

Outcomes of Cervical Cancer in HIV-Positive Women Treated With Radiotherapy at a Tertiary Care Center in India

Lavanya Gurram, MD¹; Samarpita Mohanty, MD¹; Supriya Chopra, MD¹; Surbhi Grover, MD, MPH²; Reena Engineer, MD¹; Sudeep Gupta, MD, DM³; Jaya Ghosh, MD, DM⁴; Seema Gulia, MD, DM⁴; Sheela Sawant, MD⁵; Anuprita Daddi, MD⁵; Kedar Deodhar, MD⁶; Santosh Menon, MD⁶; Bharat Rekhi, MD⁶; T.S. Shylasree, MD⁷; Amita Maheshwari, MD⁷; and Umesh Mahantshetty, MD, DNB⁸

PURPOSE There are limited data on management of cervical cancer in women living with HIV in the modern antiretroviral therapy era. The study aimed to evaluate outcomes and toxicities of these patients treated with radiotherapy.

MATERIALS AND METHODS A retrospective analysis of HIV-positive cervical cancer patients treated with radiotherapy between 2011 and 2018 was conducted at a tertiary care center in India.

RESULTS Eighty-two HIV-positive cervical cancer patients treated with radiotherapy were identified. Their median age was 45 years. Seventy-four (90%) patients received radiotherapy with curative-intent and eight patients received palliative radiotherapy. Median CD4 count at the start of treatment was 342 cells/mm³ (interquartile range: 241-531). Among patients planned for definitive radiotherapy, concurrent cisplatin was planned in 52 (70%) patients with a median of four chemotherapy cycles, and 81% (n = 60) patients received brachytherapy. Among patients who received brachytherapy, the median prescription dose was 80 Gy. Seventy-seven patients completed their prescribed treatment. At a median follow-up of 37 months, 3-year disease-free survival of patients planned with curative-intent was 54%. On multivariate analysis, treatment completion was associated with favorable disease-free survival. Grade III/IV acute gastrointestinal toxicity was seen in five (6.8%) patients, whereas 30% patients had grade III/IV acute hematologic toxicity. All these patients completed their planned radiotherapy with good supportive care.

CONCLUSION Standard treatment of chemoradiation should be planned in women living with HIV with well-managed HIV presenting with locally advanced cervical cancer. Our study highlights the need for optimal management of these patients by a multidisciplinary team with intensive supportive care to ensure completion of planned treatment to achieve better outcomes.

JCO Global Oncol 8:e2100312. © 2022 by American Society of Clinical Oncology

Creative Commons Attribution Non-Commercial No Derivatives 4.0 License 

INTRODUCTION

Cervical cancer is one of the most common cancers among women worldwide and a leading cause of cancer-related mortality. It is the second most common cancer among women in India, and majority of the patients (60%) present in locally advanced stage.¹ Radiotherapy with concurrent cisplatin-based chemotherapy remains the standard of care for locally advanced cervical cancer on the basis of phase III randomized controlled trials and meta-analyses.²⁻⁵

The incidence of cervical cancer is more common in women living with HIV (WLWH) compared with HIV-negative women.^{6,7} WLWH are susceptible to persistent human papillomavirus infection, which can subsequently lead to cervical cancer.⁸ In India, HIV incidence was estimated at 0.05 per 1,000 uninfected population in 2019.⁹ The national guidelines recommend initiation of antiretroviral therapy (ART) in all

individuals diagnosed with HIV irrespective of CD4 counts or on the basis of WHO clinical staging.¹⁰

WLWH and cervical cancer usually present at locally advanced stage, especially in developing world probably because of barriers in cervical cancer screening.^{11,12} According to the National Comprehensive Cancer Network guidelines and the International Atomic Energy Agency health report, modifications to cancer treatment are not recommended solely on the basis of HIV status.^{13,14} However, chemoradiation has been associated with high risk of acute toxicities because of the immunocompromised state of these patients. Moreover, many antiretroviral drugs cause interactions with chemotherapeutic agents leading to their altered efficacy or increased toxicity.^{15,16} Additionally, protease inhibitors have also been known to have radiosensitizing properties.¹⁷

There have been conflicting results in the outcomes of cervical cancer treatment in WLWH compared with

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on February 15, 2022 and published at ascopubs.org/journal/go on March 24, 2022; DOI <https://doi.org/10.1200/GO.21.00312>

CONTEXT

Key Objective

This study aimed to understand the impact of HIV on the outcomes of cervical cancer in patients treated with radiotherapy in the modern antiretroviral therapy era.

Knowledge Generated

HIV-positive women with cervical cancer need special attention to ensure completion of the planned treatment for optimizing their outcomes. In the current study, only 40% of patients planned for chemotherapy could receive four or more cycles of concurrent cisplatin, whereas 81% patients could complete the planned radiotherapy. The acute toxicities, especially hematologic toxicity, appear to be higher in these patients, necessitating the need for good supportive care during treatment.

