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Original Article

Clinical Profiles and Survival Analysis of Patients with Carcinoma Cervix at a Tertiary Care Center: A Retrospective Study

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Abstract

Introduction: Cervical cancer is the fourth most frequent cancer in women with an estimated 570,000 new cases in 2018 representing 6.6% of all female malignancies. Apparently 90% of deaths from cervical cancer occurred in low- and middle-income countries; the annual death rate was more than 26,600.

Aim: This study aims to assess the clinical profiles, overall survival, and disease-free survival (DFS) of carcinoma cervix and to assess the factors that determine the treatment outcome.

Materials and Methods: A total of 298 patients who met the inclusion criteria of newly diagnosed patients with histopathologically confirmed cervical carcinoma were included in the study. The clinical profile, status of presentation, staging, compliance with treatment and follow-up, as well as the response to the treatment in terms of OS and DFS of the treated patients and its contributing factors were the outcome measures.

Results: Two hundred and forty-five (82.2%) of 298 patients of the study population completed the scheduled radical treatment. The most common presentation was Stage 2B with 125 (41.9%) patients followed by 3B with 87 (29.2%) patients and 4A with 12 (4%). The common histology was squamous cell carcinoma (90.6 %). Mean duration of treatment time in concurrent chemoradiotherapy + brachy was 10.93 weeks and external beam radiotherapy + brachy was 10.63 weeks. The median follow-up duration was 4.8 years. The overall survival rate was 97.1% and the mean disease-free survival period rate was 93.4%. In the treatment group, 17 (6.9%) patients showed recurrence, 4 (1.6%) deaths of the total of 20 recurrences, and 8 deaths in the study population.

Conclusion: Similar outcome in the treatment group in terms of overall survival and DFS compared to other studies, with statistical significance in factors contributed to the recurrence. Although treatment defaulters and follow-up defaulters were reaching a good number of the study group, for which care and provision of awareness measures should be taken.

Key words: Cervical cancer, Clinical characteristics, Survival

INTRODUCTION

Cervical cancer is the fourth most frequent cancer in women with an estimated 570,000 new cases in 2018 representing 6.6% of all female malignancies. Apparently 90% of deaths from cervical cancer occurred in low- and middle-income countries; the annual death rate was more than 26,600.[1] 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, poor self-hygiene, multiple sexual partners, first coitus in young age, early childbirth, promiscuity of the spouse, human papillomavirus infections, sexually transmitted diseases, and immune-compromised states are cited as main risk factors.[2]

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

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women with cervical cancer are diagnosed at an advanced stage which is associated with poor prognosis.[3] Prognosis depends on disease stage (FIGO), tumor volume, presence of involved lymph nodes, delivered radiation dose, treatment duration, hemoglobin level, and optimum use of intra-cavitary brachytherapy.[3] Several randomized trials in 1990 compared the effects of regimen that includes cisplatin along with radiation to radiation alone. The results of these studies showed that concurrent chemoradiation lowers the risk of recurrence and death.[4-6] Squamous cell carcinoma accounts for 80% of all cervical cancers and adenocarcinoma constitutes approximately 20%. The standard of care for advanced carcinoma cervix is concurrent chemoradiation.

Aim

This study aims to assess the clinical profiles, treatment response, and overall and disease-free survival (DFS) of carcinoma cervix and to assess the factors that are determined the treatment outcome.

MATERIALS AND METHODS

The retrospective study of patients attended to the Institute of Obstetrics and Gynecology, Madras Medical College, Chennai, from January 2014 to December 2014, was carried out.

Inclusion Criteria

The following criteria were included in the study:

1. Newly diagnosed patients with histopathologically confirmed carcinoma cervix attending the hospital.
2. Performance status of 0–3.

Exclusion Criteria

The following criteria were excluded from the study:

1. Previously diagnosed patients and undergone treatment outside with histopathologically confirmed carcinoma cervix attending the hospital.
2. Performance status of 4.

The recorded data of thorough history and clinical examination performed including per speculum examination, per vaginal examination, digital rectal examination, and per abdominal examination, in all patients, investigations such as chest X-ray, ultrasonography abdomen, magnetic resonance imaging of abdomen and pelvis, complete blood count (CBC), renal function test, liver function test, and urinalysis will be obtained. Cystoscopy was done routinely and sigmoidoscopy was performed only in patients clinically suspicious of bowel invasion. Tumor size was examined clinically and by imaging before the treatment. DFS is analyzed from date of registration to local or distant relapse or death or last visit. Toxicity grading was done according to the radiation therapy oncology group (RTOG) grading; it includes neutropenia and gastrointestinal symptoms like diarrhea, assessed by weekly CBC and RFT and weekly check-up.

