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High Dose Rate Intracavitary Brachytherapy (Post External Beam Radiotherapy) For Carcinoma Of Cervix – Comparision Of Two Different Fractionation Regimens For Clinical Response And Complication In Organs At Risk

Owais A

Sumera S

Senior Resident, Department of Radiotherapy, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, U.P

Kumar P

Professor & Head, Department of Radiotherapy, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, U.P

Chauhan AK

Professor, Department of Radiotherapy, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, U.P

Nigam J

Medical Physicist, Department of Radiotherapy, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, U.P

Abstract: ***Cervical cancer is the third most common malignancy in women worldwide, accounting for 9 % of the total new female cancer cases. Primary treatment selection is guided by tumor stage. For those who are diagnosed at the locally advanced stage, concurrent chemo-radiotherapy (CCRT) is currently the standard care. Histological and quantitative pathological prognostic factors in cervical carcinoma include age, tumour size, stage of disease, tumour grade, histological type, performance status, lymph-vascular space involvement, endometrial extensions, peritoneal cytology have been shown to affect therapeutic outcome. Present study was designed to look for clinical profile of patients with carcinoma cervix presented in our department.***

I. INTRODUCTION

Cervical cancer is the third most common malignancy in women worldwide, accounting for 9 % of the total new female cancer cases.[1] 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 with an estimated 528,000 new cases diagnosed annually.[2] Cervical cancer is the second most common cancer in India accounting for 22.86% of all cancer cases in women and 12% of all cancer cases in both men and women. It is third largest cause of cancer mortality in India accounting for nearly 10% of all cancer related deaths in the country. About 1,23,000 new cases and 67,500 Deaths are registered annually. Common median age is 38 years (age 21–67 years).The relative five year survival averages to 48.7%. The survival chance of a person becomes better if the cervical cancer is diagnosed and treated at earlier stages. Therefore it is important to avail of cervical cancer screening.[3]

Primary treatment selection is guided by tumor stage. For those who are diagnosed at the locally advanced stage, concurrent chemo-radiotherapy (CCRT) is currently the standard care, as ineffective treatment is associated with increased toxicity and morbidity, accelerated tumor growth, a delay in commencing alternative, potentially effective treatment, and unnecessary expense.[4]Radiotherapy (RT) plays a major role in the treatment of invasive uterine cervical carcinoma. Early invasive tumors are managed with either radical surgery or RT. Locally advanced tumors are treated with RT with or without chemotherapy. 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. The term "brachytherapy" (BT) refers to a strategy of implanting sealed radioactive sources either in close proximity to or in contact with the target tissue. The success of brachytherapy may be attributed to the delivery of a high radiation dose to the tumour while sparing the surrounding normal tissues.[5] Brachytherapy is the only demonstrated method of providing the high dose required to control cervical cancer (80 Gray [Gy]), without causing undue side effects.[6]

The external beam portion of treatment encompasses treatment to the pelvic lymph nodes, parametria, and primary tumor, to a dose adequate to control microscopic disease. The addition of brachytherapy serves to boost the gross tumor, and improves disease control and survival. The addition of chemotherapy serves predominantly as a radio sensitizer, resulting in improvements of about 5% in overall survival.[7]

Based on the linear quadratic model, the biological effective dose (BED) to point A is a contribution from EBRT and HDR brachytherapy. The BED for the tumor may be determined for tumors using an α/β ratio of 10, which is used for early responding tissues. The total BED at rectal and bladder reference points may be determined by using aα/β ratio of 3 which is used for late responding tissues. The equation written below may be used in the calculation for total BED dose to gross tumor volume (GTV) as a contribution of both EBRT and brachytherapy as well as to critical organs (rectum, bladder and small intestines).

Total BED = BED (EBRT) + BED (HDR)

Total BED = nd[1+(d/α/β)] + Br [1+(d/α/β)]

Present study was designed to look for dose escalation to point A 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, bladder and small intestine.

II. AIM AND OBJECTIVES

Comparison of two different fractionation regimens of high dose rate intracavitary brachytherapy (post external beam radiotherapy) for carcinoma of cervix for clinical response and complication in organs at risk.

- ✓ To analyze clinical response and complications in organs at risk (Rectal, Bladder and small intestine) in Group-A receiving (6 Gy per fraction X 4 applications).
- ✓ To analyze clinical response and complications in organs at risk (Rectal, Bladder and small intestine) in Group-B receiving (7 Gy per fraction X 3 applications).
- ✓ Compare the clinical response and complications in organs at risk (Rectal, Bladder and small intestine) in Group-A and Group-B.

III. MATERIAL AND METHODS

The study was done in Department of Radiotherapy at R.R. Cancer Institute and Research Centre, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly a tertiary health care centre.