Relevance

This study highlights the importance of management of these patients by a multidisciplinary team to ensure better compliance to cervical cancer treatment for achieving better outcomes. The 3-year disease-free survival and overall survival of 54% and 60%, respectively, suggest a scope for improvement in the treatment strategy to optimize results.

patients without HIV.^{11,12,18,19} There has been heterogeneity in the treatment protocols adopted in these patients because of concerns regarding toxicity and compliance to the aggressive treatment. With paucity of data available in patients with well-managed HIV, it is imperative to understand the impact of standard treatment with respect to survival outcomes, toxicities, and compliance to the treatment. The current study aims to evaluate the outcomes of WLWH and cervical cancer treated with radiotherapy and report the toxicities and compliance to treatment.

MATERIALS AND METHODS

Patients with histologically proven invasive and preinvasive cervical cancer and enzyme-linked immunosorbent assay–confirmed HIV infection who had received radiotherapy at Tata Memorial Hospital, Mumbai, from 2011 to 2018 were included in this retrospective study. The study was approved by Institutional ethics committee (IEC) of our Institute. A waiver of consent was obtained from IEC.

Patient and Tumor Characteristics

HIV clinic database and radiation oncology information system were used to identify the patients, and their details were collected through electronic medical records and case files. Only the patients who were lost to follow-up were contacted via telephone, and their telephonic consent was taken. All the patients were evaluated with clinical history, physical examination, imaging of abdomen and pelvis, and chest x-ray, and were staged according to the FIGO staging system 2009.

ART Details

As a part of routine work-up, all patients are tested for HIV at our center. These patients were sent to ART clinics before initiation of treatment and their baseline CD4 counts were obtained. The ART regimen used in the study period included tenofovir, lamivudine and efavirenz, or tenofovir, lamivudine, and nevirapine.

Treatment Details

Patients planned to be treated with curative-intent were offered definitive (chemo)radiation followed by intracavitary brachytherapy. Patients with extensive disease in the pelvis were planned for palliative radiotherapy. External-beam radiotherapy (EBRT) was delivered to the whole pelvis with conventional technique, that is, standard antero-posterior and postero-anterior portal or box technique or conformal technique to a dose of 45-50 Gy with conventional fractionation followed by three to four fractions of intracavitary brachytherapy to a dose of 6-7 Gy per fraction. Once weekly cisplatin at 40 mg/m² was given during EBRT in patients with Eastern Cooperative Oncology Group performance score < 2, creatinine clearance > 40 mL/min, and CD4 count exceeding 200 cells/mm³. Patients were reviewed weekly to assess toxicities during treatment. Patients planned with palliative intent received 10 Gy/fraction every month for 3 months and were offered intracavitary brachytherapy in case of good response to EBRT. Grading of acute toxicities was done using Radiation Therapy Oncology Group radiation morbidity scoring criteria.

After completion of the treatment, patients were followed up with clinical history, physical examination, and imaging when needed. Late adverse effects were documented using Radiation Therapy Oncology Group scoring scheme.

Statistical Analysis

The primary objective of the study was to determine disease-free survival (DFS). DFS was defined by any recurrence or death, and overall survival (OS) was defined by death because of any cause. The patients who defaulted during treatment and were lost to follow-up were excluded from the survival analysis. Survival outcomes were obtained using Kaplan-Meier method. Univariate analysis was done using chi-square test to evaluate the impact of factors on DFS, and factors with a *P* value < .10 were included in

multivariate analysis, which was done with Cox proportional hazard regression model. All statistical analyses were performed with SPSS v23 software (SPSS Inc, Chicago, IL).

RESULTS

Patient and Disease Characteristics

Among 106 patients who were planned for radiation during the period, 24 patients were excluded (18 patients for not returning for treatment and six patients being referred to

other centers). Hence, a total of 82 HIV-positive cervical cancer patients treated with radiotherapy were included in the study. The median age of the patients was 45 years (interquartile range [IQR]: 40-50 years). Majority of them (95.1%) had locally advanced disease at presentation. The median CD4 count at the start of treatment was 342 cells/mm³ (IQR: 241-531). Sixty-three (77%) patients had history of HIV before cancer diagnosis. Among those, 53 (84%) patients were already on ART. Remaining patients commenced ART either at the beginning or during radiotherapy. Patient and disease characteristics have been summarized in Table 1.

