

A Prospective Survival Analysis in Locally Advanced Carcinoma Cervix Patients Following Concurrent Chemoradiation with Weekly Cisplatin

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Abstract

Introduction: Cervical cancer is one of the most common cancers diagnosed in female patients in developing countries. Successful treatment leading to cure is the major concern for most patients.

Aim: This study aims to analyze the tumor response, the disease-free and overall survival rate in patients with locally advanced carcinoma cervix.

Materials and Methods: Prospective cohort study was conducted in patients with confirmed carcinoma cervix. Disease-free survival is analyzed from date of registration to local or distant relapse or death or last visit.

Results: 35 (77.8%) patients received only 4 cycles of concurrent chemotherapy, and 10 (22.2%) received 5 cycles of concurrent chemotherapy. Only 8 (17.8%) patients developed recurrence, 37 (82.2%) patients not developed recurrence. Disease-free survival after 1 year is 82%. Only 1 (2.2%) patient died, the cause of death being renal failure. The overall survival after 1 year is 98%.

Conclusion: Concurrent chemoradiation treatment is an effective treatment for patients with locally advanced cervical cancer. There are many prognostic factors influencing treatment outcome.

Key words: Cervical cancer, Radiation therapy, Survival rate

INTRODUCTION

Cervical cancer is the second most common cancer in women worldwide and a major cause of death particularly in developing countries.¹ The global yearly incidence of cervical cancer in 2012 was 528,000; the annual death rate was 266,00.² The incidence of cervical cancer per 1 lakh women in India is 30.7. Incidence varies worldwide with the highest rates found in Latin America and the lowest among Jewish women in Israel. Poor nutritional

status, multiple sexual partners, first coitus in young age, early childbirth, promiscuity of the spouse, human papillomavirus infections, sexually transmitted diseases, and immunocompromised states are cited as main risk factors.³ The use of cervical screening has greatly reduced the incidence of invasive cervical cancer in the western countries, but it continues to be a major cause of cancer mortality in the rest of the world because the majority of patients have locally advanced disease at presentation. In developing or less developed countries, over 80% of women with cervical cancer are diagnosed at advanced stage which is associated with poor prognosis.⁴ Radiation therapy (RT) alone was being used as a primary treatment for patients with locally advanced - the International Federation of Gynecology and Obstetrics (FIGO)⁵ Stage IIB to IVA - cervical cancer. In 50% of cases, it failed both locally and distantly, suggesting the need of additional therapeutic modalities.⁶ Many studies suggest that inclusion

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of chemotherapy with radiation will increase the effect of radiation.⁷ Prognosis depends on disease stage (FIGO), tumor volume, the presence of involved lymph nodes, delivered radiation dose, treatment duration, hemoglobin level, and optimum use of intracavitary brachytherapy.⁸ Several randomized trials in 1990 compared the effects of cisplatin along with radiation to radiation alone. The results of these studies show that concurrent chemoradiation lowers the risk of recurrence and death.^{9,10} Squamous cell carcinoma account for 80% of all cervical cancers, and adenocarcinoma constitutes approximately 20%.

Aim

This study aims to analyze the tumor response, the disease-free and overall survival rate in patients with locally advanced carcinoma cervix.

MATERIALS AND METHODS

This prospective cohort study was conducted in Department of Radiotherapy, Government Medical College, Thrissur.

Inclusion Criteria

Newly diagnosed patients with histologically confirmed carcinoma cervix, patients with FIGO Stage IIB to IVA, and no evidence of distant metastasis. Gynecological oncologic group performance status of 0-3, age <70 years, white blood cells (WBC) count >4000 cells/ml, an absolute neutrophil count >37.5%, platelet count of 100000 platelets/ml, serum creatinine <1.5 mg/dl, creatinine clearance more than 80 ml/min, and hemoglobin value >8 g%.

Exclusion Criteria

Carcinoma cervix FIGO Stage IA-IIA, history of renal disease, coronary artery diseases, uncontrolled hypertension, the presence of distant metastasis, age more than 70 years, WBC count <4000 cells/ml, an absolute neutrophil count <37.5%, platelet count <100,000 cells/ml, serum creatinine >1.5, creatinine clearance <80 ml/min, and hemoglobin value <8 g%.

A thorough clinical examination was performed including per speculum examination, per vaginal (PV) examination, digital rectal examination, and per abdominal examination. In all patients, investigations such as chest X-ray, ultrasonography abdomen, magnetic resonance imaging (MRI), complete blood count, renal function test, liver function test, and urine analysis were done. Cystoscopy and sigmoidoscopy were performed only in patients clinically suspicious of bowel and bladder invasion. Tumor size was examined clinically by two different examiners before, and following the treatment, after the treatment MRI scan of

abdomen and pelvis will be repeated. Disease-free survival is analyzed from date of registration to local or distant relapse or death or last visit.

