No. fx	$BEDGy_{10}$ Point A	LQED Gy_{10} to Point A2 Gy/fx
A	2	25	6	3	88.8	74
B	2	25	6	4	98.4	82

Fx - fraction, Gy - Gray, No. - number

The LQED for a 2 Gy fraction to late responding tissue can be calculated by dividing the BED by 1.67 (the relative effectiveness for a 2 Gy fraction to the late responding tissues.

Assessment of response and complications: After the completion of the treatment, patients were assessed every month in order to evaluate response and adverse side effects of RT for 6 months.

In this study, the treatment outcomes and complications were assessed in each arm and compared with each other. The local control of the disease and complications were

assessed clinically up to six months post treatment in each group. Objective tumor response was made according to WHO criterion given in annexure. Radiation toxicity was assessed by RTOG acute and late morbidity scoring criteria. Doses to bladder & rectal reference point and their association with radiation induced toxicity was evaluated.

Statistical Methods: Comparison of categorical variables will be performed using Chi-square test. Statistical significance considered with p-value of <0.05 or 95% of significance.

RESULTS

In this study mean age of the patients was 50 years. The most common symptoms were post-menopausal bleeding (66%) and pain in hypogastrium (58%) which was seen most commonly in elderly women. The comorbid conditions associated with these patients were hypertension (10%), Diabites mellitus (4%) patients, and Tuberculosis (4%). All patients had common squamous cell carcinoma histopathology with majority having moderately differentiated carcinoma (32% in Group A and 48% in Group B).

Table-3: Patient Characteristics

Characteristics	Group A	Group B
	n (%)	n (%)
Age		
≤ 50 years	15 (60)	17 (68)
> 50 years	10 (40)	8 (32)
Menstrual Status		
Post menopausal	16(64)	18(72)
Peri menopausal	2(8)	3(12)
Pre menopausal	7(28)	4(16)
Parity		
Nulliparus	4(16)	0
02-Mar	6(24)	6(24)
04-Jun	12(48)	17(68)
07-Aug	3(12)	2(8)
Staging		
IB-IIA	6 (24)	7 (28)
IIB-IIIB	19 (76)	18 (72)

No grade III and IV hematological toxicity were found in the study population except one patient who had grade III Neutropenia during external concurrent chemoradiation. No grade III and grade IV radiation toxicities were seen except one patient who had grade III skin toxicity and one patient who had grade III rectal toxicity. All patients were managed conservatively for hematological and radiation toxicities.

Table 4 & 5 shows total BED and EQD2 calculated at tumor, rectum, and bladder respectively in each group A and B of all 25 patients.

Table-4: Showing BED prescribed total dose (EBRT+BT) to tumor, rectum and bladder group A and group B

S.No	Group A			Group B		
	BED Tumor	BED Rectum	BED Bladder	BED Tumor	BED Rectum	BED Bladder
1	137.3	111.03	107.35	155.3	120.64	112.94
2	137.3	129.9	92.89	155.3	112.07	100.65
3	137.3	110.17	93.11	155.3	119.09	117.53
4	137.3	112.09	91.02	155.3	114.37	113.84
5	137.3	117.54	103.19	155.3	186.58	187.05
6	137.3	106.47	118.25	155.3	120.48	115.06
7	137.3	111.41	93.29	155.3	122.78	99.09
8	137.3	112.18	109.44	155.3	123.03	110.74
9	137.3	105.045	114.03	155.3	105.81	108.5
10	137.3	104.64	88.92	155.3	117.55	93.09
11	137.3	103.19	106.23	155.3	108.47	97.31
12	137.3	104.12	99.73	155.3	140.52	102.76
13	137.3	117.2	93.64	155.3	124.11	98.38
14	137.3	120.73	98.11	155.3	119.79	126.52
15	137.3	113.23	92.61	155.3	108.62	101.54
16	137.3	116.45	93.16	155.3	114.34	118.37
17	137.3	117.5	98.58	155.3	154.29	135.07
18	137.3	110.35	108.97	155.3	108.06	93.8
19	137.3	107.71	91.72	155.3	110.99	105.89
20	137.3	107.93	104.57	155.3	121.47	113.26
21	137.3	113.51	102.67	155.3	114.23	98.84
22	137.3	109.2	102.94	155.3	131.18	104.19
23	137.3	111.1	99.71	155.3	108.36	96.69
24	137.3	105.75	113.74	155.3	120.18	113.14
25	137.3	134.82	162.99	155.3	117.78	107.48
MEAN	137.3	112.53	103.23	155.3	120.98	111.95

