Original Research Article

Assessment of response to weekly cisplatin-based hypofractionated radiotherapy in carcinoma of cervix

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Abstract

Background: External beam radiotherapy along with concurrent weekly cisplatin followed by brachytherapy is the standard practice for managing advanced carcinoma cervix. Hypofractionated radiotherapy in carcinoma of cervixis more convenient for patients and is of benefit in resource constraint health systems. **Aim:** To assess the response to weekly cisplatin-based hypofractionated radiotherapy in carcinoma of cervixas compared to conventional treatment protocol. **Material and Methods:** In thishospital based prospective comparative study, 60 patients with carcinoma cervix were equally divided into Arm-A and Arm-B groups. In Arm-A, 30 patients were treated with conventional fractionated radiotherapy (CFR) with weekly inj. Cisplatin 35mg/m^2i.v. where, the EBRT of total dose 50Gy (Gray) in 25 fractions, 200cGy (centigray) per fraction daily for 5 days a week was given. In Arm-B, 30 patients were treated with hypofractionated radiotherapy (HF) with weekly inj. Cisplatin 35mg/m^2i.v. where, the EBRT of total dose 42Gy in 15 fractions, 280cGy per fraction on alternate day for 3 days a week was given.Patient evaluation consisted of subjective response to the symptoms, ECOG score, objective response using RECIST 1.0 criteria and treatment complications of chemoradiotherapy. **Results:** 66.67% patients in Arm-A and 60% patients in Arm-B had complete response. 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. Treatment complications like proctitis, cystitis, nausea and vomiting, were statistically more common with hypofractionation. **Conclusion:** Hypofractionated radiotherapy can be considered in selected group of patients where local disease is extensive and unsuitable for conventional fractionation.

Key Words: Carcinoma of cervix, Hypofractionated radiotherapy, conventionalradiotherapy, Cisplatin, response, complications.

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INTRODUCTION

Cervical cancer is the second most common cancer in women aged 15-44 years.[1] National Cancer Registry Program (NCRP) indicates that the most common sites of cancer among women are the breasts and the cervix.[2]India has a population of 432.2 million women aged 15 years and older who are at risk of developing cancer. In India, every year 122,844 women are diagnosed with cervical cancer and 67,477 die from the disease.[1] Conventional fractionated radiation therapy is an established radiotherapy regimen for most solid tumors since last three decades. There are several types of altered fractionation regimens aimed to achieve an optimal

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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. Hypofractionation involves giving a smaller number of larger doses per fraction. Treatment regimens involving fewer fractions, is clearly more convenient for patients and is of benefit in resource constraint health systems.Stage IIIB cervical cancer patients with bilateral parametrial involvement have a poor prognosis with low survival rates. Previous randomized trials have evaluated the role of cisplatin, alone or in combination with other chemotherapy agents, administered concurrently with external beam radiotherapy to patients with locally advanced cervical cancer.[3-5]The purpose of this study was to assess the response to weekly cisplatin-based hypofractionated radiotherapy in carcinoma of cervixas compared to conventional treatment protocol.

MATERIAL AND METHODS

This prospective comparative study included patients registered in the Out-patient section (OPD) of Department of Radiation Therapy and Oncology in Tertiary Care Institute. Approval from institutional ethics committee was taken before commencing the study. After informed and written consent, the study participants were interviewed and examined according to the preformed and pretested format and then enrolled alternately in each arm of this study.

Sample size: 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, (1-β) %= 80% and α-error= 20%, minimum sample required for study in Arm-B, n=30. Hence, 30 patients in each arm were included in our study.[6] Thus, a total of 60 patients were enrolled in this study and were alternately assigned to Arm-A (n=30) and Arm-B (n=30) after matching for variables like age.

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.

Pre-treatment Evaluation: History of vaginal discharge and pelvic discomfort was noted. Pretreatment ECOG score was recorded. Patients were examined for approximate size of lesion, type, lower one third vaginal extension of lesion, parametrial involvement and palpable lymph node if any. 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. All patients were investigated with baseline complete blood count, kidney function test, X-ray chest PA view and ultrasonography of abdomen-pelvis.