External Beam Radiotherapy

All patients were irradiated by external beam radiation with megavoltage beams on telecobalt (Co^{60}) machine with a total dose of 45 Gy–54 Gy given in 23–28 fractions of 1.8–1.95 Gy per fraction, five fractions per week starting the 1st day of the first chemotherapy.[7,8]

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 imaging. Lateral borders are 2 cm outside the bony pelvic sidewalls. The anterior border must encompass the gross tumor volume-T (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.[7,8]

Chemotherapy

With respect to the performance status, patients were received either weekly inj. cisplatin 40 mg/m^2 or 3 weekly inj. cisplatin + inj. 5 FU regimen given intravenously starting on day 1 of radiation. Premedication where administered as per hospital protocol. Antiemetic prophylaxis will be continued with 5HT3 receptor

Table 1: Survival rate

DFS	*n*	Minimum	Maximum	Mean	Std. deviation
Disease-free survival – descriptive statistics					
DFS days	245	91	1918	1643.89	335.526
DFS weeks	245	13.00	274.00	234.8417	47.93234
Overall survival – descriptive statistics					
OS days	245	520	1918	1705.23	182.019
OS weeks	245	74.29	274.00	243.6040	26.00277
Valid N (listwise)	245				

Table 2: Comparison survival rate

Study	Number of patients	Overall survival	Disease-free survival
GOG 120[16,17]	526	70% (30 months) 60% (5 years)	63% (30 months) 58% (5 years)
Donelly *et al*.[8]	236	-	69% (5 years)
Kato *et al*.[9]	120	55.1% (5 years)	-
Present study	245	97.1% (4.8 years)	93.4% (4.8 years)

antagonist orally for 3 days after each cycle of chemotherapy.[9,10]

Brachytherapy

After completion of the external beam therapy, all patients were advised to high-dose-rate brachytherapy, with the dosage of 7–9 Gy to Point A in two-three sittings (1 sitting/week) was given for patients with minimal residual disease after external beam radiation.[7,8] Brachytherapy was planned 1 week after external beam radiation. The regimen was administered on admission 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 RTOG grading.

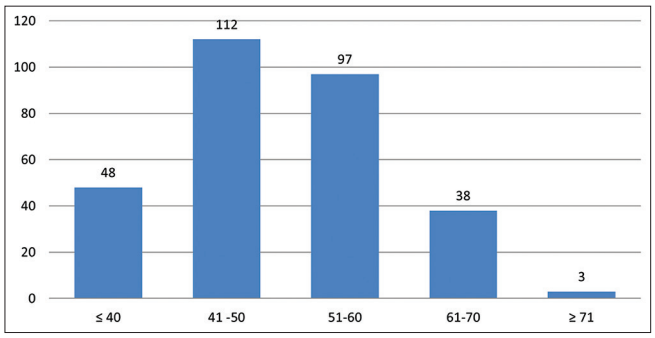

Figure 1: Age-wise distribution

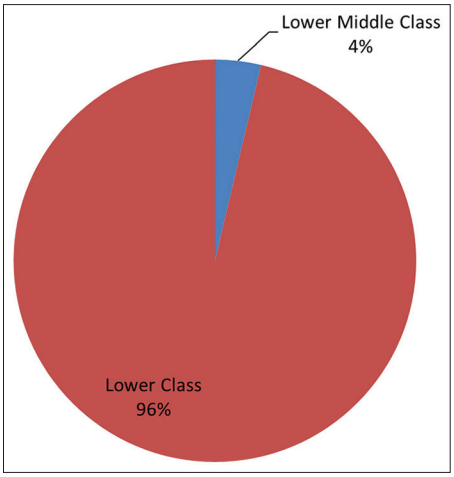

Figure 2: Socioeconomic status. #The socioeconomic status was assessed based on per capita monthly income, using Modified BG Prasad SES, revised income categories for all India (Industrial Workers) 2014

