Original article

Study of comparison of outcome between conventional versus hypofracti onated radical radiotherapy alongwith Cisplatin as a Radiosensitizer in Stage IIIB cancer cervix

[1]Dr Vijay Kumar Mahobia , [2]Dr Mahesh Rewadkar

[1].Assistant Professor,Dept of Radiotherapy,Government Medical College, Nagpur,

[2].Assistant Professor,Dept of Radiotherapy ,Kama Hospital, Mumbai

Corresponding author : Dr Vijaykumar Mahobia

Abstract

The purpose of this study was to evaluate the results of this hypofractionated treatment (outcome and complications) by decreasing the number of fractions and increasing the dose per fraction as compared to standard (conventional) treatment protocol.

Key words: Disease-Free Survival, Radiotherapy dosage, carcinoma cervix

Introduction:

Cervical cancer, the third most common cancer among women in the world, is responsible for nearly 5,00,000 new patients and 2,75,000 deaths in 2008, 88% of which occurred in developing countries and 159,800 in Asia[1]. Although cervical cancer is the most frequent cancer diagnosed in Indian women, age-adjusted incidence rates vary from 8.8 per 1, 00,000 women population in urban areas to 22.5 per 1,00,000 women population in rural areas[2]. The screening coverage in Asian countries is low and varies from 50 percent in Singapore to 2.6-5 percent in India[3,4].

Conventional fractionated radiation therapy (180-200cGy per day, 5 days a week) is established radiotherapy regimen for most solid tumors since last 3 decades. Efforts are on to improve the local control with alterations in radiotherapy schedules. There are several types of altered fractionation regimens aimed to achieve an optimal combination of total dose, dose per fraction, time interval between fractions, dose rate (if any) and overall treatment time so that it offers highest probability of tumor control with lowest possible normal tissue damage. The choice of an altered fractionation regimen requires knowledge of biological characteristics of both tumor and normal tissues, such as intrinsic radiosensitivity, sublethal and potentially lethal damage repair, and proliferative activity during treatment. The fractionation designs are based on the tumor doubling time, alpha/beta ratio, response of early and late reacting tissues.

The various fractionation regimens practised in clinical radiotherapy includes; Conventional fractionation, Split course radiotherapy, Hyperfractionation - Late hyperfractionation and Continuous accelerated hyperfractionation radiotherapy(CHART), Hypofractionation, Accelerated fractionation.Stage IIIB cervical cancer patients with bilateral parametrial involvement have a poor prognosis with low survival rates. The purpose of this study was to evaluate the results of this hypofractionated treatment (outcome and complications) by decreasing the number of fractions

and increasing the dose per fraction as compared to standard (conventional) treatment protocol.

Material and methods

Our study was a prospective, randomized, double arm open label study carried out in outpatient department (OPD) of Department of Radiation Therapy in a tertiary care institute for a period of two years. Sample size was estimated on the assumption that rectal complications in the reference study on hypofractionated radiotherapy in cervical cancer, P= 27%. Expected rectal complications in our study, P= 45%. With power of the study 80% and α-error of 20%, the sample size was derived to 60 (30 subject in each arm). [5]The study was approved by institutional ethics committee. A written informed consent was obtained from each participant prior to enrollment in the study.

Inclusion criteria:

1) Patients were histologically proven squamous cell carcinoma cervix.
2) Patients of FIGO stage IIIB cervical cancer.
3) Patients previously not treated for cervical cancer.
4) Patients' age less than 60 years.
5) Patients' Eastern Cooperative Oncology Group (ECOG) score 0 to 2 before initiation of treatment.

Exclusion criteria:

1. Pregnant and lactating mothers with cervical cancer.
2. Patient with any other synchronous or metachronous malignancy.

