Research Article

Study of response and outcome of treatment of radiotherapy in patients of carcinoma cervix Stage IIB–IV with concurrent cisplatin

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Received: April 10, 2018; Accepted: May 02, 2018

ABSTRACT

Background: Carcinoma cervix is most common carcinoma among middle and low socioeconomic countries due to illiteracy and unhygienic conditions. **Objectives:** The objectives of the study were to evaluate the response and outcome of radiotherapy along with cisplatin as chemotherapy in carcinoma cervix Stage II B–IV. **Materials and Methods:** This is a prospective analytical study on 93 patients for 2 years in tertiary care hospital. **Results:** In the present study disease-free survival rate at 1 year after treatment was 72.04%. Follow-up was in the range of 4–18 months. In the present study, overall survival rate at 1 year after treatment was 77.4%. In our study, of 93 patients, 21 patients succumbed to death at the end of 1 year. Among them, 10 patients (47.61%) died due to acute renal failure and rest died due to cardiorespiratory failure. **Conclusion:** Conventional fractionation radiotherapy holds its utility in terms of efficacy and safety profile in the management of carcinoma cervix. The use of External Beam Radiation Therapy with chemotherapeutic drugs, i.e., cisplatin has showed high compliance to radiotherapy.

KEY WORDS: Carcinoma Cervix; Disease-Free Survival; Radiotherapy; Chemotherapy

INTRODUCTION

Cervical cancer is the most common cancer-causing death among women in developing countries.[1] Mortality due to cervical cancer is also an indicator of health inequities, as 86% of all deaths due to cervical cancer are in developing, low- and middle-income countries.[2,3] Cervical cancer is the most frequent cancers occurring in Indian women and together with ovarian and breast cancer, account for more than half of all female cancers. Every year in India, 122,844 women are diagnosed with cervical cancer and 67,477 dies from the disease.[4] The mean age for cervical cancer in the US is 47 years with bimodal distribution peak at 35–39 years and 60–64 years of age.[5] India also has the highest age-standardized incidence of cervical cancer in South Asia at 22, compared to 19.2 in Bangladesh, 13 in Sri Lanka, and 2.8 in Iran. Therefore, it is vital to understand the epidemiology of cervical cancer in India. The differential pattern of cervical cancer and the wide variation in incidence is possibly related to environmental differences.

Radiotherapy is the primary local treatment for most patients with locoregionally advanced cervical carcinoma. The success of treatment depends on a careful balance between external-beam radiotherapy and brachytherapy that optimizes the dose to the tumor and normal tissues and the overall duration of treatment. Barring medical contraindications, most patients with these advanced tumors should also receive concurrent chemotherapy with radiotherapy. Conventional fractionated radiation therapy (180–200 cGy per day, 5 days a week) is established radiotherapy regimen for most solid tumors since past three decades. The choice of an altered fractionation

Access this article online	
Website: http://www.ijmsph.com	Quick Response code
DOI: 10.5455/ijmsph.2018.0413702052018	

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 effectiveness of radiotherapy might also be improved through decreased tumor cell hypoxia and subsequently improved radiosensitivity with platinum-based agents used as chemotherapy drugs along with radiation therapy. Concurrent chemotherapy is now considered to be the standard treatment for many patients with locally advanced cervical cancer who requires radiation therapy.

MATERIALS AND METHODS

This is a prospective analytical study done on patients registered in the out-patient section outpatient department (OPD) of the Department of Radiation Therapy and Oncology and indoor patients in gynae oncology ward in tertiary care institute with histopathologically proven carcinoma of cervix were included in the study. A total of 93 patients were included in the study. Period of study duration was 2 years. The study was approved by Institutional Ethics Committee. A written informed consent was obtained from each participant before enrollment in the study.

Inclusion Criteria

The following criteria were included in this study:

1. Patients were histologically proven cases of carcinoma cervix.
2. Patients with federation of gynecology and obstetrics (FIGO) IIB to IV cervical cancer.

Exclusion Criteria

The following criteria were excluded from the study:

1. Patients with carcinoma cervix with FIGO stage other than IIB to IV.
2. Patients who have undergone surgery.
3. Patients who are medically unfit for radiotherapy.
4. Patients who are diagnosed other cancer along with cervical malignancy.

Pre-treatment Evaluation

History

A detailed history regarding age, parity, socioeconomic status, age at marriage, age at the onset of sexual activity, contraception, symptoms of vaginal discharge and its characteristics (i.e., watery, white, or foul smelling), bleeding per vaginum and its characteristics (i.e., frank, blood-stained, or post-coital), and pelvic discomfort was noted.