Treatment

- 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.
- In Arm-A, 30 patients were treated with conventional fractionated radiotherapy (CFR) with weekly inj. Cisplatin 35mg/m^2i.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^2i.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^2i.v. where, the EBRT of total dose 42Gy in 15 fractions, 280cGy per fraction on alternate day for 3 days a week was given. Inj. cisplatin 35mg/m^2i.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. ICRT with central tandem and two ovoids. During treatment all patients were evaluated for the treatment complications, especially patients with chemotherapy induced nausea and vomiting was 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 subjective response to the symptoms, ECOG performance status score, objective response clinically and with USG abdomen-pelvis using RECIST 1.0 criteria and treatment complications of chemoradiotherapy.

Statistical Analysis: Statistical software STATA version 10.0 and SPSS-Windows version 16.0 was used for statistical analysis. Continuous variables were presented as Mean±SD. Categorical variables were compared by using chi-square test. P-value <0.05 was considered as statistically significant.

RESULTS

A total of 60 patients were enrolled, alternately allotted to either arm; such that, 30 patients in each arm. Mean age of patients in Arm-A was 43.66±7.42 years and in Arm-B was 42.43±6.63 years. Patients from both arms were age matched and there was statistically not significant difference in their ages between two arms (p=0.5003). In Arm-A, all 30 patients had completed EBRT and weekly chemotherapy. ICRT was feasible in 27 patients (90%) and not feasible 3 patients (10%) due to lesion occluding the site of ICRT. In Arm-B, all 30 patients had completed EBRT and weekly chemotherapy. ICRT was feasible in 26 patients (86.67%) and not feasible in 4 patients (13.33%) due to lesion occluding the site of ICRT. There was statistically not significant difference in feasibility of ICRT after EBRT between two arms (p=0.688).

Table 1: Analysis of Subjective response to treatment

Symptom	Arm-A	Arm-B
Vaginal discharge		
Relieved	26/29 (89.65%)	25/27 (92.59%)
Persistent	3/29 (10.34%)	2/27 (7.40%)
Vaginal bleeding		
Relieved	19/21 (90.47%)	26/26 (100%)
Persistent	2/21 (9.52%)	0/26 (0%)
Pelvic discomfort		
Relieved	4/11 (36.36%)	6/13 (46.15%)
Persistent	7/11 (63.63%)	7/13 (53.85%)

There was statistically not significant difference of subjective response to the symptom of vaginal discharge between two arms (p=0.718).In Arm-A, 21 patients had presenting complain of vaginal bleeding, out of which 19 patients (90.47%) were free of vaginal bleeding after treatment. In Arm-B, 26 patients had presenting complain of vaginal bleeding, all patients (100%) were free of vaginal bleeding after treatment. This was statistically significant (p=0.037). In Arm-A, 2 patients (9.52%) had persistent bleeding after treatment, but this was statistically not significant (p=0.492).There was statistically not significant difference of subjective response to the symptom of pelvic discomfort between two arms (p=0.488). 7 patients each in Arm-A and Arm-B had persistent pelvic discomfort after treatment, but this was statistically not significant (p=1.000).

Table 2: ECOG score and RECIST 1.0 criteria after 1 month of whole treatment

Response	Arm-A (n=30)	Arm-B (n=30)
ECOG score		
1	8(26.67%)	6(20%)
2	17(56.67%)	15(50%)
3	5(16.67%)	9(30%)
RECIST 1.0 criteria		
Complete response	20(66.67%)	18(60%)
Partial response	7(23.33%)	9(30%)
Stable disease	3(10%)	3(10%)

There was statistically not significant difference of performance status after 1 month of treatment (p=0.406). 20 patients (66.67%) from Arm-A and 18 patients (60%) from Arm-B had complete response, but this was statistically not significant (p=0.592). 7 patients (23.33%) from Arm-A and 9 patients (10%) from Arm-B had partial response, but this was statistically not significant (p=0.559). 3 patients (10%) from both arms had stable disease which was statistically not significant (p=1.000). No patient from both arms had progressive disease.

Table 3: Treatment complications

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%)

Treatment complications like proctitis, cystitis, nausea and vomiting, were statistically more common with hypofractionation than conventional fractionation; while other treatment complications like vaginal stenosis, subacute bowel obstruction and subcutaneous fibrosis were comparable between conventional fractionation and hypofractionation.