Table-5: Showing EQD2 prescribed total dose (EBRT+BT) to tumor, rectum and bladder group A and group B

S.No	Group A			Group B		
	EQD2 Tumor	EQD2 Rectum	EQD2 Bladder	EQD2 Tumor	EQD2 Rectum	EQD2 Bladder
1	74	66.61	64.42	82	58.39	67.77
2	74	63.94	55.74	82	53.25	60.39
3	74	52.1	55.87	82	57.46	70.52
4	74	53.26	54.62	82	54.63	68.3
5	74	56.53	61.92	82	97.95	112.23
6	74	49.88	70.95	82	58.29	69.04
7	74	52.85	55.98	82	59.67	59.45
8	74	53.31	65.67	82	59.82	66.45
9	74	49.03	68.42	82	49.49	65.1
10	74	48.79	53.35	82	56.54	55.86
11	74	47.92	63.74	82	51.09	58.39
12	74	48.48	59.84	82	70.32	61.66
13	74	56.32	56.19	82	60.47	59.03
14	74	58.44	58.87	82	57.88	75.91
15	74	53.94	55.56	82	51.17	60.93
16	74	55.87	55.89	82	54.61	71.02
17	74	56.5	59.15	82	78.58	81.04
18	74	52.22	65.38	82	50.84	56.23
19	74	50.63	55.03	82	52.6	63.53
20	74	50.76	62.75	82	58.88	67.96
21	74	54.11	61.61	82	54.54	59.31
22	74	51.52	61.77	82	64.71	62.52
23	74	52.66	59.83	82	51.02	58.01
24	74	49.45	68.25	82	58.11	67.89
25	74	66.89	97.79	82	56.67	64.49
MEAN	74	54.08	61.94	82	59.18	66.6

Total point A BED in group A was 137.3 Gy and in group B was 155.3 Gy. Total rectal BED mean in group A 112.53 Gy (103.19-134.82 Gy) and in group B 121.69 Gy (105.81-186.59 Gy) and the total bladder BED mean 103.23 Gy (88.92-162.99 Gy) and in group B 111.01 Gy (93.09-187.05 Gy) (Table-6).

Table-6: Treatment characteristics

Characteristics(Gy)	Group A (n=25)	Group B (n=25)
RT Duration (days)	56	56
No. of ICRT	3	4
Total EBRT dose	50	50
ICRT point A dose	18	24
Total point A dose	68	74
Total point A BED	137.3	155.3
Total rectal dose	54.08 (47.92-66.89)	59.18(49.49-97.95)
Total rectal BED	112.53(103.19-134.82)	121.69(105.81-186.59)
Total bladder dose	61.94 (53.35-97.79)	66.60(55.86-112.23)
Total bladder BED	103.23(88.92-162.99)	111.01(93.09-187.05)

Rectal & Bladder Reactions: There were no significant early rectal reactions (p=0.115) and early bladder reactions (p=0.55) in both the groups. Similarly there were no significant late reactions in rectum and bladder (p=1.00).

The individual BED of patients having Grade II rectum and bladder reactions in both groups was calculated (Table-7).

Table-7: Characteristics of patients with rectal or bladder late complications of grade II

S.No.	Group	Age	FIGO	Rectum	Months	Bladder	Months	Rectal BED (Gy)	Bladder BED (Gy)
1	A	55	IIA	Bleeding	8	--	--	111.033	107.36
2	A	65	IIB	Bleeding	12	--	--	106.47	118.5
3	A	58	IIA	Bleeding	7	--	--	105.04	114.03
4	B	60	IIB	Bleeding	5	--	--	114.37	113.84
5	B	55	IIB	Bleeding	10	--	--	105.81	108.5
6	B	45	IIIA	Bleeding	9	--	--	117.5	93.09
7	B	67	IB	Bleeding	12	--	--	124.11	98.38
8	A	40	IIB	--	--	Hematuria	7	116.45	93.16

Response Evaluation: In follow up, in Group A twenty one patients had complete response, four patients had partial response and in Group B twenty patients had complete response, four patients had partial response and one patient reported with progressive disease. The difference was not significant (p=0.71).