External Beam Radiotherapy

All patients were irradiated by external beam radiation with megavoltage beams on telecobalt machine with a total dose of 45 Gy given in 23 fractions of 1.95 Gy per fraction, 5 fractions per week starting 1st day of the first chemotherapy. The upper border of the individualized treatment beam is at the lower margin of L4 to include distal common iliac nodes. The inferior border is 3 cm below the most inferior disease in the vagina as palpated or seen on MRI. Lateral borders are 2 cm outside the bony pelvic sidewalls. The anterior border must encompass the GTV-T as well as the common iliac nodes and is usually placed through the anterior third of the symphysis pubis. The posterior border is 2 cm from the GTV-T including the posterior extension of tumor, uterosacral ligaments, and upper presacral nodes and is commonly situated 0.5 cm posterior to the anterior border of the S2/3 vertebral junction.

Chemotherapy

All patients received weekly cisplatin 40 mg/m² given intravenously starting on day one of radiation. Premedication consisted of dexamethasone 8 mg IV, and a 5-HT₃ receptor antagonist as antiemetic with hydration with 1000 ml NS followed by mannitol 20 g followed by cisplatin in 500 ml normal saline followed by injection calcium gluconate 1 ampule in 500 ml normal saline followed 500 ml ringer lactate. Antiemetic prophylaxis will be continued with 5-HT₃ receptor antagonist orally for 3 days after each cycle of chemotherapy.

Brachytherapy

After completion of the external beam therapy, all patients were subjected to high-dose rate brachytherapy, with dosage of 7 Gy to point A in three sittings (one sitting/week) were given for patients with minimal residual disease after external beam radiation and 8 Gy to point A in two sittings were given for those with no residual after external beam radiation. Brachytherapy was planned 1 week after external beam radiation.

The regimen was administered on outpatient basis. All patients were monitored closely weekly during the course of concurrent chemoradiation for assessing the toxicity of therapy. Toxicity grading was done according to the RT Oncology Group grading.

Treatment Monitoring and Follow-up

The patients require to follow-up at 6 weeks from completion of therapy to assess response, toxicity, and disease status. Subsequent follow-up visits scheduled at

monthly up to 1 year. At follow-up, patients undergo thorough clinical examination for detection of locoregional disease. Patients who drop out or do not complete planned course of treatment will be excluded.

RESULTS

45 patients satisfied the inclusion criteria and were taken up for the study with their consent. The mean age of the study population was 57 years, ranging from 35 to 70 years. 20 patients (44.1%) are in the age group of 61-70 years old. 11 patients (24.1%) are below the age of 50 years, 14 patients (31.1%) are the age group of 51-60 years. Of the 45 patients, 34 (75.6%) are homemaker and 11 (24.4%) are manual labor. 24 patients (53.3%) were below poverty line, and 21 patients (46.7%) were above poverty line. Bleeding PV and discharge PV was present in 38 (84.4%) patients; pain was present in 25 (55.6%) of patients. 11 (24.4%) patients have habit of tobacco chewing. No one has smoking and alcohol habits. 22 (48.9%) patients out of 45 have ECOG 0, and 23 (51.1%) patients have ECOG 1. 20 (44.4%) patients have vaginal involvement, 25 (55.6%) patients do not have vaginal involvement. 21 (46.7%) patient have 4 cm size lesion, 13 (28.9%) have 5 cm lesion, 5 (11.1%) have 6 cm lesion, 3 (6.7%) have 3 cm lesion, 2 (4.4%) have 5.5 cm lesion, and 1 (2.2%) has 2.8 cm lesion. 7(15.6%) have adjacent structure involvement, 38 (84.4%) patient not have adjacent structure involvement. 26 (57.8%) patients have initial stage of 2B, 13 (28.9%) have 3B, 5 (11.1%) have 4A, and only 1 (2.2%) has 3A stage. 35 (77.8%) patients received only 4 cycles of concurrent chemotherapy, and 10 (22.2%) received 5 cycles of concurrent chemotherapy. Only 8 (17.8%) patients developed recurrence, 37 (82.2%) patients not developed recurrence (Table 1).

37 (82.2%) patients did not develop recurrence of disease, 6 (13.3%) developed recurrence in the cervix, 1 (2.2%) developed recurrence in the bladder, and 1 (2.2%) developed recurrence in the brain (Table 2).

After a follow-up period of 1 year, 6 (13.3%) patients developed recurrence in the cervix, 1 (2.2%) patient developed brain metastasis, and 1 (2.2%) patient developed bladder recurrence. No recurrence was seen in 37 (82.2%). Hence, disease-free survival after 1 year is 82%.