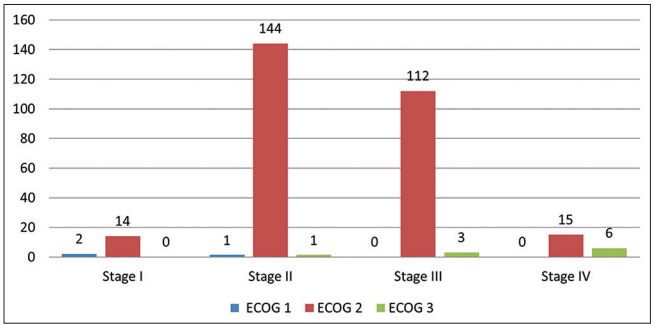

Figure 3: Stage-wise performance status

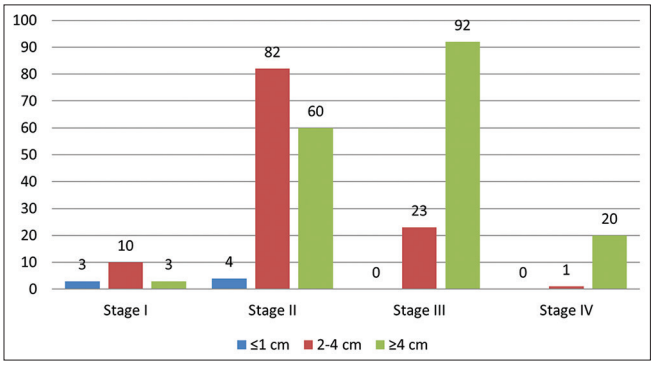

Figure 4: Size of the lesion versus stage of the disease

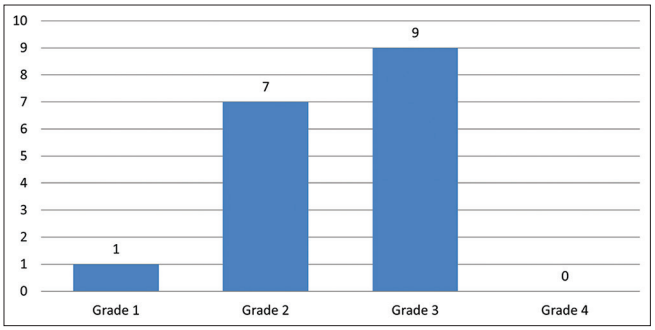

Figure 5: Grade of the tumor

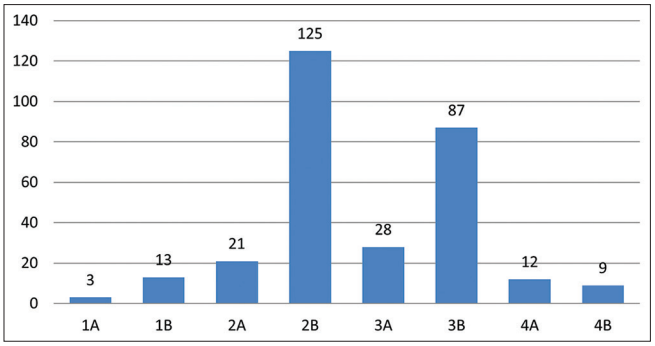

Figure 6: Stage distribution

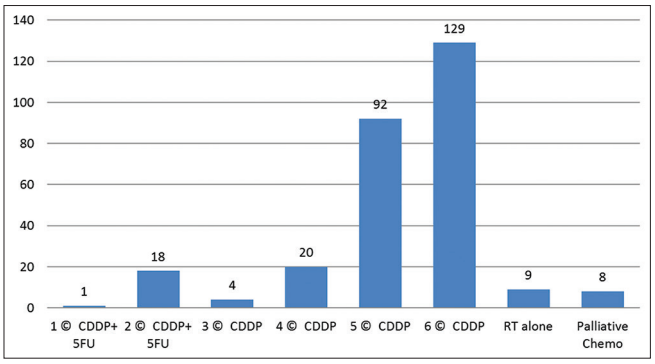

Figure 7: Number of chemotherapy/external beam radiotherapy

Treatment Monitoring and Follow-up

The patients were followed-up monthly for the first 3 months followed by 3 monthly for 3 years, then 6 monthly from completion of therapy to assess response, toxicity, and disease status. At follow-up, patients were undergone thorough clinical examination for the detection of locoregional disease. Patients who drop out or do not complete the planned course of treatment were excluded from the study.