Treatment

Table 2 highlights the treatment-related characteristics. Seventy-four (90.2%) patients received radiotherapy with curative-intent, whereas eight patients were offered palliative radiotherapy. A single patient diagnosed with cervical intraepithelial neoplasia grade III received definitive high-dose-rate brachytherapy to a dose of 7 Gy/fraction for five fractions. The median EBRT dose for patients of invasive cervical cancer treated with curative-intent was 50 Gy (IQR 46-50 Gy). All the patients received planned dose of EBRT, except four (5.4%) patients, of whom three (4%) discontinued treatment and were lost to follow-up. A single patient had disease progression during EBRT and received palliative radiotherapy afterward. Concurrent cisplatin was planned for 52 (71.2%) patients. Among those, 29 (40%) patients received at least four cycles of weekly cisplatin. CD4 count < 200 cells/mm³ was the most common reason for chemotherapy not being planned (n = 8, 40%), followed by defaulted visits to medical oncology clinics (n = 3, 15%) and poor renal function (n = 2, 10%). Among 52 patients, for whom chemotherapy was planned, it was withheld during treatment in 15 patients, most commonly because of hematologic (n = 5) and gastrointestinal (n = 4) toxicities. Majority of the patients (80.8%) received brachytherapy. Noncompliance to the treatment was the most common reason for patients not receiving brachytherapy. The data on equivalent dose at 2 Gy to point A were available for 33 patients. The median equivalent dose at 2 Gy to point A in these patients was 80.6 Gy (IQR: 77.5-85 Gy).

Toxicities

Among 73 patients who received curative treatment, grade III/IV acute toxicity was seen in 24 (33%) patients. Most of these patients (83.3%) had received concurrent chemotherapy. Five patients (6.8%) developed grade III acute gastrointestinal toxicity. A single patient developed grade III skin toxicity and was managed conservatively. Grade III neutropenia was reported in 13 (17.8%) patients, whereas grade IV neutropenia was noted in one patient (1.2%). Any grade III/IV hematologic toxicity was seen in 22 (30%) patients. Among those 19 (86%) patients had received concurrent chemotherapy. However, all these patients

TABLE 1. Patient and Disease Characteristics

Characteristic	No. (%); N = 82
Median age at diagnosis (IQR), years	45 (40-50)
Age, years	
≤ 45	43 (52.4)
> 45	39 (47.6)
Baseline ECOG PS	
< 2	75 (91.5)
≥ 2	3 (3.7)
Missing	4 (4.9)
Education	
Primary school or less	60 (73.2)
More than primary school	22 (26.8)
Background	
Urban	57 (69.5)
Rural	25 (30.5)
Median monthly income (IQR), □	3,000 (2,000-8,000)
Histology	
Squamous cell carcinoma	74 (90.2)
Adenocarcinoma	6 (7.3)
Adenosquamous	1 (1.2)
CIN	1 (1.2)
Disease stage	
FIGO stage I (IB1, IB2)	8 (9.8)
FIGO stage II (IIA, IIB)	30 (36.6)
FIGO stage III (IIIA, IIIB)	39 (47.6)
FIGO stage IVA	2 (2.4)
CIN III	1 (1.2)
Median hemoglobin (IQR), g/dL	11.1 (10.1-11.95)
Median serum albumin (IQR), g/dL	4 (3.8-4.2)
Median serum creatinine (IQR), mg/dL	0.8 (0.7-0.85)
CD4 count at the start of treatment, median (IQR), cells/mm ³	342 (242-531)
Patients diagnosed to have HIV before cancer diagnosis	63 (77)
Duration of ART before cancer diagnosis (IQR), months	35 (14-74)

Abbreviations: ART, antiretroviral therapy; CIN, cervical intraepithelial neoplasia; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range.

TABLE 2. Treatment Characteristics of Patients Treated With Curative-Intent

Characteristic	No. (%); n = 73
Median EBRT dose (IQR), Gy	50 (46-50)
Completion of EBRT as planned	
Yes	69 (94.6)
No	4 (5.4)
Concurrent chemotherapy planned	
Yes	52 (71.2)
No	20 (27.4)
Missing	1 (1.4)
Reason for chemotherapy not being planned	
CD4 < 200 cells/mm ³	8 (40)
Unfit for chemotherapy	2 (10)
Patients defaulting visit to clinic	3 (15)
Missing	7 (35)
No. of chemotherapy cycles (when planned for chemotherapy)	
1	6 (11.5)
2	7 (13.5)
3	6 (11.5)
4	17 (32.7)
5	12 (23.1)
Received brachytherapy	59 (80.8)
Reasons for not receiving brachytherapy	
Discontinued treatment during/after EBRT	10 (66.7)
Death after EBRT	1 (6.7)
Disease progression on EBRT	1 (6.7)
Missing	2 (14.3)
Median EQD2 point A (IQR), ^a Gy	80.6 (77.5-85)
Received radiation with at least four cycles of cisplatin and brachytherapy	28 (38.4)
Treatment response after 6 months of treatment ^b	
Complete response	25 (67.5)
Residual disease	12 (32.5)

Abbreviations: EBRT, external-beam radiotherapy; EQD2, equivalent dose at 2 Gy; IQR, interquartile range.