Pretreatment Evaluation:

- History of vaginal discharge and its characteristics i.e. watery, white or foul smelling was noted.
- History of vaginal bleeding and its type i.e. frank, blood stained or post-coital was noted.
- History of pelvic discomfort was noted.
- Pretreatment ECOG score was recorded.
- Patients were examined for approximate size of lesion, type (exophytic, ulcerative, infiltrative or mixed); lower one third vaginal extension of lesion, parametrial involvement i.e. unilateral or bilateral and palpable lymph node if any.
- All patients were investigated with baseline CBC (complete blood count), KFT (kidney function test), X-ray chest PA (posteroanterior) view and USG (ultrasonography) of abdomen-pelvis.
- Since, vaginal bleeding and anemia is common in cervical carcinoma, Hb>/= 8 gm %, TLC >/= 4000/mm^3 and platelet count >/= 1, 00,000 were considered as normal for enrolling patient in this study.
- On USG, size of lesion, presence/absence of hydroureter, hydronephrosis, and any loss of fat planes with bladder, rectum or both were noted. X-ray chest PA view of each patient was done to rule out any metastasis.

Treatment arms:

- Co-60 (Cobalt-60) and Ir-192 (Iridium-192) was used as source of External Beam Radiation Therapy (EBRT) and brachytherapy i.e. Intracavitary Radiation Therapy (ICRT), respectively in both arm. EBRT was followed by ICRT within 15 days. During EBRT, all patients were on oral hematinic with multivitamin supplements and investigated weekly for CBC. All patients were treated on OPD (out-patient department) basis and admitted only for vomiting, not controlled with oral anti-emetics. Such admitted patients were then treated with i.v.

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(intravenous) anti-emetics, steroids and i.v. fluids.

- In Arm-A, 30 patients were treated with conventional fractionated radiotherapy (CFR) with weekly inj. cisplatin 35mg/m^2 i.v. where, the EBRT of total dose 50Gy (Gray) in 25 fractions, 200cGy (centigray) per fraction daily for 5 days a week was given. Inj. cisplatin 35mg/m^2 i.v. over 1 hour infusion was given weekly during EBRT course. ICRT to Point A where, the total dose of 21Gy was given in 3 fractions, single fraction of 700cGy a week.
- In Arm-B, 30 patients were treated with hypofractionated radiotherapy (HF) with weekly inj. cisplatin 35mg/m^2 i.v. where, the EBRT of total dose 42Gy (Gray) in 15 fractions, 280cGy (centigray) per fraction on alternate day for 3 days a week was given. Inj. cisplatin 35mg/m^2 i.v. over 1 hour infusion was given weekly during EBRT course. ICRT to Point A where, the total dose of 21Gy was given in 3 fractions, single fraction of 700cGy a week.

- All patients were treated with standard pelvic portals with anteroposterior or box field technique and all fields were treated in same sitting. During treatment all patients were evaluated for the treatment complications, especially patients with chemotherapy induced nausea and vomiting were identified. Patients were admitted to ward for treatment if not responding to OPD based treatment.

Post-treatment Evaluation:

- Patients from both Arm-A and Arm-B were evaluated monthly for first three months after completion of treatment, three monthly for remaining first year and four monthly during second.
- Evaluation consisted of-
  1. Subjective response to the symptoms of vaginal discharge, vaginal bleeding, and pelvic discomfort
  2. ECOG performance status score
  3. Objective response clinically and with USG abdomen-pelvis using RECIST 1.0 criteria.
  4. Treatment complications of chemoradiotherapy like nausea and vomiting, cystitis, proctitis, vaginal stenosis, subcutaneous fibrosis and sub-acute bowel obstruction.
- Patients were considered to have recurrence (local, distant or both) when disease was seen after initial complete response.

Statistical analysis:

- Continuous variables (age, hemoglobin) were presented as Mean ± SD (standard deviation). Follow-up in months was presented as median and range. Categorical variables were expressed in actual numbers and percentages. Age and hemoglobin were compared between two arms by performing unpaired t-test. Median follow-up in months was compared between two arms by using median test. Categorical variables were compared by using chi-square test. For small numbers, Fisher's exact test was applied whenever required. Kaplan-Meier

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survival curve was plotted to compare overall survival rate and disease free survival rate between two arms. Log rank test was used for significance of equality of overall survival rate and disease free survival rate between two arms. All the tests were two sided. P-value <0.05 was considered as statistically significant. Statistical software STATA version 10.0 and SPSS-Windows version 16.0 was used for statistical analysis.

Eastern Cooperative Oncology Group **(ECOG) Score for Performance status[6]:**

- Score 0 – Asymptomatic (Fully active, able to carry on all pre-disease activities without restriction).
- Score 1 – Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work).
- Score 2 – Symptomatic, <50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours).
- Score 3 – Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours).
- Score 4 – Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair).
- Score 5 – Dead.