Eastern Cooperative Oncology Group (ECOG) score

Pre-treatment ECOG score was recorded.

Examination

Patients were examined, and FIGO staging was done, 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 were examined.

Investigations

All patients were investigated with baseline complete blood count (CBC), kidney function test, X-ray chest posteroanterior (PA) view, and computed tomography (CT) scan of abdomen-pelvis.

- Since, vaginal bleeding and anemia are common in cervical carcinoma, Hb ≥ 8 g%, TLC ≥ 4000/mm^3, and platelet count ≥ 1,00,000 were considered as normal for enrolling patient in this study.

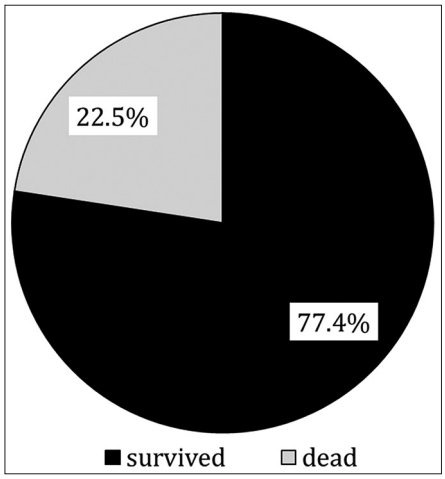

Figure 1: Overall survival status at the end of 1 year after treatment

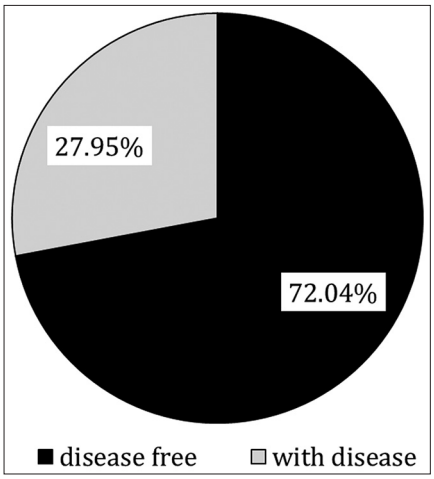

Figure 2: Disease-free survival at the end of 1 year after treatment

Table 1: Patient and disease characteristics

Parameter	Number of patients (%)
Age (in years)	
<30	02 (2.1)
31–40	15 (16.1)
41–50	24 (25.8)
51–60	36 (38.7)
>60	16 (17.2)
Symptoms of vaginal discharge	
Watery	13 (13.9)
White	44 (47.3)
Foul smelling	28 (30.1)
No discharge	8 (8.6)
Symptoms of vaginal bleeding	
Bloodstained	42 (45.1)
Frank	15 (16.1)
Post coital	10 (10.7)
No bleeding	25 (26.8)
Symptoms of pelvic discomfort	
Absent	39 (41.9)
Present	54 (58.06)
Performance status (ECOG) at presentation	
0	10 (10.7)
1	52 (55.91)
2	31 (33.33)
Type of lesion at presentation	
Infiltrative	39 (41.93)
Exophytic	30 (32.25)
Ulcerative	12 (12.9)
Endophytic	12 (12.9)]
Size of lesion at presentation (cm)	
<4	53 (56.98)
>4	40 (43.01)
FIGO staging at presentation	
IIB	42 (45.1)
IIIA	12 (12.9)
IIIB	31 (33.3)
IVA	8 (8.6)

ECOG: Eastern Cooperative Oncology Group, FIGO: Federation of gynecology and obstetrics

- On CT scan, 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 just to rule out any metastasis.

Treatment

LINEAR ACCELERATOR and Iridium-192 were used as source of External Beam Radiation Therapy (EBRT) and brachytherapy, i.e., intracavitary radiation therapy (ICRT), respectively. 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 with conventional fractionated radiotherapy (CFR) with weekly injection cisplatin 35 mg/m^2 i.v. where, the EBRT of total dose 50 Gy (Gray) in 25 fractions, 200 cGy (centigray) per fraction daily for 5 days a week was given. Injection cisplatin 35 mg/m^2 intravenous over 1 h infusion was given weekly during EBRT course. ICRT to Point A where, the total dose of 21 Gy was given in 3 fractions, single fraction of 700 cGy a week.

All patients were treated with standard pelvic portals with anteroposterior or box field technique, and all fields were treated in the same sitting. ICRT was given 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 the ward for treatment if not responding to OPD based treatment.

Post-treatment Evaluation

Patients were evaluated monthly for first 3 months after completion of treatment, 3 monthly for remaining 1st year, and 4 monthly during second.