^aData available for 33 patients.

^bData available for 37 patients.

could complete their planned radiotherapy with good supportive care. One patient (1.4%) developed grade IV late rectum toxicity in the form of rectovaginal fistula and underwent diversion colostomy for the same. The toxicity profile of these patients has been shown in [Table 3](#).

Outcomes

A total of 66 patients treated with curative-intent were considered for DFS analysis. The median follow-up in these patients was 37 months (IQR: 19-74 months). Seven patients who discontinued treatment and were lost to follow-up were not considered for DFS analysis. The 3-year DFS

TABLE 3. Acute Toxicities Associated With (Chemo)Radiation

Toxicities (RTOG grading)	No. (%); n = 73
Skin	
≤ Grade 2	70 (95.9)
> Grade 2	1 (1.4)
Missing	2 (2.7)
GI	
≤ Grade 2	66 (90.4)
> Grade 2	5 (6.8)
Missing	2 (2.7)
Genitourinary	
≤ Grade 2	71 (97.3)
> Grade 2	0 (0)
Missing	2 (2.7)
Anemia	
≤ Grade 2	54 (74)
> Grade 2	10 (13.7)
Missing	9 (12.3)
Neutropenia	
≤ Grade 2	50 (68.5)
> Grade 2	14 (19.2)
Missing	9 (12.3)
Thrombocytopenia	
≤ Grade 2	57 (78.1)
> Grade 2	7 (8.6)
Missing	9 (12.3)
Late toxicities	
Bladder	
≤ Grade 2	45 (61.7)
> Grade 2	2 (2.7)
Missing	26 (35.6)
Rectum	
≤ Grade 2	46 (63)
> Grade 2	1 (1.4)
Missing	26 (35.6)
Subcutaneous tissue	
≤ Grade 2	47 (64.4)
> Grade 2	0 (0)
Missing	26 (35.6)

Abbreviation: RTOG, Radiation Therapy Oncology Group.

and 3-year OS for this cohort of patients was 53.5% and 86.1%, respectively, as depicted in [Figures 1](#) and [2](#). However, when lost to follow-up were considered as events for survival analysis assuming that they received no salvage treatment, the 3-year OS was found to be 60%. The results of univariate analysis and multivariate analysis for various factors predicting DFS are listed in [Table 4](#). On univariate

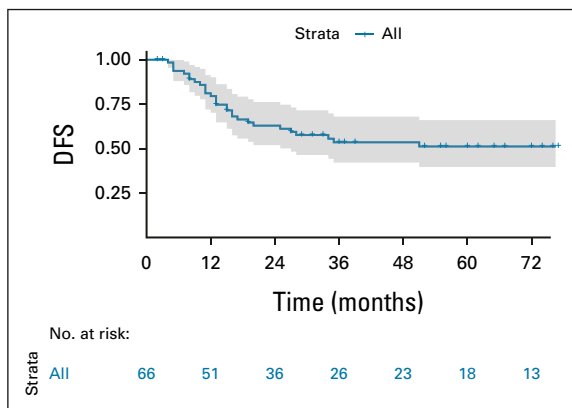


FIG 1. Kaplan-Meier curve showing DFS of 66 patients who completed treatment with curative-intent. DFS, disease-free survival.

analysis, CD4 counts more than 200 cells/mm³, administration of chemotherapy, completion of radiotherapy, and completion of chemoradiation followed by brachytherapy were associated with favorable DFS. Multivariate analysis demonstrated that completion of radiotherapy was the most important predictor of DFS. The local, pelvic nodal, para-aortic nodal, and distant relapses were seen in 19.7%, 4.5%, 6%, and 16.7% patients, respectively. Out of those, only a single patient with local recurrence and another with isolated para-aortic recurrence were salvaged with brachytherapy and EBRT, respectively.

DISCUSSION

Chemoradiation has been the standard of care for locally advanced cervical cancer on the basis of level I evidence.²⁻⁴ However, it has been a challenge in WLWH and cervical cancer, in view of the interplay of multiple factors including immunocompromised status, toxicities of the treatment, drug interactions, poor nutritional status, and, to some extent, social factors. Modern ART has led to dramatic improvement in the immune status and, subsequently, survival in WLWH.²⁰ HIV