Patterns of Failure: Pelvic failure was seen in 1 patient (FIGO stage IA-IIA) and in 8 patients (FIGO stage IIB-IIIB) which was not statistically significant (p=0.71). Pelvic failure seen in both the study groups was almost similar (Group A 4; Group B 5; p=0.71).

DISCUSSION

The combination of doses in EBRT and ICBT has varied in the literature. In our institute, we used to deliver three fractions of 6Gy HDR brachytherapy at weekly intervals after EBRT of 50 Gy in 5 weeks. In our present study, dose escalation is tried to point A as recommended by American Brachytherapy Society consensus guidelines. Hence this study was done to assess the clinical response and complications in organs at risk (Rectal and Bladder).

In this study, age of the patients ranged between 26 to 67 years and average age was 50 years. Majority of the patients studied were postmenopausal. Most of the patients in the study group were multiparous.

Symptom assessment during the initial presentation shows that post menopausal bleeding, yellowish or whitish discharge per vagina , pain in hypogastrium,back pain and unexplained weight loss were the predominant symptoms. None of the patients complaint about rectal bleeding or hematuria. Gastrointestinal symptoms were seldom noted.

All the patients were of squamous cell carcinoma, among which moderately differentiated grade was the commonest (around 40%).Around half of the patients (44%) had stage IIB diagnosis and next common stage was stage IIIB (around 24%). Stage I was seen in a very small percentage (8%).

The over-all treatment duration has been reported by several authors to be of prognostic significance in patients with cervical cancer treated by radiation therapy[6,7]. The American Brachytherapy Society[8,9] recommends keeping the total treatment duration to less than 8 weeks, because prolongation of total treatment duration can adversely affect local control and survival[7,9,10]. In this present study, the duration of treatment is almost same (58 days vs 57 days) and did not influence significantly on local control. Further, the follow up time is too short to assess definitively the local control as only response was assessed at 6 months.

Analysis of hematological toxicity: All patients received concurrent Cisplatin 35mg/m^2 on weekly basis along with Radiotherapy. Overall incidence of anemia was seen slightly more in group A (48% vs 40%) which was not statistically significant (p=0.57). Most of the patients had grade 1 toxicity. Similarly overall incidence of leukopenia was seen slightly higher in group A (40 % vs 24%) which

was again not statistically significant (p=0.26). There was no grade 3 or 4 hematological toxicity in any of the patients in either group.

Analysis of gastro-intestinal toxicity: Most of the patients had grade 1 gastro-intestinal toxicity. Diarrhea was the commonest symptom observed in either groups (Group A > Group B; 44% vs 28%);(p=0.53).

The next common symptom was abdominal pain, seen slightly more in Group A (28% vs 20%) (p=0.51). It was predominantly seen in first two weeks. There was a moderate decline in 3rd and 4th week, however it persisted even on completion.

Nausea was the third most common symptom which was predominantly seen during first week of treatment (around 16%) and almost disappeared after the completion of treatment. It can be attributed to the emetic chemotherapy drug cisplatin, though precautions were taken by prescribing anti-emetics intravenously pre-chemotherapy and oral post-chemotherapy.

In the study of Akbarov et al[11] the incidence of Grade 1 upper GI toxicity (nausea, vomiting, dyspepsia and pain abdomen) was 93.3% which is negligible in our study. In fact, our study reveals around 16% of grade 2 reactions. The reason of lesser reactions grade 1 reactions may be due to increased support of prophylactic oral medications. Grade 1 lower GI toxicity (diarrhea) was 73.3% in the same study which is again more than our study, but the grade 2 toxicity is higher in our cases (38%). But the incidence of grade 2 diarrhea is almost similar to the study by Bhavraju et al (38% vs 34%)[12]. The reason for increased grade 2 toxicity in our study may be that our group of Indian patients are already malnourished. Further, they are illiterate to understand and practice the diet counseling done to them[11]. The overall percentage of Grade 2 toxicity in our study was 38% when compared to Keys et al[13] 26.7%, Rose et al[14] 32 % and Gupta et al[15] 50%. The overall percentage of Grade 3 toxicity in our study was 2% when compared to Keys et al[13] 9.2%, Rose et al[14] 4.5%, Gupta et al[15] 4.7% and Saibish Kumar et al[16] 8.8%. None of the patients in our study had Grade 4 toxicity when compared to Keys et al 4.9%, Rose et al 2.2% and Gupta et al 0%[13-15].