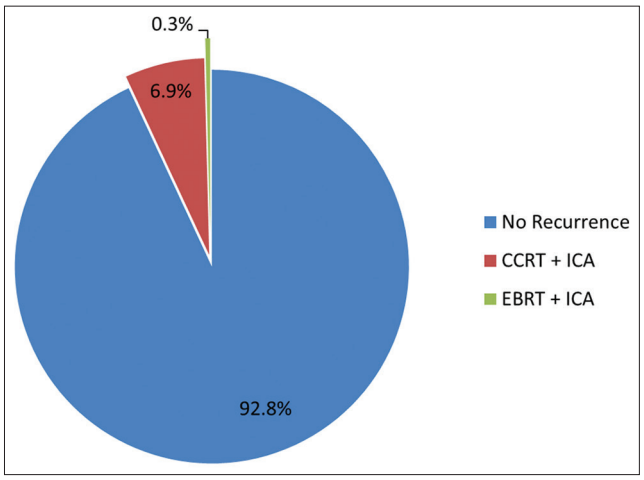

Figure 8: Treatment group recurrence

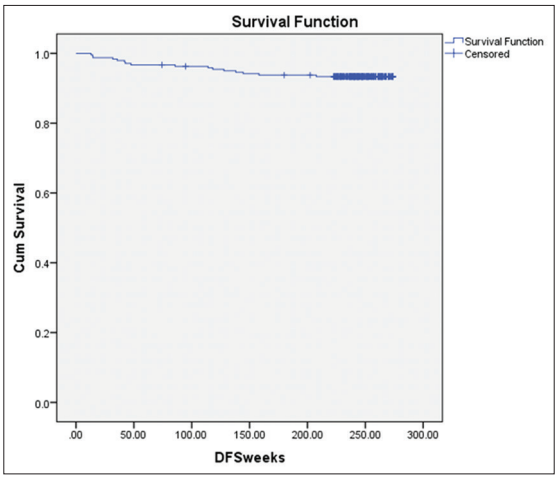

Figure 9: Disease-free survival

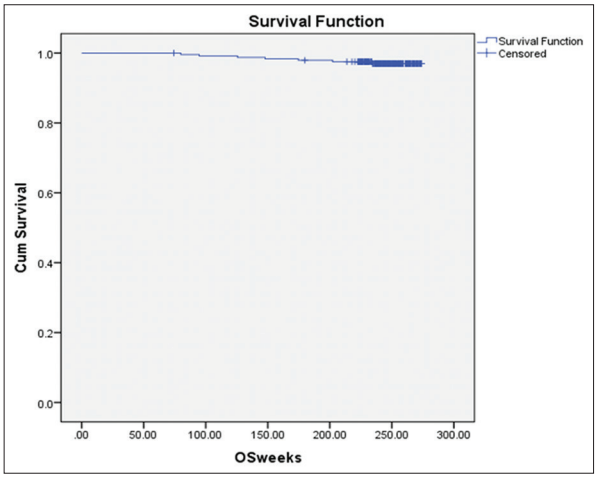

Figure 10: Overall survival

RESULTS

A total of 298 patients who fulfilled the criteria were included in the study. Of 298 patients of the study population, 245 patients completed the treatment schedule. There were 17 dropouts before the commencement of any mode of intervention; eight patients were assigned for palliative chemotherapy due to the disease burden at the time of presentation.

The mean age of this study population was 51.04 years, ranging from 30 to 80 years. Majority 37.58% of patients were in the age group of 41–50 years. Forty- eight patients (16.1%) are below the age of 40 years and 3 patients (1.02%) were the age group of above 71 years Figure 1.

The mean parity of the study population was 3.09, ranging from 0 to 11. Nulliparous being 8 patients, the majority of the population were having 3 childbirths (33.9%). Of the 298 patients, 264 (88.6%) were housewives and 34 (11.4%) were manual labors; 287 patients (96%) were lower class and 11 patients (4%) were lower middle class Figure 2.

Fifty patients had regular medication for hypertension and 65 patients were on diabetic treatments.

Bleeding PV and discharge PV were present in 57.4% and 65.4% of patients, respectively; the pain was present in 51.6% of patients. About 19.1% presented with dysperonia and 16.4% presented with postcoital bleeding and most of them were young below the age group of 50 years.