Evaluation consisted of:

- Subjective response to the symptoms of vaginal discharge, vaginal bleeding, and pelvic discomfort.
- ECOG performance status score,
- Objective response clinically and with USG abdomen-pelvis using response evaluation criteria in solid tumors (RECIST) 1.0 criteria.
- Treatment complications of chemoradiotherapy such as nausea and vomiting, cystitis, proctitis, vaginal stenosis, subcutaneous fibrosis, and sub-acute bowel obstruction.

Cystitis was diagnosed clinically and using USG pelvis (for features of inflammation). Proctitis was diagnosed clinically on rectal examination and using transrectal ultrasonography (USG) for features of inflammation. Vaginal stenosis was diagnosed clinically. Subcutaneous fibrosis was diagnosed clinically and on USG. Sub-acute bowel obstruction suspected clinically; confirmed on X-ray abdomen-upper pelvis in standing position and using USG abdomen-pelvis. Patients were considered to have a recurrence (local, distant, or both) when disease was seen after the initial complete response (CR).

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

Table 2: Treatment analysis

Parameter	*n* (%)
Vaginal discharge	
Relieved	70 (82.3)
Persistent	15 (17.6)
Vaginal bleeding	
Relieved	58 (86.56)
Persistent	9 (13.4)
Pelvic discomfort	
Relieved	24 (61.5)
Persistent	15 (38.4)
ECOG score after complete treatment	
0	3 (3.22)
1	37 (39.7)
2	45 (48.38)
3	8 (8.6)
Response as per the RECIST 1.0 criteria	
CR	69 (74.1)
PR	13 (13.9)
SD	7 (7.5)
Progressive disease	4 (4.3)

ECOG: Eastern Cooperative Oncology Group, FIGO: Federation of gynecology and obstetrics, RECIST: Response evaluation criteria in solid tumors, CR: Complete response, PR: Partial response, SD: Stable disease

(restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework and 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.

RECIST[7]

Evaluation of target lesion after 1 month of completion of whole treatment:

- 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.

RESULTS

All patients were treated with CFR with weekly injection cisplatin 35 mg/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. Injection cisplatin 35 mg/m^2 intravenous over 1 h infusion was given weekly during EBRT course. ICRT to Point A was given. The total dose of ICRT 21 Gy was given in 3 fractions, single fraction of 700 cGy a week. Response was assessed as a symptomatic improvement by ECOG grading and tumor response by RECIST 1.0 criteria.

In the present study, out of 93 patients, maximum patients were in age group of 51–60 years. 91.3% patients had vaginal discharge while 72.04% had vaginal bleeding as presenting symptoms. Pelvic discomfort was present in 58.06%. 55.91% patients presented with ECOG status as score 1.

FIGO staging at the time of presentation was IIB in 42, IIIA in 12, and IIIB in 31 while rest were in Stage IV A.

The response of patient was analyzed according to the RECIST 1.0 criteria. CR, i.e. complete regression of lesion was seen in 74.1% patients while progressive disease, i.e. at least 20% increase in size of lesion or appearance of new lesion was seen in 4.3% patients, 7.5% had SD, and 13.9% showed PR.

Vaginal discharge was relieved in 82.3% patients and vaginal bleeding in 86.56% of them. ECOG score after complete treatment was score 2 in 45 patients, score 1 in 37, while 8 were of score 3 and rest score 0. This suggests that maximum patients were ambulatory and capable of all self-care but unable to carry out any work activities.

DISCUSSION

In our study, all patients were treated with CFR with weekly injection cisplatin 35 mg/m^2 i.v. where, the EBRT of total dose 50 Gy (Gray) in 25 fractions, 200 cGy (centigray) per fraction daily for 5 days a week was given with linear accelerator along with injection cisplatin 35 mg/m^2 intravenous over 1 h infusion was given weekly during EBRT course. ICRT was given within 15 days of EBRT to Point A where, the total dose of 21 Gy was given in 3 fractions, single fraction of 700 cGy a week.

Recist 1.0 criterion was used for assessment of the objective response to treatment. In present study, 74.7% patients had CR, PR was seen in 13.9% patients, SD was seen in 7.3 % patients, and 4.3% patients had progressive disease. It was comparable with the previous studies done. The observed tumor response rate in the present study after EBRT with concurrent chemotherapy 1 month after completed treatment, i.e., 25 cycles of EBRT followed by concurrent chemoradiotherapy and IBRT was 88.1% (74.1% CR and 13.9% PR), overall and disease-free survival were 77.4% and 72.04%, respectively. This response and survival rate was comparable with the relevant studies. As the duration of

the present study was less (approximately 2 years) disease-free survival at 5 year could not be calculated. In the present study disease-free survival rate at 1 year after treatment was 72.04%. Follow-up was in the range of 4–18 months. In the present study, overall survival rate at 1 year after treatment was 77.4%. In our study, of 93 patients, 21 patients succumbed to death at the end of 1 year. Among them, 10 patients (47.61%) died due to acute renal failure and rest died due to cardiorespiratory failure.