Table 4: Status at the end of one year after treatment

Status at the end of one year	Arm-A(n=30)	Arm-B(n=30)
Survival status		
Survived	18(60%)	17(56.67%)
Dead	12(40%)	13(43.33%)
Disease free Survival		
Without disease	17(56.67%)	15(50%)
With disease	13(43.33%)	15(50%)

Follow up for Arm-A was in range of 4-18 months. Mean follow up for Arm-A was 8.03±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±2.64 months. Median follow-up for Arm-B was 7.5 months. Overall survival rate at 1 year after treatment and disease free survival rate at 1 year after treatment with conventional fractionation and hypofractionation was comparable in the present study.

DISCUSSION

Cervical cancer is one of the most common gynecological malignancies in India. Majority of the 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. 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 haemoglobin value during treatment and feasibility of ICRT after EBRT. There was statistically no significant difference in these parameters between both arms (p>0.05). 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). RECIST 1.0 criterion 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 was statistically not significant (p=0.592). 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 was statistically not significant. In the study done by Souhami *et al*[7] the complete response rate with conventional radiotherapy and concurrent cisplatin was 88%. In the study done by Campbell OB *et al*[8] complete response rate was similar in conventional arm and hypofractionated arm. In the study done by Muckaden MA*et al*[6] complete response rate with hypofractinated radiotherapy was 85%. Complete response rate was less in the present study in conventional arm and hypofractionated arm as compared to studies done by Souhami *et al*[7], Campbell OB *et al*[8] and Muckaden MA*et al*[6] due to poor nutrition and low level of haemoglobin in majority of patients causing decrease oxygenation of tissue which in turn decreases response to radiation.However in overall, complete response rate of conventional fractionation and hypofractionation arms were comparable. Subjective response was evaluated one month after completion of whole treatment. In present study, subjective response to vaginal bleeding was statistically higher with hypofractionation than conventional fractionation; while subjective response to the symptom of vaginal discharge and pelvic discomfort with conventional fractionation and hypofractionation was comparable. Since our objective was simple comparison of number of patients with treatment complications in conventional fractionation arm and hypofractionation arm; hence, grading of each complication for comparative evaluation of each grade in two arms was not done. In our study, proctitis was significantly more common in hypofractionated arm than conventional arm. From the study done by Souhami *et al*[7] and Muckaden MA *et al*[6] it was noted that proctitis, cystitis was more common with hypofractionation than conventional fractionation. Nausea and vomiting was significantly more common in hypofractionated arm than conventional arm with weekly cisplatin in both arms. In the study done by Souhami *et al*,52% patients developed nausea and vomiting with conventional fractionation and weekly cisplatin based chemotherapy.[7] In the study done by Viegas *et al*, 67.5% patients developed nausea and vomiting with conventional fractionation and weekly cisplatin based chemotherapy.[9] As the duration of present study was less (approx. 2 years) overall survival at 5 year could not be calculated. In the present study overall survival rate at 1 year after treatment was 60% and 56.67% in conventional arm and hypofractionated arm respectively. The difference of overall survival rate at 1 year after treatment between conventional arm and hypofractionated arm was statistically not significant (p=0.434, log rank test value =0.617). In the present study overall survival at 1 year was more than the studies done by Souhami *et al*[7], Campbell OB *et al*[8] and Muckaden MA*et al*[6] because we have considered overall survival at 1 year after completion of treatment and in the study done by Souhami *et al*[7] overall survival was mentioned at 3 year; in the study done by Campbell OB *et al*[8] and the study done by Muckaden MA*et al*[6] overall survival was mentioned at 5 year. In the present study, disease free survival at one year after treatment was less as compared to studies done by Morris M *et al*[10] and Viegas *et al*[9] due to less number of patients with complete response in both arms of present study. Survival in patients, in various

studies with hypofractionated radiotherapy was comparable to conventional fractionated radiotherapy, though the complications were more common with hypofractionated radiotherapy.

CONCLUSION

Response rate and local tumor control is comparable with conventional fractionation and hypofractionation. The treatment complications are comparatively more common with hypofractionation. Overall survival at 1 year and disease free survival at 1 year with hypofractionation are comparable to conventional fractionation. Conventional fractionation with concurrent cisplatin is preferrable treatment for carcinoma cervix stage IIIB. Hypofractionated radiotherapy can be considered in selected group of patients where local disease is extensive and unsuitable for conventional fractionation.

Limitations: In the present study, overall survival and 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 overall survival and disease free survival at 5 year.

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