Twenty-five (8.4%) patients had habit of tobacco chewing and one had smoked, none with alcohol habit. Two hundred and eighty-five (96%) patients had ECOG 2 and 10 (3%) patients had ECOG 3, due to the locally advanced disease status Figure 3.

Two hundred and seventy-six (93%) patients had vaginal involvement, parametrial and pelvic sidewall involvement was documented in 257 and 107 patients, respectively, at the time of presentation. One hundred and seventy-five (58.7%) patients had more than 4 cm size lesion, 116 (38.9%) had 2–4 cm lesion, and 7 (2.3%) had <1 cm size lesion Figures 4 and 5.

Seventeen (5.7%) had adjacent structure involvement, in the study population.

The most common histology was squamous cell carcinoma constituting 90.6%, followed by adenocarcinoma 18% and other histological variants including clear cell, small cell, and anaplastic verities all together 3.4% (10 patients). The most common presentation was Stage 2B with 125 (41.9%) patients followed by 3B with 87 (29.2%) patients; eight patients presented with distant metastasis before the commencement of any kind of treatment Figure 6.

Of 298 patients, 17 patients defaulted before the starting of any kind of treatment and eight patients dropped out during and in between the time of proposed external beam radiotherapy (EBRT) or concurrent chemotherapy regimen, 264 patients received concurrent chemo RT with either CDDP weekly or CDDP+5FU 3 weekly schedule, and nine patients were assigned for RT alone, for disease status either being early stage or following their surgery, or those who were not willing for chemotherapy. Eight patients were given palliative chemotherapy due to their disease burden, those who were not fit for radical intervention Figure 7.

Twenty-three (9%) developed Grade 2 neutropenia, 92 (35%) developed Grade 1 neutropenia, 149 (56%) developed Grade 0 neutropenia, and none developed Grade 3 neutropenia. Cystitis and diarrhea were noticed in 26 and 80 patients, respectively, during the concurrent chemo RT. Of 264 patients who completed concurrent chemoradiotherapy (CCRT), 28 patients failed to attend or undergo advised brachytherapy. Excluding them, the mean duration of treatment time in CCRT+ICA was 10.93 weeks and the minimum treatment duration was 8 and maximum is 15 weeks. The mean treatment duration of EBRT + ICA was similar to 10.63 weeks. Two hundred and fifty-three (92.8%) patients did not develop a recurrence of disease those who underwent any kind of treatment modality and 20 (7.2%) developed recurrence either local or distant one. Among them, 12 patients had local site, cervix, and lymph node (4.2%) recurrence and 8 (3%) developed recurrence at distant sites, being bone (7) and lung (1) metastasis. Three recurrences were reported in those 28 patients who failed to turn up for brachytherapy following the CCRT.

Sixteen patients of 236 patients developed recurrence who had undergone proposed treatment of CCRT + brachy, 220 (93.3%) patients did not develop recurrence. One patient of nine who had undergone the EBRT + brachy treatment developed local recurrence. Six patients developed metastasis in the treatment completed group (CCRT + ICA or EBRT + ICA), till their last follow-up period documented. Four deaths in the treatment group noted, one patient (at 82 years) suffered cardiac failure, one patient due to local site disease recurrence, and three patients due to distal metastasis.

Increased chances of recurrence were noted in patients with prolonged treatment duration (12.81 ± 1.291 standard deviation [SD]) compare to non-recurrent group patients (10.72±1.403 SD), which is statistically significant (significant at 0.01 levels, sig. [two tailed] on *t*-test). One of 10 lower-middle-class patients developed recurrence, 16 of 235 lower-class patients developed recurrence, though statistically not significant, the recurrence was high in lower socioeconomic status patients. Tobacco consumption failed to show the significance of recurrence may be due to lesser no study population. None of four patients who had ECOG score 1 developed recurrence, 15 of 230 patients who had ECOG score 2 developed recurrence, and 2 of 11 patients who have ECOG score 3 developed recurrence. Although it failed to show the significance, the percentage-wise rise in recurrence was noted in poor performance status patients. Two of nine patients who had adjacent structure involvement developed recurrence, which was statistically significant ($P < 0.001$). Sixteen of 236 patients who had CCRT with cisplatin alone chemotherapy developed recurrence, none of 14 patients who underwent 2 cycles CDDP+5FU had not developed recurrence. Six of 26 patients who had two sittings of brachytherapy developed recurrence and 11 of 219 patients who had three sittings of brachytherapy developed recurrence which were statistically significant ($P = 0.01$) on the recurrence of disease in two sittings of the brachytherapy group. One of 14 patients in Stage I, 7 of 126 patients in Stage II, 7 of 92 patients in Stage III, and 2 of 13 patients in Stage IV were developed recurrence Figure 8.