Analysis of bladder toxicity: Cystitis, vaginal discharge, bleeding per vagina, perineal pain were predominatly seen in early and middle of treatment (week 1-week 3) and incidence of these symptoms gradually decreased during later phases of treatment and completion.

Genitourinary toxicity was significantly less. Bladder and urinary symptoms such as cystitis, urethral pain, urinary frequency and urgency were seen in the first 6 weeks post treatment, which gradually declined over the next 6 weeks.

The overall percentage of Grade 1 GU toxicity in our study was noted in 28% of patients when compared to Akbarov et al[11] 23.4%, Keys et al[12] 23.4%, Rose et al[13] 6.25% and Gupta et al[14] 57%. The overall percentage of Grade 2 GU toxicity in our study was noted in 4% when compared to Akbarov et al 0%, Keys et al 7.6%, Rose et al 3.4% and Gupta et al 7%. There was no Grade 3 or 4 GU toxicity in our study when compared to Keys et al 0.5%, Rose et al 1.7%, Gupta et 0% and Akbarov et al 0% for grade3 reactions and . when compared to Key et al 1%, Rose et al 1.1%, Gupta et al 0% and Akbarov et al 0% for grade 4 reactions. Our results are consistent with the national and international studies[11, 13-15].

Correlation between ICRU rectal and bladder reference point BED doses and severity of reactions in these organs at risk

A retrospective study done in Japan showed[17] that concurrent chemo-radiotherapy using HDR-ICBT is feasible and efficacious for patients with loco regionally advanced uterine cervical cancer. They demonstrated that those patients who received a cumulative rectal BED of more than 100 Gy_3 had significantly higher incidences of proctitis than those who received less than 100 Gy_3 ($p = 0.013$).

Similarly, a study done in Brazil[18] found that the 5 years actuarial incidence of late complication depends on total BED dose to the organ at risk.

The significant correlation was found between the dose calculated and measured at the rectal point defined by the ICRU and the incidence of late rectal complications. Using the linear quadratic model, they established a threshold value for the possibility of developing late rectal complication of 125 Gy_3, which is unrelated to the number of HDR fractions but rather to the total dose delivered to the rectal point by the combination of EBRT and HDR brachytherapy. Thus, keeping the biologically effective dose below 125 Gy_3 at the defined ICRU rectal point will minimize the risk of late rectal toxicity. The late rectal damage is a function of total biological effective dose to ICRU rectal point and not of the number of HDR BRT fractions[18].

In our present study, the mean BED values at the ICRU 38 rectal reference point for group A and B are 112.53 Gy_3 (range: 103.19-134.82 Gy_3) and 120.98 Gy_3 (range: 105.81-186.59 Gy_3) respectively. There are three patients in group A and four patients in group B who had grade 2 rectal reactions. Rest of patients had grade 0-1 and none of the patient had grade 3-4 rectal reactions. The details of the seven patients of grade 2 rectal reactions has been shown in Table 7. The rectal BED dose of all three patients in group A is less than their median values (i.e less than 112.53 Gy_3). In group B, the rectal BED dose of three patients is less than their median values (less than 120.98 Gy_3) while the fourth patient had rectal BED of 124.11 Gy_3 (slightly more than the median value). There is no correlation identified between BED dose to rectum and rectal reactions. The incidence of grade 2 rectal reactions in group A and B is 12% vs 16%. The difference is statistically not significant (P=1.00) .

The rectal BED dose relationship with the rectal reactions could not be established in this study, may be, because of small group of patients and lesser time of follow up. Long term follow up as well as greater cohort of patients is required to find out the optimum rectal BED Gy_3 at which grade 2 or more reactions will be precipitated.

The mean BED values at the ICRU 38 bladder reference point for group A and B are 103.23 Gy_3 (range: 88.92-162.99 Gy_3) and 111.01 Gy_3 (range: 93.09-187.05 Gy_3) respectively. There is only a single patient in group A and none in group B who had grade 2 bladder reaction. Rest of patients had grade 0-1 while none of the patient had grade 3-4 bladder reactions. The patient presented with grade 2 bladder reaction after 2 months and had the bladder BED dose of 93.16 Gy_3 which is less than the mean value (103.23 Gy_3). The incidence of bladder reactions is group A and B is 4% vs 0%. Similar to rectal reactions the difference in bladder reaction is also not statistically significant (p=1.00).

