Original research article

CONVENTIONAL VERSUS THREE-DIMENSIONAL CONFORMAL EXTERNAL RADIOTHERAPY IN CANCER CERVIX: A COMPARATIVE STUDY FOR COMPLIANCE, RESPONSE AND TOXICITY

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Abstract

Introduction: Cervical cancer is the second most frequent cancer among Indian women. Radiotherapy is the cornerstone of treatment in all its stages. Three-dimensional conformal radiotherapy (3DCRT) combines multiple radiation fields to deliver precise dose of radiation to the affected area. Tailoring each of the radiation fields to focus on the tumor delivers a high dose of radiation to the tumor and avoids nearby healthy tissue. The present study is done to compare conventional radiotherapy versus 3DCRT in cancer cervix for compliance, clinical response and toxicity.

Material and Methods: Fifty patients were enrolled and randomised into two radiotherapy plans with radical intent - Group A treated by conventional radiotherapy and group B treated by 3DCRT. Concurrent cisplatin was delivered on weekly (35mg/m^2) or tri-weekly (75mg/m^2) basis during external beam Radiotherapy and was followed by High Dose Radiotherapy Brachytherapy. Clinical response and complication assessment were evaluated.Collected data was analyzed using standard statistical methods and softwares to calculate level of significance using "p" value by chi square test.

Results: In this study mean age of the patients was 48 years (26-67 years). The anemia was the most common side effect seen in both groups (96% vs 88%, p=0.29). Neutropenia was more in group B (36% vs 44%, p= 0.56). Lower GI toxicity was seen only in patients in group A (20% vs 0%, p=0.018). In follow up there were no significant early rectal and bladder reactions in both groups and 2 patients in each group had late rectal reactions of grade I and II (p= 0.312). No significant skin, bladder and small intestinal toxicity were seen in both groups.

Conclusions: Conventional radiotherapy gives equally efficacious response though accompanied by toxicities which were acceptable.

Keywords: Cancer cervix, radiotherapy, conventional, conformal, response, toxicity

INTRODUCTION

Conventional techniques have historically used blocks based on bone landmarks, potentially under dosing the target, and including large volumes of the bowel, rectum, bladder, bone and Bone Marrow (BM) in the treatment port. Studies have found higher incidence of adverse reactions by using conventional concurrent chemoradiation.[1,2] Classic pelvic dose distributions therefore do not maximize the therapeutic ratio of radiation therapy.

One of the methods to reduce toxicity and improve therapeutic ratio is better target delineation and sparing of normal tissues. This concept led to the exploration of using conformal techniques like Three Dimensional Conformal Radiotherapy (3DCRT). It uses information obtained from MRI and CT scanning to identify visible tumour and organs at risk that need to be included or excluded. 3DCRT has been shown to give better and more precise target coverage (20% reduction in the risk of a geographical miss) and has significantly reduced the volume of radiation-exposed bladder and bowel.[3,4] Thus, 3DCRT improves patient tolerance to curative treatment and further allows for dose escalation.[5]

Present study was done to assess the compliance, clinical response and toxicities in patients with cancer cervix treated with external beam radiotherapy by either conventional or three dimensional conformal radiotherapy.

MATERIAL AND METHODS

Fifty biopsy proven cancer cervix patients with age>18 years and normal hematological and biochemical

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parameters along with normal kidney, liver and cardiac functions were enrolled in this study. Patients with FIGO stage IV and metastatic diseases were excluded. Patients were randomised into two radiotherapy groups - Group A treated by conventional radiotherapy and group B treated by 3DCRT. All patients received 50 Gy in 25 fractions at 2 Gy per day.Concurrent cisplatin was delivered on weekly (35mg/m^2) basis during External Beam Radiotherpy (EBRT) and was followed by 3 applications of intracavitary brachytherapy of 6 Gy/ fraction each.

Conventional radiotherapy was planned by four field box technique (AP-PA and two laterals) using standard bony landmarks. Anterior/Posterior field- Superior: L4/L5 junction; Inferior: 3 cm distal to vaginal marker placed in vagina, Lateral: 1.5 to 2.0 cm beyond pelvic brim. Lateral field- Superior and inferior: As in AP field; Anterior- Anterior border of pubic symphysis; Posterior- S2/S3 junction.