Response Evaluation Criteria In Solid Tumors (RECIST)[7]:

Evaluation of Target Lesion after 1 month of completion of whole treatment-

- Complete Response (CR) - Complete regression of lesion.
- Partial Response (PR) - At least 30% reduction of lesion.
- Stable Disease (SD) - Neither PR nor PD.
- Progressive Disease (PD) - At least 20% increase in size of lesion or appearance of new lesion.

Observations and Results

Patient characteristics:

Patients from conventional fractionated arm (Arm-A) and hypofractionated arm (Arm-B) were comparable in age, presenting symptom, performance status, clinical findings, USG abdomen-pelvis findings, average hemoglobin value during treatment and feasibility of ICRT after EBRT. The individual p-value of each of these parameters was more than 0.05. Hence there was statistically no significant difference in these parameters between conventional fractionation and hypofractionation arms (p >0.05) and patients from both arms were comparable.

Table 1: Patient and disease characteristics

Parameter	**Arm A (n=30)**	**Arm B (n=30)**
Age (yrs)		
• 30-39	12(40%)	11(36.7%)
• 40-49	14(46.67%)	13(43.33%)
• 50-59	4(13.33%)	6(20%)

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Symptoms of vaginal discharge • Watery • White • Foul Smelling • No discharge	 7(23.33%) 16(53.33%) 6(20%) 1(3.33%)	 7(23.33%) 14(46.67%) 7(23.33%) 2(6.67%)
Symptoms of vaginal bleeding • Blood stained • Frank • Post Coital • No bleeding	 12(40%) 9(30%) 0(0%) 9(30%)	 16(53.33%) 9(30%) 1(3.33%) 4(13.33%)
Symptoms of Pelvic Discomfort • Present 3. Absent	 11(36.67%) 19(63.33%)	 13(43.33%) 17(56.67%)
Performacnce status (ECOG) at presentation • 0 • 1 • 2	 2(6.67%) 15(50%) 13(43.33%)	 0(0%) 15(50%) 15(50%)
Size of lesions at presentation • Less than 4 cm • More than 4 cm	 8(26.67%) 22(73.33%)	 7(23.33%) 23(76.67%)
Type of lesions at presentation • Exophytic • Ulcerative • Infiltrative • Mixed	 13 (43.33%) 5(16.67%) 8(26.67%) 4(13.33%)	 15(50%) 3(10%) 7(23.33%) 5(16.67%)
Status of lower 1/3rd vaginal extension of lesion • Present • Absent	 21(70%) 9(30%)	 20(66.67%) 10(33.33%)
Parametrial involvement • Unilateral • Bilateral	 18(60%) 12(40%)	 16(53.33%) 14(46.67%)
Hydroureter • Present • Absent	 16(53.33%) 14(46.67%)	 11(36.67%) 19(63.33%)
Hydronephrosis • Present • Absent	 11(36.67%) 19(63.33%)	 9(30%) 21(70%)

Feasibility of ICRT after EBRT:

In present study, ICRT in 10% patients in conventional arm and in 13.33% patients in hypofractionated arm was not feasible due to extensive lesion. This difference between conventional arm and hypofractionated arm was statistically not significant (p=0.688). Hence feasibility of ICRT after EBRT in the conventional arm and hypofractionated arm was comparable. This finding of present study was relatively similar to finding of study done by **Mary A. et al**[5] in which ICRT was not feasible due to extensive lesion in 8.33% patients.

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Table 2: Treatment analysis

Parameter	Arm A	Arm B
ICRT		
• Not feasible	3(10%)	4(13.33%)
• Feasible	27(90%)	26(86.67%)
Average Hemoglobin in gm%		
• 8-9	14(46.67%)	9(30%)
• 9.1-10	8(26.67%)	11(36.67%)
• >10	8(26.67%)	1(3.33%)
Vaginal Discharge		
• Relieved	26(89.65%)	25(92.59%)
• Persistant	3(10.34%)	2(7.40%)
Vaginal Bleeding		
• Relieved	19(90.47%)	26(100%)
• Persistant	2(9.52%)	0(0%)
Pelvic Discomfort		
• Relieved	4(36.36%)	6 (46.15%)
• Persistant	7(63.63%)	7 (53.85%)
Performance status (ECOG) score after 1 month of whole treatment		
• 1	8(26.67%)	6(20%)
• 2	17(56.67%)	15(50%)
• 3	5(16.67%)	9(30%)
Response as per RECIST 1.0 criteria		
• Complete Response	20(66.67%)	18(60%)
• Partial Response	7(23.33%)	9(30%)