Again, the bladder BED dose relationship with the bladder reactions could not be established in this study because of small group of patients and lesser time of follow up. Long terms follow up as well as greater cohort of patients will be required to find out the optimum bladder BED Gy_3 at which grade 2 or more reactions will be seen.

In general, there is more variability in the rectal dose reports. As in some series, the point for calculation of the rectal dose is pre-determined and others take into account several points along the anterior rectal wall. Nevertheless, the different series do show a correlation between rectal dose and complications[19]. In spite of the variations in the way the rectal doses are calculated, a cumulative dose of 75 Gy can result in a 10% incidence of proctosigmoiditis. With higher rectal doses, the incidence of proctosigmoiditis also increases[20,21]

Esche et al[20,22] showed that the frequency and severity of proctitis increases with cumulative rectal doses and volume treated. The majority of the recto-sigmoid complications occurred with cumulative rectal dose in excess of 70 Gy. Perez et al[3] has reported on the correlation of the dose with genitourinary and recto-sigmoid complications.

In our present study, only two patients in group B received rectal dose 78.58Gy and 97.95 Gy, but they did not present with any rectal reactions in 6 months follow up. Long term follow up is needed to confirm.

In another study by Tigeneh W et al[23] the frequency of the grade II and III irradiation induced complications with bladder and rectal doses of 80 Gy is 5% but rises steeply with doses above this level. Grade 3 and 4 rectal complications increased when the dose to the rectal reference points was beyond 105 Gy_3. The chance of grade 3 and 4 bladder irradiation induced toxicity increased when the dose to the bladder reference point was above 120 Gy_3. The rate of radiation induced grade 3 and 4 bladder and rectal toxicity increased in those patients received prescribed EBRT in two fields than four fields. Among 12 patients who developed grade 3 and 4 radiation induced toxicity, seven of them were stage IIIB and the remaining five patients were stage IIB.

In our study, majority of our patients (92%) had rectal reference dose beyond 105 Gy_3 and only one patient had bladder reference dose more than 120Gy_3. None of our patients have shown grade 3 o 4 rectal or bladder reactions in a follow up of 6-12 months. The results are not consistent with the previous study. Long term results will show the authenticity of our results.

There are usually limitation factors in most of the studies with the respect of to the analysis and data may affect the accuracy of the results. Limitation of this study (limited frame time and limited number of patients) are the possible causes of some of the results differing to the other studied that are done previously.

Patterns of Failure: There was no significant difference (P=0.71) in the patterns of failure seen in both the groups.

Local disease control: In previous years, different studies have shown that HDR brachytherapy with concomitant chemo-radiotherapy is safe and effective in management of locally advanced cervical cancer. Patel et al[24] studied 412 patients diagnosed with stage III cancer of the cervix treated with EBRT. Patients were randomized to receive either 18 Gy in 2 fraction of 9 Gy each or 35 Gy by continued low dose rate BT. The five years survival, local control and distant failure were not significantly different and there was no evidence of increased toxicity in HDR group. More recently at the end of 2001 a study done in Albert Einstein College of Medicine[25] showed that 2 fraction of HDR brachytherapy of 9 Gy each with concomitant EBRT to the pelvis provided similar local control without increasing toxicity.

In the present study, all the patients of both groups were under follow up till six months. There was complete response in 80% and 84% patients of group A and B respectively. These patients did not show any local or regional recurrence during the follow up of 6 months. Therefore, there was no significant difference seen in the local disease free survivals. Though we have delivered high dose to point A in group B, long term follow up will dictate whether it will be helpful to have better local control or not.

CONCLUSION

With the recent American Brachytherapy Society consensus guidelines, we need to increase the local tumor dose with tolerable reactions to rectum and bladder.

This can be achieved by careful attention in the application of intracavitary and thereafter using TPS for radiotherapy planning and modulating it according to the dose tolerances of normal tissues. This would help to deliver higher dose to the tumor with acceptable acute and long term toxicities to rectum and bladder.

In our present study, we increased one application of 6Gy HDR brachytherapy to increase the dose to point A and in a follow up of 6 months we did not find any significant difference in toxicities of rectum and bladder. Long term follow up is needed to see for late rectal and bladder toxicites.

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