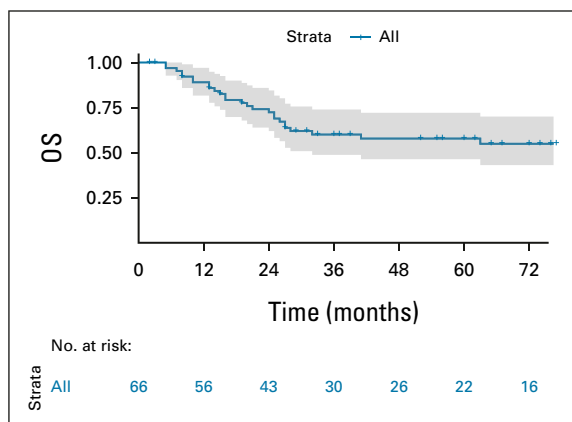


FIG 2. Kaplan-Meier curve showing OS of 66 patients who completed treatment with curative-intent. OS, overall survival.

management along with appropriate cervical cancer treatment remains the cornerstone for the management of these patients for optimal outcomes. The current study adds to the existing limited literature regarding their management in modern ART era. It represents one of the largest cohorts of WLWH and cervical cancer treated with radiotherapy at a tertiary care center. With a reasonable burden of HIV in India, it is also essential to understand the impact of HIV on the outcomes and toxicities of cervical cancer treatment in our patient population and improvise their management protocols.

There have been discordant findings in the outcomes of radiotherapy in WLWH and cervical cancer. An early prospective study from Botswana¹¹ and another retrospective Brazilian study¹² comparing outcomes of cervical cancer treatment in HIV-positive and HIV-negative patients revealed that HIV infection nearly doubled the risk of death. Similarly, a study by Simonds et al²¹ showed significantly lesser 5-year OS in HIV-positive patients, compared with HIV-negative patients. However, a subsequent study from Botswana¹⁹ reported no difference in the OS in patients with well-managed HIV receiving chemoradiation, compared with HIV-negative women. The reasons for the discrepancy as noted by Grover et al include higher median CD4 count, longer median duration of ART, and all patients receiving curative treatment with chemoradiation in the latter study.

CD4 counts have been an important parameter for determining immune status in HIV-positive patients.²² In our study, only 71% patients planned for curative treatment could be prescribed concurrent chemotherapy. CD4 count < 200 cells/mm³ was considered to be the most common reason for not planning chemotherapy. Similarly, a study by Simonds et al²³ revealed that only 61% of their HIV-positive patients were prescribed chemoradiation, and the authors cited the same reason for not planning chemotherapy in most of their patients. Although the data regarding addition of concurrent chemotherapy to definitive radiotherapy in patients with cervical cancer with CD4 count < 200 cells/mm³ are lacking, chemotherapy has usually been omitted in most of the studies because of concerns regarding tolerability in those patients. Furthermore, in the current study, CD4 cell count < 200 cells/mm³ was found to be associated with adverse DFS on univariate analysis. Hence, it is crucial to optimize ART and maintain CD4 count level to plan effective cancer treatment strategies.

The data regarding toxicity profile of these patients are relatively sparse. Most of the earlier studies have reported higher rates of skin and gastrointestinal toxicities in WLWH treated with radiotherapy.²⁴ The only study from India evaluating the outcome of radiotherapy in these patients showed enhanced toxicity, poor response, and compliance to treatment.²⁵ Grade III/IV dermatitis and gastrointestinal toxicity was observed in 27% and 14% patients, respectively, who received radiotherapy alone. However, data regarding CD4 count and management of HIV were lacking in the study. In the current study, grade III/IV acute gastrointestinal toxicity was seen in

TABLE 4. Univariate and Multivariate Analyses for DFS

Factors	Univariate Analysis		Multivariate Analysis	
	3-Year DFS	P	HR (95% CI)	P
Age, years		.47	—	—
≤ 45	52			
> 45	55			
CD4 count, cells/mm ³		.05	1.04 (0.31 to 3.44)	.955
≥ 200	61.5			
< 200	22			
Duration of ART, years		.055	2.15 (0.81 to 5.69)	.122
≥ 2	67.6			
< 2	44.3			
Hemoglobin, g/dL		.53	—	—
≤ 10	53.8			
> 10	51.5			
Received concurrent chemotherapy		.05	2.98 (0.30 to 29.99)	.355
Yes	58.2			
No	35.6			
Completion of EBRT and brachytherapy		.0001	12.71 (2.15 to 75.34)	.005
Yes	59.2			
No	0			
Completion of chemoradiation (at least one cycle of cisplatin) followed by brachytherapy	57.5	.012	0.13 (0.01 to 2.123)	.154
	0			
Overall treatment time, days		.63	—	—
≥ 60	71.5			
< 60	54.7			
EQD2 to point A, Gy		.49	—	—
≥ 80	67.7			
< 80	54.5			
FIGO 2009 stage		.18	—	—
Stage I (IB1, IB2)	57.1			
Stage II (IIA, IIB)	67.3			
Stage III (IIIA, IIIB)	39.3			

NOTE. Bold entries indicate significant *P* value (<0.05).