For 3DCRT, Gross Tumor Volume(GTV). Clinical target Volume1 (Tumor CTV1) (including GTV, uterus, vagina, bilateral parametrium), CTV2 (Nodal CTV) (including pelvic lymph nodes – common iliac, external iliac, internal iliac, obturator and presacral) were delineated. PTV was taken 1.5 cm beyond CTV.

Clinical Response Assessment: Clinical response was assessed during radiotherapy and every month after radiotherapy for atleast 6 months. The patients were assessed for objective tumor response according to WHO criterion: Complete response (CR), Partial response (PR), Stable disease (SD) and Progressive disease (PD).

Complication Assesment: Patient were assessed weekly during chemoradiation and thereafter on monthly basis during follow up for radiation reactions. Radiation toxicity was assessed by Radiation Therapy Oncology Group (RTOG) acute and late morbidity scoring criteria. Complete blood counts, kidney function tests and liver function tests were repeated in all patients every week before each chemotherapy cycle. Haematological toxicities were graded according to common toxicity criteria 2.

The patients were followed monthly up to at least 6 months from day of completion of treatment.

Statistical Analysis: Collected data was analyzed by chi square test. Statistical significance considered with p-value of <0.05.

RESULTS

Compliance: Patients characteristics have been shown in Table-1. All patients completed the planned radiotherapy treatment. There was no prolongation of treatment in patients in both groups as all patients completed the treatment within eight weeks. (Table-2)

Table-1 : Patient Characteristics

	Group A No of Patients (%)	Group B No of Patients (%)
Age (years)		
21-30	2(8)	0(0)
31-40	2(8)	5(20)
41-50	18(72)	10(40)
51-60	3(12)	5(20)
61-70	0(0)	5(20)
Co- morbidities		
Hypertension	01(04)	03(12)
Diabites mellitus	02(08)	00(00)
Tuberculosis	02(08)	01(04)
Stage		
IB	0(0)	1(0)
IIA	1(4)	9(36)
IIB	16(64)	7(28)
IIIA	1(4)	2(8)
IIIB	7(28)	6(24)
Histopathology		
Squamous Cell Ca	24(48)	24(48)
Adenocarcinoma	01(02)	01(02)
Parametrial Extension		
Unilateral	12(50)	03(23)
Bilateral	12(50)	10(77)
Lymph nodes		
Not present	23(92)	14(56)
Present	02(08)	11(44)

Table-2 : Treatment Characteristics

	Group A	Group B
EBRT Duration		
Mean	34	36
Median	34	35
Overall treatment time		
Mean	55	54
Median	54	54

Response Evaluation: Following EBRT, 64% of patients in group A and 56% of patients in group B had CR. At 6th month follow up, 84% of the patients in group A and 88% of patients in group B had CR. 3 patients in group A had progressive disease. The pelvic failure was found in stage IIB-IIIB, in 4 patients of group A and 3 patients of group B. The difference was not statistically significant (p=0.130). (Table-3)

The pelvic failure in stage IA-IIA is only in 1 patient which belonged to group B. In stage IIB-IIIB, pelvic failure was seen in 4 patients of group A and 3 patients of group B. The

Table-3 : Response Evaluation

Response evaluation	Response	Group A	Group B	p-value (Chi-square test)
At the end of Treatment	CR	16(64)	14(56)	0.564
	PR	09(36)	11(44)	
At 6 Months Post treatment	CR	21(84)	22(88)	0.091
	PR	01(04)	03(12)	
	PD	03(12)	00(00)	

Table-4 : Pelvic Failure Versus Stage

Stage	Group A	Group B	p-value (Chi-square test)
IA-IIA	0	0	0.13
IIB-IIIB	4	3	
	0.656	0.132	

difference was not statistically significant (p=0.329). (Table 4)

Hematological toxicites during treatment (Table-5): All 50 patients during treatment underwent weekly assessment of hematological parameters. It was seen that 04(08%) patients had normal hemoglobin level, 25(50%) patients had grade I toxicity and 21(42%) patients had grade II reaction. Hemoglobin was tried to maintain throughout the treatment by blood transfusion, oral hematinics and the dietary advice. Grade 2 anemia was seen in 13(52%) patients in group A and 8(32%) patients in group B, but the difference was not statically significant (p=0.152).