STUDY DESIGN: Prospective study

STUDY POPULATION: All the patients included in this study were histologically proven cases of cancer cervix taken from our OPD. Fifty patients of cancer cervix were enrolled into this study.

STUDY DURATION: July 2014 to June 2016

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/m^2

INCLUSION CRITERIA

- ✓ Biopsy proven cancer cervix
- ✓ Age $\geq$ 18 years
- ✓ Karnofsky performance scale above 70
- ✓ Stage IB_1 to IIIB
- ✓ No history of previous malignancy
- ✓ Hepatic, Renal, and Cardiopulmonary functions are adequate

EXCLUSION CRITERIA

- ✓ Carcinoma of the cervix FIGO stage IV patients
- ✓ Metastatic disease
- ✓ Any previous pelvic surgery, radiotherapy or chemotherapy

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. Radiation toxicity was assessed by RTOG acute and late morbidity scoring criteria. The doses to bladder and rectal reference point and their association with radiation induced toxicity was evaluated.

IV. RESULTS

In this study mean average age of the patients was 48 years (30-67 years) and the most common age group was 41-50. Most of the women were post menopausal and multiparus. Most common symptoms seen are bleeding p\v, whitish discharge, pain in abdomen, and pain in lumbo sacral area, unexplained weight loss. There was no symptoms of rectal bleeding, hematuria are seen in any patients. There is no any significant relationship seen between in co morbid conditions like hypertension, Diabetes mellitus and Tuberculosis. Most common FIGO stage seen is IIB. All patient had same histopathology sguamous cell carcinoma. The anemia is the most common side effect seen in both group A 64% and group B 36% patients with p-value 0.477 which was not significant. Diarrhea 20% in group A and 40% in group B with p-value 0.122 which is also not significant. Neutropenia seen in 28% in group A and 24% in group B with p-value 0.747. In few patients abdominal pain and nausea/vomiting was also noted. Few patients were there with no any significant complaint. The treatment characteristics in group A and group B. Showing total point A BED in group A was 98.40 Gy and group B 95.91 Gy. Total rectal BED mean in group A 116.77 Gy and in group B 114.09 Gy and the total bladder BED mean in group A was 107.63Gy and in group B 112.09 Gy.

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In follow up there were no cases of any grade of early rectal reaction noted in Group A or B. p-value was not applicable. There was one patient reported with Grade I reaction in Group A rest all patient in Group A had no any significant early genito-urinary symptoms. In group B one patients presented with a Grade II reactions and no any genito-urinary symptoms noted in Group B. The p-value was one which is not significant. There were three patient reported with Grade I reaction in Group A rest all patient in Group A had no any significant early small intestinal symptoms. In group B no patients presented with any reactions. The p-value was 0.740 which is not significant. In analyzing late lower gastrointestinal symptoms we observed that six patient with grade I rectal reactions in Group A and in Group B no patient was reported with any reactions. The p-value was 0.0090 which was significant. In Group A there were one patient of Grade II genitourinary symptoms. In Group B there were no patients of any genitourinary symptoms. The p-value was one which was not significant. In Group A there were one patient of Grade I small intestinal reaction. In Group B there were no patients of any small intestinal reaction. The p-value was one which was not significant.

In follow up we were observed that in Group A Twenty one patients had complete response and four patients had partial response and in Group B twenty two patients had complete response and three patient had partial response and no patient was reported with progressive disease. The p-value was 0.712 which was not significant. There was no failure in any stage of any group. The p-value is not applicable. 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, long term follow up will dictate whether it will be helpful to have better local control or not. In our present study, dose escalation at point A was done to see whether our group of Indian patients can tolerate such dose escalation without increase in toxicity to the organs at risk – rectum, bladder and small intestine. 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 toxicities.

Number of patients showing hematological toxicity during treatment						
hematological parameters	Grade 1		Grade 2		Grade 3	
	A	B	A	B	A	B
Hemoglobin	13(52%)	8(32%)	2(8%)	2(8%)	0	0
Tlc	4(16%)	6(24%)	2(8%)	3(12%)	1(2%)	0
Platelet	0	0	0	0	0	0
serum urea	0	1(2%)	0	0	0	0
serum creatinine	0	0	0	0	0	0
serum bilirubin	0	0	0	0	0	0

Showing hematological toxicity grading

Response	Group A	Group B	P-value
CR	21	20	0.712
PR	4	4	
SD	0	0	
PD	0	1	

Characteristics(Gy)	Group A (n=25)	Group B (n=25)
RT Duration(days)	57	55
No. of ICRT	4	3
Total EBRT dose	50	50
ICRT point A dose	24	21
Total point A dose	74	71
Total point A BED	98.40	95.70
Total rectal dose	65.44	62.18
Total rectal BED	116.77	114.14
Total bladder dose	61.27	61.53
Total bladder BED	107.63	107.03

V. DISCUSSION

In our present study, dose escalation is tried at point A to see whether our group of Indian patients can tolerate such dose escalation without increase in toxicity to the orga.