Abbreviations: ART, antiretroviral therapy; DFS, disease-free survival; EBRT, external-beam radiotherapy; EQD2, equivalent dose at 2 Gy; HR, hazard ratio.

6.8% patients, which is comparable to that in the study by Simonds et al.²³ The incidence of grade III/IV hematologic toxicities in our study is higher than that in previous studies. Thirty-percent of our patients had grade III/IV hematologic toxicity, and most of them had received concurrent chemotherapy. Hence, both hematologic and nonhematologic grade III/IV toxicities appear to be higher in patients of the current study when compared to that of HIV-negative patients in the

chemoradiation randomized controlled trial of stage IIIB patients conducted at our institute.⁵ Chemotherapy had to be interrupted in 29% of our patients because of hematologic and gastrointestinal toxicities. This subsequently led to administration of inadequate cycles of chemotherapy in those patients. This is in contrast to the study by Simonds et al,²⁶ wherein the authors reported renal dysfunction to be the most common reason for incomplete cisplatin-based chemotherapy. Hence, careful monitoring of hematologic parameters during chemoradiation needs to be done and intensive supportive care needs to be provided in case of toxicities. In the recent study by Grover et al¹⁹ and in another study by Mdletshe et al,²⁷ there was no difference in acute hematologic and nonhematologic toxicities in patients receiving chemoradiation on the basis of HIV status. Similarly, in the study of AIDS malignancy consortium, appropriately selected WLWH and cervical cancer were found to tolerate standard treatment of chemoradiation with slightly higher but manageable hematologic toxicity.²⁸ This emphasizes the fact that concurrent chemotherapy needs to be planned carefully, considering the immune status of the patient.

There have been concerns of nephrotoxicity in patients with tenofovir-based ART regimens receiving cisplatin. Hence, AIDS malignancy consortium study had avoided tenofovir along with cisplatin.²⁸ Although most of our patients received either tenofovir, lamivudine, and efavirenz, or tenofovir, lamivudine, and nevirapine regimens, tenofovir was replaced by stavudine (from 2011 to 2017) and abacavir (from 2018 onward) in case of decreased renal clearance at our center. However, there was no report of renal dysfunction in our study. Similarly, the study by Dryden-Peterson et al,¹¹ which had used tenofovir-based ART regimen, had also reported only one case of renal failure. Recently, ART centers in India have switched to dolutegravir-based regimen (Tenofovir-Lamivudine-Dolutegravir [TLD]), which is more effective and has lesser risk of drug resistance. Although dolutegravir may augment serum creatinine level, its potential interaction with cisplatin is not well documented and remains an area of research.

As mentioned earlier, OS has been reported to be lower in the early Botswana study and in another study from South Africa.^{11,21} Even the recent study by Grover et al¹⁹ reported 2-year OS being 65% in the patients receiving standard treatment of chemoradiation. Although the OS appears to be superior in this study (3-year OS: 86%) compared with others, the retrospective nature of the study with many patients lost to follow-up and censored precludes any such interpretations being made. Moreover, it is very likely that recurrences in patients who were lost to follow-up would not have been salvaged. When lost to follow-up for patients who had recurrences were considered as events in the analysis, the 3-year OS was found to be 60%.

Not surprisingly, completion of radiotherapy including brachytherapy was the most important predictor of DFS in this study. Poor compliance to planned treatment has been cited to be the most common reason for failure to complete

treatment. Although the exact reasons for discontinuing further treatment could not be ascertained, toxicities of the aggressive treatment coupled with social factors can be the possible explanations. Hence, intensive supportive care including nutritional support and motivation to have good adherence to the treatment needs to be provided. Management by a multidisciplinary team consisting of radiation oncologist, medical oncologist, HIV specialist, dietician, and medical social worker is of paramount importance.

The strength of the study is in the fact that the patients received good-quality oncologic and infectious disease management. All patients had CD4 counts routinely done and were closely managed by HIV specialists. The study remains one of the few series reporting pattern of recurrences in this patient population. All the patients were clinically examined during each follow-up and therefore, data on tumor response and recurrence and late toxicities could be noted. The limitation of the study includes its retrospective nature. Furthermore, no direct matched comparison was done with outcomes and toxicities of HIV-negative patients. Some patients were lost to follow-up over years and could not contribute to the recurrence and survival data. Additionally, although HIV viral load is the most important marker

determining ART effectiveness, it was not routinely tested during the study period. However, routine monitoring of HIV viral load is being done at our center recently and is the appropriate step to assess response to ART. Despite the above limitations, this study confirms the importance of completion of the planned treatment, along with a need for good supportive care during treatment in these patients. Moreover, we intend to plan a future study comparing outcomes with HIV-negative patients.