Comparing TLC levels, 30 (60%) patients had normal TLC level, 14(28%) patients had grade I neutropenia and 5(10%) patient had grade II neutropenia. 1(2%) patient had grade III neutropenia who belonged to group A. In 43(86%) patients the DLC was normal, while 04(08%) and 02(04%) patients showed grade I and grade II toxicity, respectively. There was no decrease seen in the count of platelets.

There was grade I toxicity seen in 03(06%) patients and the remaining patients had serum creatinine within normal limits. The level of serum urea did not show much difference in all patients. There was no change seen in level of serum bilirubin except 01(02%) patient who had grade I toxicity.

Table-5 : Hematological Toxicity Grading During Treatment

Hematological Parameters	No. of Patients							
	Group A				Group B			
	Grades				Grades			
	0	1	2	3	0	1	2	3
Hemoglobin	1	11	13	0	3	14	8	0
TLC	16	6	2	1	14	8	3	0
DLC(Neutrophils)	21	3	1	0	22	1	2	0
Platelet	25	0	0	0	25	0	0	0
Serum urea	25	0	0	0	25	0	0	0
Serum creatinine	24	1	0	0	23	2	0	0
Serum bilirubin	25	0	0	0	24	1	0	0

No grade III & IV hematological toxicity was found except one patient who had grade III Neutropenia in group A.

Acute radiation toxicities: Grade 1 skin toxicity was seen in 20(80%) patients of group A and 21(84%) patients of group B. Grade 2 and 3 skin toxicity was found in 16% patients of group A and 8% patients in group B (p value= 0.38).

Mucosal reactions of grade 2 were seen in 3(12%) patients in group A and 5(20%) patients in group B (p value= 0.44). Grade 1 bladder reactions were present in 2 patients, one each in group A and group B.

Grade 2 rectal reactions were found in 5(20%) patients of group A but none (0%) in group B (p value= 0.018, significant).

Small intestine toxicity was seen in both groups. Grade 1 toxicity was seen in 10(40%) patients of group A and 14(56%) patients of group B. Grade 2 toxicity was seen in 4(16%) patients of group A and 2(8%) patients of group B (p value= 0.38). All patients were manageable conservatively for radiation reactions. (Table- 6)

Late radiation reactions: Grade 1 mucosal reaction was seen in 1(4%) patient of group A and in group B, 5(20%) patients had grade 1 reactions and 1(4%) patient had grade 2 reaction.

Bladder reaction was seen in 1(4%) patient in group A which was grade 1. Rectal reactions were seen in 2 patients each in group A and group B. Grade 2 reaction was present in 1(4%) patient in group A, while the rest were grade 1 reactions. None of the patients showed skin reactions or small intestinal toxicity on follow-up. None of the patients

Table-6 : Acute Reactions During Treatment

	No. of Patients							
	Group A				Group B			
	Grades				Grades			
	0	1	2	3	0	1	2	3
Skin	1	20	4	0	2	21	1	1
Vaginal Mucosal	0	22	3	0	0	20	5	0
Bladder	24	1	0	0	24	1	0	0
Rectal	14	6	5	0	20	5	0	0
Small Intestine	11	10	4	0	9	14	2	0

Table-7 : Late Radiation reactions

	No. of Patients								p-value (Chi-square test)
	Group A				Group B				
	Grades				Grades				
	0	1	2	3	0	1	2	3	
Skin	25	0	0	0	25	0	0	0	-
Mucosal	24	1	0	0	19	5	1	0	0.12
Bladder	24	1	0	0	25	0	0	0	0.513
Rectum	23	1	1	0	23	2	0	0	0.312
Small Intestine	25	0	0	0	25	0	0	0	-

in both groups showed grade 3/4 toxicities. (Table 7)

DISCUSSION

Sectional CT enables the visualization and delineation of the cervix, uterus, vagina, iliac vessels, and organs at risk such as bladder, rectum, and intestine and therefore, 3DCRT has become a preferred treatment for gynecologic malignancies. It gives better, more precise target coverage while reducing the risk of a geographical miss by 20%.[6] Studies have shown that 3DCRT improves patient tolerance to curative treatment and allows for dose escalation.[7]

Hence this study was done to assess the compliance, clinical response and toxicities in patients with cancer cervix treated with external beam radiotherapy by either conventional or three dimensional conformal radiotherapy along with concurrent chemotherapy followed by HDR Brachytherapy applications.