Objective response to treatment as per RECIST 1.0 criteria:

RECIST 1.0 criteria was used for assessment of the response to treatment. In present study 66.67% patients in conventional arm and 60% patients in hypofractionated arm had complete response. This difference in complete response rate between conventional arm and hypofractionated arm was statistically not significant (p=0.592). Hence the complete response rate in conventional arm and hypofractionated arm was comparable. Partial response was seen in 23.33% patients in conventional arm and 30 % patients in hypofractionated arm (p=0.559). Stable disease was seen in 10 % patients each in conventional arm and hypofractinated arm (p=1.000). No patient in conventional arm or hypofractionated arm had progressive disease. This difference of partial response and stable disease between conventional arm and hypofractionated arm was statistically not significant. Hence partial response, stable disease and progressive disease with conventional fractionation and hypofractionation was comparable.

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Treatment complications:

Table 3: Analysis of Complications of treatment

Treatment complications	Arm-A (n=30)	Arm-B (n=30)
Proctitis	6(20%)	14(46.67%)
Cystitis	14(46.67%)	23(76.67%)
Vaginal stenosis	9(30%)	7(23.33%)
Nausea and vomiting	13(43.33%)	22(73.33%)
Subcutaneous fibrosis	10(33.33%)	11(36.67%)
Bowel obstruction	3(10%)	2(6.67%)

Our study documented a statistically significant difference in incidence of proctatitis (p=0.028), cystitis (p=0.017) and nausea with vomiting (p=0.020) in both the arms. Patients undergoing hypofractionated therapy developed a higher incidence of proctitis, cystitis, nausea and vomiting than patients undergoing conventional therapy. The incidence of vaginal stenosis, subacute bowel obstruction, subcutaneous fibrosis were comparable between conventional fractionation and hypofractionation. Patients with nausea and vomiting were treated with oral/i.v. anti-emetics with or without i.v. fluids depending on features of dehydration. Cystitis was treated with antispasmodics, adequate oral rehydration, anti-inflammatory agents, oral antibiotics and bladder irrigation depending on severity. Proctitis was treated with small enemas with hydrocortisone and anti-inflammatory suppositories containing benzyl benzoate and zinc oxide. Liquid paraffin was used as soothing agent. A low-residue diet with no grease or spices with more fiber was advised to such patients. Non responsive patients were treated with oral steroids like dexamethasone and betamethasone. Vaginal stenosis was treated with gentle per vaginal manipulation with speculum and breaking the synechiae. Sub-acute intestinal obstruction was treated conservatively with oral laxatives, per anal stimulation and advised for high fibre diet with plenty of oral fluids.

Survival:

Disease free survival:-

Follow up for Arm-A was in range of 4-18 months. Mean follow up for Arm-A was 8.03 months with standard deviation (SD) of 3.5 months. Median follow-up period for Arm-A was 8.5 months. Follow-up for Arm-B was in range of 3-13 months. Mean follow-up for Arm-B was 7.53 months with standard deviation (SD) of 2.64 months. Median follow-up for Arm-B was 7.5 months. Out of 30 patients in Arm-A, 17 patients (56.67%) were disease free and 13 patients (43.33%) had disease after 1 year after completion of whole treatment. Out of 30 patients in Arm-B, 15 patients (50%) were disease free and 15 patients (50%) had disease after 1 year of completion of whole treatment. Disease free Survival rate at 1 year after treatment for Arm-A and Arm-B was 56.6 and 50% respectively. The difference in Disease free Survival rate at 1 year after treatment between Arm-A and Arm-B was statistically **not significant** (**p=0.494; log rank test value=0.468**). Hence, disease free survival rate at 1 year after treatment with conventional fractionation and hypofractionation was comparable.