Only 1 (2.2%) patient developed distant metastasis, 44 (97.8%) patients not developed distant metastasis (Table 3).

Only 1 (2.2%) patient died, the cause of death being renal failure. The remaining 44 (97.8%) patients are alive. Only one patient died out of 45 patients. The overall survival after 1 year is 98% (Table 4).

Analysis using paired *t*-test shows there is a significant reduction in the size of the tumor after concurrent chemoradiation irrespective of the recurrence status (Table 5).

Only one patient had metastasis, and she developed recurrence. Death occurred in only one case. She had bleeding PV, discharge, and pain. No comorbidities and no substance abuse were observed. The adjacent structure was involved and the stage was 4A. 4 cycles of concurrent chemotherapy were given. Death was due to renal failure.

DISCUSSION

In the present study, 26 (57.8%) patients were Stage 2B, 1 (2.2%) patient was Stage 3A, 13 (28.9%) patients were

Table 1: Recurrence

Response	Frequency (%)
No recurrence	37 (82.2)
Have recurrence	8 (17.8)
Total	45 (100.0)

Table 2: Site of recurrence

Response	Frequency (%)
No recurrence	37 (82.2)
Bladder	1 (2.2)
Brain	1 (2.2)
Cervix	6 (13.3)
Total	45 (100.0)

Table 3: Metastasis

Response	Frequency (%)
No	44 (97.8)
Yes	1 (2.2)
Total	45 (100.0)

Table 4: Living status

Response	Frequency (%)
Not alive	1 (2.2)
Alive	44 (97.8)
Total	45 (100.0)

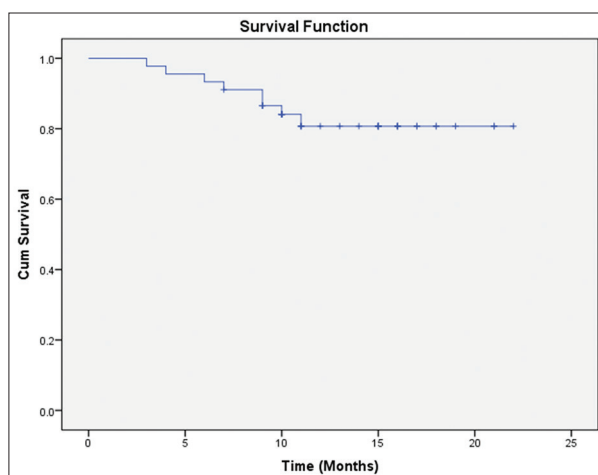
Table 5: Comparison of tumor size before and after treatment between groups with or without recurrence

Recurrence	Mean size (before treatment)	Mean size (after treatment)	t value	P value
Present (n=8)	4.813	0.250	13.72	<0.0001
Absent (n=37)	4.414	0.343	28.02	<0.0001

Table 6: Comparison of study results

Study	Number of patients	Overall survival (%)	Disease-free survival (%)
GOG 120 ¹⁴	526	70 (30 months) 60 (5 years)	63 (30 months) 58 (5 years)
Donnelly <i>et al.</i> ¹²	236	-	69 (5 years)
Kato <i>et al.</i> ⁷	120	55.1 (5 years)	-
Kim <i>et al.</i> ¹³	158	67 (4 years)	-
Present study	45	98 (1 years)	82 (1 year)

GOG: Gynecologic Oncology Group Study

**Figure 1: Disease-free survival**

Stage 3B, and 5 (11.1%) patients were Stage 4A. Out of these, 2 (7.7%) patients in Stage 2B, 2 (15.4%) patients in Stage 3B, and 4 (80.0%) patients in Stage 4A developed recurrence. Treatment was well tolerated. The overall survival after 1 year in this study group is 98%. Only one patient died. The patient had recurrence and the cause of death was renal failure. The disease-free survival in this study group was 82% after 1 year (Figure 1). 8 patients developed recurrence (7 developed local recurrence and one had distant metastasis). Cervix was the most common site of recurrence and brain was the site of distant metastasis. There was significant reduction of the size of the tumor after concurrent chemoradiation. In the study by Verma *et al.*,¹¹ the overall survival at 10.4 months is 68.8%. In the study by Geara *et al.*,⁸ the overall survival after 2 years was 78%. In a study by Donnelly *et al.*,¹² the disease-free survival was 69% at 5 years. Study by Kim *et al.*¹³ showed an overall survival of 67% at 4 years (Table 6).

CONCLUSION

Concurrent chemo-RT is an effective treatment for patients with Stage IIB to Stage IVA cervical cancer. There are many prognostic factors influencing treatment outcome.

Chemotherapy must be added in appropriate patients to improve the outcome. Future prospective trials should be undertaken to confirm the validity of these factors and to individualize the treatment strategy for every patient.

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