In conclusion, our study adds to the existing literature regarding management of WLWH and cervical cancer. The study highlights the fact that standard treatment of chemoradiation should be planned for appropriately selected patients with well-controlled HIV for obtaining optimal outcomes. It also emphasizes the pressing need to have a multidisciplinary team involved in their management and facilitating intensive supportive care to improve tolerability of the treatment and adherence to planned treatment. Larger prospective trials are needed to study the impact of use of advanced radiotherapy techniques in these patients including intensity-modulated radiotherapy to spare bone marrow and bowel to improve the toxicity profile and thus, compliance to the prescribed treatment protocols.

AFFILIATIONS

¹Department of Radiation Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India

²Department of Radiation Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

³Advanced Centre for Training, Research Education in Cancer, Navi Mumbai, India

⁴Department of Medical Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India

⁵Department of Medicine, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India

⁶Department of Pathology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India

⁷Department of Gynecologic Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India

⁸Homi Bhabha Cancer Hospital and Research Centre, Visakhapatnam, India

CORRESPONDING AUTHOR

Lavanya Gurram, MD, Department of Radiation Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Dr Ernest Borges Rd, Parel, Mumbai, Maharashtra 400012, India; e-mail: naidu.lavanya@gmail.com.

PRIOR PRESENTATION

Presented as a poster at the Annual Global Meeting of the International Gynecologic Cancer Society 2021, Rome, Italy, August 29 - September 2, 2021.

SUPPORT

S.G. has mentored Patient Oriented Career Research Development Award (1-K08CA230170-01A1).

AUTHOR CONTRIBUTIONS

Conception and Design: Lavanya Gurram, Samarпита Mohanty, Supriya Chopra, Surbhi Grover, Umesh Mahantshetty

Administrative support: Surbhi Grover

Provision of study materials or patients: Reena Engineer, Santosh Menon, Bharat Rekhi, T S Shylasree

Collection and assembly of data: Lavanya Gurram, Samarпита Mohanty, Supriya Chopra, Jaya Ghosh, Seema Gulia, Sheela Sawant, Anuprita Daddi, Bharat Rekhi, Umesh Mahantshetty

Data analysis and interpretation: Lavanya Gurram, Samarпита Mohanty, Supriya Chopra, Surbhi Grover, Reena Engineer, Sudeep Gupta, Kedar Deodhar, Santosh Menon, T.S. Shylasree, Amita Maheshwari, Umesh Mahantshetty

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Supriya Chopra

This author is an Associate Editor for *JCO Global Oncology*. Journal policy recused the author from having any role in the peer review of this manuscript.

Honoraria: Varian Medical Systems

Speakers' Bureau: Varian Medical Systems (Inst)

Research Funding: Lilly (Inst)

Research Funding: Varian Medical Systems

Surbhi Grover

Honoraria: Varian Medical Systems

Consulting or Advisory Role: GenesisCare

Research Funding: Varian Medical Systems

Sudeep Gupta

Research Funding: Roche (Inst), Sanofi (Inst), Johnson & Johnson (Inst), Amgen (Inst), Celltrion (Inst), Oncostem Diagnostics (Inst), Novartis (Inst), AstraZeneca (Inst), Intas (Inst)

Seema Gulia

Consulting or Advisory Role: Eisai (Inst), Novartis (Inst)

Kedar Deodhar

Stock and Other Ownership Interests: Glenmark Pharma, Zydus Pharmaceuticals, Sun Pharma

Umesh Mahantshetty

Research Funding: Varian Medical Systems (Inst)

No other potential conflicts of interest were reported.