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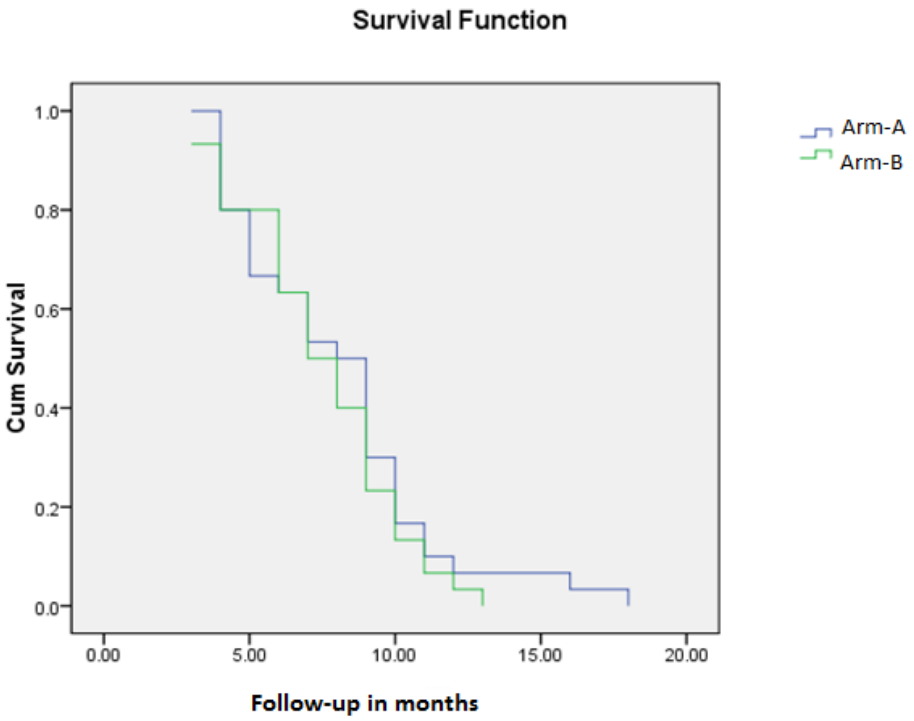
Graph 1: Disease Free survival



Discussion

Cervical cancer is one of the most common gynecological malignancies in India. It is more common in rural population and lower socioeconomic group. Low education and poor socioeconomic status is potential barrier between patient and medical system. Such patients seek medical help in advanced stage of their disease. Conventional fractionation delivers 180 to 200 cGy per fraction five days a week. This fractionation scheme was developed because it offers highest probability of tumor control with tolerable acute reactions and acceptable delayed effects. In an attempt to improve the therapeutic ratio, various fractionation schedules have been attempted. Hypofractionation has been used in various head and neck, bladder, cervical and breast malignancies.[5,8,9,10,11,12,13] Survival in patients, in various studies with hypofractionated radiotherapy was comparable to conventional fractionated radiotherapy, though the complications were more common with hypofractionated radiotherapy.Carcinoma cervix IIIB forms a heterogeneous group of patients ranging from small volume disease with or without lower 1/3rd vaginal involvement and with or without bilateral parametrial involvement. A subgroup of these patients has extensive local disease at presentation, general condition from fair to poor. There are some patients who cannot withstand multiple fractions of radiotherapy.

Our study has shown that both the treatment modalities give comparable response rate and local tumor control in patients with Ca cervix. The disease free survival was also found to be comparable with both the arms. However the incidence of adverse effects in terms of treatment complications was found to be more in the patients treated with hypofractionated radiotherapy, hence limiting its usefulness. In accordance with the current literature, the authors recommend the use of

hypofractionated radiotherpy in selected group of patients where local disease is extensive and unsuitable for conventional fractionation.

Limitations of the study

In the present study, disease free survival was calculated at 1 year after treatment as the duration of present study was less (approx. 2 year). Grading for each treatment reaction and complication was not done in the present study. Hence it is suggested that, in future comparative study on Conventional fractionation versus Hypofractionation should be framed with large sample size, in such a way that grades of each complications between two arms can be compared. Duration of such study should be long enough to calculate the disease free survival at 5 year.

Conclusion

Conventional fractionation radiotherapy holds its utility in terms of efficacy and safety profile in the management of carcinoma cervix. Hypofractionated radiotherapy also produces comparable efficacy but is associated with higher incidence of treatment complications like proctatitis, cystitis which restricts its usefulness for widespread use.

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