Of 298 study population, a total of eight deaths reported include one patient who undergone palliative chemotherapy due to lung metastasis, one patient due to local site disease recurrence who denied ICA following CCRT, one patient due to distant metastasis who denied concurrent chemo, and four patients from the treatment group.

Of four patients in the treatment Group 1 patient (at 82 years) suffered cardiac failure, one patient due to local site disease recurrence, and three patients due to distal metastasis. The overall survival after a mean follow-up period of 4.8 years in the treatment group is 97.1% and the DFS in this treatment group was 93.4% [Tables 1 and 2, Figures 9 and 10].

DISCUSSION

In the early stage (FIGO Stage Ib and IIa), cervical cancers, surgery, irradiation, or combinations have been advocated, each claiming to yield higher cure rates and less morbidity. Although surgery results in accurate staging and appropriate adjuvant therapy, combined surgery and

radiation result in increased morbidity. Patients without risk factors have a 5-year survival rate of 82–92%.[7] In the 1990s, the use of adjuvant therapy with stratified risk factors has shown benefit in survivals and is the standard of care today.[8] However, in the 1970s–1980s, adjuvant therapy was empirical and practiced in patients with high-risk features such as pelvic nodal involvement and cut margins positive.

A combination of radiation and surgery has been used to improve therapeutic outcome. Pre-operative radiation (5000–6000 mgh, alone or combined with whole pelvis irradiation) has been administered with a rationale to render tumor biologically non-viable, decrease pelvic and distant relapses. The 5-year survival rate was 89% versus 55% for patients with negative versus positive nodes after pre-operative RT, results comparable with our series of 283 patients, in which short course hypofractionated radiation regimens had better outcome with DFS of 62% at 8 years, 6% incidence of post-operative wound infection, 1.2% intestinal obstruction/fistulae, and 2% mortality. The major criticism of these studies has been conflicting reports of higher rates of complications without significant benefit in outcome.[9]

Since decades, radiation has played a major role in the treatment of locally advanced cervical cancer. Standard treatment has been radical radiation, with the key to success is the administration of appropriate doses to the central tumor and pelvic sidewall.[10] In different series, 5-year survival rates of 65–75%, 35–50%, and 15–20% have been reported in patients who received radiotherapy alone for Stage IIB-IV tumors.[11] Furthermore, the American Brachytherapy Society recommends keeping the total treatment duration to <8 weeks because prolongation of total treatment duration can adversely affect local control and survival.[12] Modern approach to the management of cervical cancer has changed to concomitant chemoradiation in advanced cervical cancer with Level 1 evidence today with significant improvement in local control and survivals. However, hematological and gastrointestinal toxicities were significantly more with chemoradiation and no concrete data on late toxicities.[13,14]

The study by Geara *et al*.[15] the overall survival after 2 years was 78%. The toxicities included 19% leucopenia Grade 1–4, 12% Grade 3–4 hematological toxicities, and 37% Grade 3–4 diarrhea.

GOG 120[16,17] study showed an overall survival of 70% (30 months) and 60% (5 years). This study also has 16.8% Grade 3–4 gastrointestinal toxicities. DFS at 30 months and 5 years was 63% and 58%, respectively.

In a study by Donnelly *et al*.,[18] the DFS was 69% at 5 years. A study by Kato *et al*.[19] showed overall survival 55% at 5 years.

CONCLUSION

In this study, the mean follow-up of 4.8 years, the DFS was 93.4%, and the overall survival was 97.1%, which is comparable to other published studies. The statistical significance was seen between the recurrence with treatment duration, adjacent structure involvement, and number of brachytherapies in the present retrospective study. Further studies with large sample sizes are needed to confirm the predictive factors for disease-free and overall survivals. The need for any adjuvant treatment to decrease the recurrence rate in the poor prognostic group also warrants further evaluation. Treatment defaulters and follow-up defaulters were reaching a good number of the study group, for which care and provision of awareness measures should be taken.

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