REFERENCES

- Mathur P, Sathishkumar K, Chaturvedi M, et al: Cancer statistics, 2020: Report from National Cancer Registry Programme, India. *JCO Glob Oncol* 6:1063-1075, 2020
- Morris M, Eifel PJ, Lu J, et al: Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 340:1137-1143, 1999
- Rose PG, Bundy BN, Watkins EB, et al: Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 340:1144-1153, 1999
- Green J, Kirwan J, Tierney J, et al: Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix, *Cochrane Database Syst Rev*:CD002225, 2005
- Shrivastava S, Mahantshetty U, Engineer R, et al: Cisplatin chemoradiotherapy vs radiotherapy in FIGO stage IIIB squamous cell carcinoma of the uterine cervix: A randomized clinical trial. *JAMA Oncol* 4:506-513, 2018
- Frisch M: Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst* 92:1500-1510, 2000
- Stelzle D, Tanaka LF, Lee KK, et al: Estimates of the global burden of cervical cancer associated with HIV. *Lancet Glob Health* 9:e161-e169, 2021
- Liu G, Sharma M, Tan N, et al: HIV-positive women have higher risk of human papilloma virus infection, precancerous lesions, and cervical cancer. *AIDS* 32:795-808, 2018
- National AIDS Control Organization & ICMR-National Institute of Medical Statistics (2020). India HIV Estimates 2019: Report. New Delhi: NACO, Ministry of Health and Family Welfare, Government of India. <https://www.aidsdatahub.org/sites/default/files/resource/india-hiv-estimates-2019.pdf>
- National AIDS Control Programme- National Technical Guidelines on Anti Retroviral Treatment (2018): NACO, Ministry of Health and Family Welfare, Government of India. [https://nms.naco.gov.in/frontend/content/NACO%20-%20National%20Technical%20Guidelines%20on%20ART_October%202018%20\(1\).pdf](https://nms.naco.gov.in/frontend/content/NACO%20-%20National%20Technical%20Guidelines%20on%20ART_October%202018%20(1).pdf)
- Dryden-Peterson S, Bvochora-Nsingo M, Suneja G, et al: HIV infection and survival among women with cervical cancer. *J Clin Oncol* 34:3749-3757, 2016
- Ferreira MP, Coghill AE, Chaves CB, et al: Outcomes of cervical cancer among HIV-infected and uninfected women treated at the Brazilian National Institute of Cancer (2001–2013). *J Virus Erad* 3:6, 2017
- National Comprehensive Cancer Network. Cancer in People with HIV (Version 1.2022). https://www.nccn.org/professionals/physician_gls/pdf/hiv.pdf
- International Atomic Energy Agency. *Management of Cervical Cancer: Strategies for Limited-resource Centres; a Guide for Radiation Oncologists*. Internat. Atomic Energy Agency, 2013. https://www-pub.iaea.org/MTCD/Publications/PDF/Pub1556_web.pdf
- Rubinstein P, Aboulsfia D, Zloza A: Malignancies in HIV? AIDS: From epidemiology to therapeutic challenges. *AIDS* 28:453-465, 2014
- Einstein MH, Phaëton R: Issues in cervical cancer incidence and treatment in HIV. *Curr Opin Oncol* 22:449-455, 2010
- Garcia-Soto AE, McKenzie ND, Whicker ME, et al: Phase 1 trial of nelfinavir added to standard cisplatin chemotherapy with concurrent pelvic radiation for locally advanced cervical cancer. *Cancer* 127:2279-2293, 2021
- Coghill AE, Shiels MS, Suneja G, et al: Elevated cancer-specific mortality among HIV-infected patients in the United States. *J Clin Oncol* 33:2376-2383, 2015
- Grover S, Bvochora-Nsingo M, Yeager A, et al: Impact of human immunodeficiency virus infection on survival and acute toxicities from chemoradiation therapy for cervical cancer patients in a limited-resource setting. *Int J Radiat Oncol* 101:201-210, 2018
- Lee FJ, Amin J, Carr A: Efficacy of initial antiretroviral therapy for HIV-1 infection in adults: A systematic review and meta-analysis of 114 studies with up to 144 weeks' follow-up. *PLoS One* 9:e97482, 2014
- Simonds HM, Botha MH, Neugut AI, et al: Five-year overall survival following chemoradiation among HIV-positive and HIV-negative patients with locally advanced cervical carcinoma in a South African cohort. *Gynecol Oncol* 151:215-220, 2018
- Human immunodeficiency virus type 1 RNA level and CD4 count as prognostic markers and surrogate end points: A meta-analysis. *AIDS Res Hum Retroviruses* 16:1123-1133, 2000
- Simonds HM, Neugut AI, Jacobson JS: HIV status and acute hematologic toxicity among patients with cervix cancer undergoing radical chemoradiation. *Int J Gynecol Cancer* 25:884-890, 2015
- Gichangi P, Bwayo J, Estambale B, et al: HIV impact on acute morbidity and pelvic tumor control following radiotherapy for cervical cancer. *Gynecol Oncol* 100:405-411, 2006
- Shrivastava SK, Engineer R, Rajadhyaksha S, et al: HIV infection and invasive cervical cancers, treatment with radiation therapy: Toxicity and outcome. *Radiother Oncol* 74:31-35, 2005
- Simonds HM, Wright JD, du Toit N, et al: Completion of and early response to chemoradiation among human immunodeficiency virus (HIV)-positive and HIV-negative patients with locally advanced cervical carcinoma in South Africa. *Cancer* 118:2971-2979, 2012
- Mdletshe S, Munkupa H, Lishimpi K: Acute toxicity in cervical cancer HIV-positive vs. HIV-negative patients treated by radical chemo-radiation in Zambia. *South Afr J Gynaecol Oncol* 8:37-41, 2016
- Einstein MH, Ndlovu N, Lee J, et al: Cisplatin and radiation therapy in HIV-positive women with locally advanced cervical cancer in sub-Saharan Africa: A phase II study of the AIDS malignancy consortium. *Gynecol Oncol* 153:20-25, 2019