Overall Treatment Time (OTT): 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.[8,9] The American Brachytherapy Society[10,11] recommends keeping the total treatment duration to less than 8 weeks, because prolongation of total treatment duration can adversely affect local control and survival.[8,9,12]

According to a univariate analysis done in Brazil, the overall treatment time with cohort value of 50 days was a statistically significant factor for five years actuarial local control rate (84% vs 53%, p = 0.008).[13]

According to a retrospective case-control study (Bhagat et al., 2015) minimizing the treatment time and avoiding any planned or unplanned interruptions or delays by timely integration of external beam and intra-cavitary irradiation may yield a better local control in locally advanced cervical cancer.[14]

In this present study, the mean duration of treatment is almost same (55 days vs 54 days) and did not influence significantly on local control. Further, the follow up time is too short to assess definitively the local control as response was assessed at 6 months only.

Hematological Toxicities During Treatment: Hematologic toxicity can lead to delayed or missed chemotherapy cycles and treatment breaks, which potentially may compromise disease control. The hematopoietic stem cells of the bone marrow are very sensitive to radiation.[15] It is shown that increased dose to the bone marrow and increased volume of the marrow in the field of radiation can proportionately increase the risk of acute hematological toxicities.[16] Pelvic bones, proximal femur and lumbar vertebra contain 34.5%, 4.5%, and 16.6% of the functional bone marrow in an adult.[17] Nearly 50% of body bone marrow is in pelvic and neighboring bones, which come in the field of radiation in the treatment of carcinoma cervix.

In the study by Che SM et al, the rate of bone marrow depression between the 3DCRT and conventional RT groups were respectively 71% and 63% with no significant difference (p>0.05).[18]

In the three dimensional conformal planning, we shielded the proximal femur, thereby reducing the volume of marrow in the radiation field. As a result we found that grade 2 anemia was less in conformal arm (32% versus 52%). However, the difference was not statistically significant (p-value=0.152).

Acute Radiation Reactions: Hanks et al have shown that conformal RT (compared with standard techniques of external beam therapy) decreases RTOG-EORTC grade 2 acute morbidity in prostate cancer patients, improves patient tolerance to curative treatment and allows for dose escalation.[19]

Hsieh CH found that side effects of 3DCRT were significantly lower than those of 2DRT (31% vs 23%).[20]

In the study by Che et al, it was seen that the rate of acute radiation reactions of the rectum between the 3DCRT group and conventional RT group were respectively 46% and 80% , with a significant difference (P < 0.05). The rates of acute radiation reaction of the bladder between two groups were respectively 7% and 3% with no significant difference (p>0.05).[18]

In the study by Zhou et al, on comparing conventional and 3D-conformal radiotherapy for toxic effects, except for the I–II grade rectal and bladder reaction which was lower in the 3DCRT group (P = 0. 007 and P = 0. 006), the side effects were similar and well tolerated in both groups.[21]

In our study, grade 2 and 3 skin toxicity was more in conventional arm (16% versus 8%) which was not found to be statistically significant. Grade 2 mucosal reactions were slightly more in conformal arm (20% versus 12%), but this difference was also statistically not significant. Grade 2 rectal reactions were found to be significantly higher in conventional arm (20% versus 0%) (p value= 0.018).

Response Evaluation: Our results are in conjunction with the results of various studies in which concurrent chemotherapy was used with conventional radiotherapy.

Sorbe B et al conducted a study in which carcinoma cervix patients were treated with concurrent chemoradiotherapy (conventional radiotherapy) and intracavitary brachy therapy. It was observed in this study that patients with squamous cell carcinoma had a complete response rate of 96%.[22] In a retrospective study by Tharavichitkul E et al it was observed that local control rates in patients who received conventional radiotherapy with concurrent chemotherapy (cisplatin) was between 84 to 96% depending on the number of cycles received.[23]

In the study by Che SM et al, in which the clinical treatment effect of 3DCRT in cervical carcinoma was compared with conventional radiotherapy, it was observed that the local control rates in the treatment group and the control group were respectively 96% and 97%, with no significant difference ($P > 0.05$).[18]

In our study, the local control rates were 84% and 88% respectively in groups A and B (p value= 0.091) and were similar to the results of Che SM et al study.

CONCLUSION

In the present study, we conclude that conventional radiotherapy gives equally efficacious response though accompanied by toxicities which were acceptable. Hence, conventional radiotherapy is an acceptable technique for management of cancer cervix in developing countries where higher technologies are not available in each centre.

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