Recist 1.0 criterion was used for assessment of the response to treatment. In present study, 74.7% patients had CR, PR was seen in 13.9% patients, SD was seen in 7.3% patients, and 4.3% patients had progressive disease. In study done by Mahobia *et al*.[9] 66.7% patients had CR in conventional arm treatment with conventional radiotherapy and cisplatin and PR was seen in 23.33% patients. 10% patients had SD whereas no patient had progressive disease in conventional arm. In the study done by Souhami *et al*.,[10] the CR rate with conventional radiotherapy and concurrent cisplatin was 88%. From the study done by Souhami *et al*. and Mahobia *et al*. it was noted that CR rate with conventional fractionation in our study was comparable. CR rate was less in the present study as compared to studies done by Souhami *et al*. due to one or more the following reasons - 1. Low level of hemoglobin in majority of patients, i.e. mean hemoglobin was <10 g% causing decrease oxygenation of tissue which, in turn, decreases response to radiation - 2. Poor nutrition of patients, as the majority of the patient in our set up, was from poor socioeconomic group. The observed tumor response rate in the present study after EBRT with concurrent chemotherapy 1 month after completed treatment, i.e. 25 cycles of EBRT followed by concurrent chemoradiotherapy and IBRT were 88.1% (74.1% CR and 13.9% PR), overall and disease-free survival were 77.4% and 72.04%, respectively. This response and survival rate was comparable with the relevant studies. In the present study disease-free survival rate at 1 year after treatment was 72.04%. In the study done by Morris *et al*., the disease-free survival rate at 5 year was 73% with conventional fractionation and concurrent cisplatin. In study done by Mahobia *et al*., patients treated with conventional radiation fractionation with cisplatin 56.67%, patients were disease-free whereas 43.33% had disease at the end of 1 year of treatment. In a study done by McCormack *et al*. (2013), where the patient was given neoadjuvant chemotherapy (NACT) with paclitaxel and carboplatin before radical chemoradiation (CRT), and progression-free survival at 3 years was 68%. Hence, in the present study, disease-free survival at 1 year after treatment was comparable to studies done by Morris *et al*.,[12] Mahobia *et al*., and McCormack *et al*.(2013). In the present study, overall survival rate at 1 year after treatment was 77.4 %. In our study, of 93 patients, 21 patients succumbed to death at the end of 1 year. Among them, 10 patients (47.61%) died due to acute renal failure and rest died due to cardiorespiratory failure. In the study done by Campbell *et al.,*[13] overall survival at 5 year was 42.5% and 40.2% with conventional fractionation and hypofractionation, respectively. In the study done by Souhami *et al*., overall survival at 44 months was 55% with conventional fractionation and weekly cisplatin. In study done by McCormack *et al*. (2013), overall survival at 3 years of NACT with paclitaxel and carboplatin before radical chemoradiation (CRT) was 67%. From the studies done by Souhami *et al*., Campbell *et al*., and McCormack *et al*. (2013), it was noted that overall survival was comparable. In the present study, overall survival at 1 year was more than the studies done by Souhami *et al*., Campbell *et al*., and McCormack *et al*. (2013) because we have considered overall survival at 1 year after completion of treatment and in the study done by Souhami *et al*. and McCormack *et al*. (2013) overall survival was mentioned at 3 years and in the study done by Campbell *et al*. overall survival was mentioned at 5 years cumulatively, overall survival rate at 1 year after treatment was 77.4%, and disease-free survival rate at 1 year after treatment was 72.04%.

Limitations of Study

In the present study, overall survival and disease-free survival were calculated at 1 year after treatment as the duration of the present study was less (approximately 2 years).

CONCLUSION

Conventional fractionation radiotherapy holds its utility in terms of efficacy and safety profile in the management of carcinoma cervix. The use of EBRT with chemotherapeutic drugs, i.e. cisplatin has shown high compliance to radiotherapy.

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How to cite this article: Vinaik T. Study of response and outcome of treatment of radiotherapy in patients of carcinoma cervix Stage IIB–IV with concurrent cisplatin. Int J Med Sci Public Health 2018;7(8):661-666.

Source of Support: Nil,**Conflict of Interest:** None declared.