ANALYSIS OF HEMATOLOGICAL TOXICITY

All patients received concurrent Cisplatin along with RT. Overall incidence of anemia was seen slightly more in group A (64% vs. 36%) which was not significant statistically (p=0.477). Most of the patients had grade 1 toxicity. Very few had grade 2 toxicity. Similarly overall incidence of leucopenia was seen slightly higher in group A (28 % vs 24%) which was again not statistically significant (p=0.747). Grade 3 leucopenia was seen in only one patient of group A. There was no grade 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 B > Group A; 40% vs 20%). The difference was not statistically significant (p=0.122).

The next common symptom was abdominal pain, seen slightly more in Group A (52% vs. 36%) which was again not statistically significant (p=0.254). It was predominantly seen in first two weeks. There was a moderate decline in third and fourth week, however it persisted even on completion.

Nausea was the third most common symptom which was predominantly seen during first week of treatment more in group A (40% vs 36%) 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 the incidence of Grade 1 upper GI toxicity (nausea, vomiting, dyspepsia and pain abdomen) was 93.3% which is about 40%in our study. In fact, our study reveals around 40% (4 % in group A and 36% in group B) 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 I toxicity is higher in our cases

(group A-16% vs group B-12%). Also, in the study by Serkies et al the incidence of grade 2 diarrhea is 5% which is again less than our study. But the incidence of grade 1 diarrhea is less than to the study by Bhavraju et al (38% vs. 0%)[35]. The reason for increased grade 1 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 1 toxicity in our study was 28% when compared to Keys et al 26.7%, Rose et al 32 % and Gupta et al 50%. The overall percentage of Grade 3 toxicity in our study was 0% when compared to Keys et al 9.2%, Rose et al 4.5%, Gupta et al 4.7% and Saibish Kumar et al 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% .

ANALYSIS OF BLADDER TOXICITY

Cystitis, vaginal discharge, bleeding per vagina, perineal pain were predominately 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 very less group of patients particularly 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 10% of patients when compared to Akbarov et al 23.4%, Keys et al 23.4%, Rose et al 6.25% and Gupta et al 57%. The overall percentage of Grade 2 GU toxicity in our study was noted in 0% 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. [12,13,14,15]

ns at risk – rectum, bladder and small intestine.

In our present study, the mean BED values at the ICRU 38 rectal reference point for group A and B are 116.77 Gy and 114.09 Gy respectively. There are four patients in group A and three patients in group B who had grade 1 rectal reactions. Rest of patients had grade 0 reactions and none of the patient had grade 2,3 or 4 rectal reactions. The rectal BED dose of all three patients in group A is less than their median values (i.e. less than 116.77 Gy). In group B, the rectal BED dose of three patients is less than their median values (less than 114.09 Gy) 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 difference is statistically not significant.

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 1 or more reactions will be precipitated.

The mean BED values at the ICRU 38 bladder reference point for group A and B are 107.63 Gy and 112.22 Gy respectively. There were two patient in group A and three patients in group B who had grade 1 bladder reaction. None of the patient had grade 2, 3 or 4 bladder reactions. The patient presented with grade 1 bladder reaction after 2-3 months and bladder BED in both patients of group A was less than there mean i.e. less than mean valve of 107.23Gy. In group B one patient had bladder BED more than mean valve i.e. 118.54Gy. The incidence of bladder reactions is group A and B is 8% vs. 12%. Similar to rectal reactions the difference in bladder reaction is again not statistically significant.

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 1 or more reactions will be seen.

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. Esche et al 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, has reported on the correlation of the dose with genitourinary and recto-sigmoid complications. [16,17]

In our present study, no patients in group a received rectal dose more than cumulative rectal dose of 75Gy , but three patients in group B received rectal dose more the cumulative rectal dose of 78.05Gy, 76.08Gy and 76.14 Gy respectively did not present with any rectal reactions in 6 months follow up. Long term follow up is needed to confirm.

In the present study, all the patients of both groups were under follow up till six months. There was complete response in 92% 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.

VI. 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 study, dose escalation at point A was done to see whether our group of Indian patients can tolerate such dose escalation without increase in toxicity to the organs at risk – rectum, bladder and small intestine. and in a follow up of 6 months we did not find any significant difference in toxicities

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of rectum and bladder. Long term follow up is needed to see for late rectal and bladder toxicities.

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