Original Article

HIV Infection Is Not Associated With the Initiation of Curative Treatment in Women With Cervical Cancer in Botswana

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BACKGROUND: Cervical cancer is the leading cause of cancer death in Sub-Saharan Africa. The risk of developing cancer is increased for women living with human immunodeficiency virus (HIV) infection. It is unknown which factors predict the initiation of curative chemoradiotherapy (CRT) in resource-limited settings and whether HIV is associated with initiating curative CRT in settings with a high HIV burden. **METHODS:** All women living with and without HIV infection who were initiating curative and noncurative CRT for locally advanced cervical cancer in Botswana were prospectively enrolled in an observational study. The factors associated with receiving CRT were evaluated in all patients and the subgroup of women living with HIV. **RESULTS:** Of 519 enrolled women, 284 (55%) initiated CRT with curative intent. The curative cohort included 200 women (70.4%) who were living with HIV and had a median CD4 count of 484.0 cells/μL (interquartile range, 342.0-611.0 cells/μL). In the noncurative cohort, 157 of 235 women (66.8%) were living with HIV and had a median CD4 count of 476.5 cells/μL (interquartile range, 308.0-649.5 cells/μL). HIV status was not associated with initiating curative CRT (odds ratio [OR], 0.95; 95% confidence interval [CI], 0.58-1.56). The factors associated with receiving curative CRT treatment on multivariable analysis in all patients included baseline hemoglobin levels ≥10 g/dL (OR, 1.80; 95% CI, 1.18-2.74) and stage I or II versus stage III or IV disease (OR, 3.16; 95% CI, 2.10-4.75). Women aged >61 years were less likely to receive curative treatment (OR, 0.43; 95% CI, 0.24-0.75). Among women who were living with HIV, higher CD4 cell counts were associated with higher rates of CRT initiation. **CONCLUSIONS:** The initiation of CRT with curative intent does not depend on HIV status. Significant predictors of CRT initiation include baseline hemoglobin level, disease stage, and age. ***Cancer* 2019;125:1645-1653**. © *2019 American Cancer Society*.

KEYWORDS: Botswana, CD4, cervical cancer, chemoradiotherapy, human immunodeficiency virus (HIV).

INTRODUCTION

Cervical cancer, the fourth most common malignancy presenting in women around the world, is the leading cause of cancer-related death among women in Sub-Saharan Africa.[1] The development of cervical carcinoma is highly correlated with longstanding human papillomavirus (HPV) infection.[2] Women living with HIV (WLWH) are more likely to maintain a chronic HPV infection that results in cellular transformation and subsequent cancer.[3] In regions with a high burden of HIV infection[4] as well as limited HPV screening capabilities and vaccination access,[5] addressing the long-term effects of coinfection is a public health imperative.

In Botswana, an estimated 22% of individuals aged 15 to 49 years are living with HIV infection,[6] yet HIV prevalence exceeds 34% in women aged 25 to 45 years,[4,6] putting this population at particularly high risk of developing cervical cancer. Although an effective national antiretroviral treatment (ART) program[7] covers 83% of patients with HIV infection and has dramatically increased the lifespan of patients living with HIV, many of these patients subsequently suffer from immune-mediated and infection-mediated cancers, including cervical cancer.[6] Despite increased access to ART, the incidence of cervical cancer has not declined in Botswana.[8,9] Given the high rates of HIV and cervical

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See related editorial on pages 1597-9, this issue.

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cancer in Botswana, there is a pressing need to identify and implement the optimal treatment for cervical cancer in WLWH.

Currently, the global standard of care for the treatment of locally invasive cervical cancer with the goal of a cure requires radiotherapy (RT) and concurrent cisplatin-based chemotherapy.[10-12] However, it remains controversial whether women who have cervical cancer with HIV infection have outcomes similar to those of women who have cervical cancer without HIV infection. Although some studies suggest that HIV infection may be associated with decreased survival,[13,14] our previous findings in Botswana have suggested that patients with HIV infection who initiated chemoradiation treatment (CRT) with curative intent have outcomes similar to those of patients without HIV infection.[15] The factors associated with improved survival in this group were hemoglobin levels ≥10 g/dL and total radiation dose received, but not HIV infection.[15] However, it is unknown whether HIV infection plays a role in the initiation of curative CRT in the modern ART era with well managed HIV infection, because of either physician bias or the sequela of HIV infection, which makes it challenging for patients with HIV infection to receive chemotherapy or curative-dose RT.[16-18] The objective of the current study was to identify the predictors of initiating curative CRT in an effort to inform future care decisions for patients in limited resource settings, particularly in regions with a high burden of HIV infection.

MATERIALS AND METHODS

Women with histologically confirmed cervical carcinoma who presented for RT or CRT at a Gaborone Private Hospital (GPH) or Princess Marina Hospital gynecologic multidisciplinary clinic were approached for enrollment in this prospective observational cohort study between July 2013 and July 2017. Because GPH houses the sole radiation oncology facility in Botswana, the government maintains a public-private partnership that covers the cost of primary therapy for patients with cervical cancer at GPH, including RT and chemotherapy.[8,19] All patients from Princess Marina Hospital are referred to GPH for treatment. Patients aged <18 years and those who did not wish to participate were excluded. After participants provided written informed consent, they were interviewed by designated research associates in their preferred language about demographics, marital status, and distance from their home to the treatment facility. Disease stage, baseline laboratory values, cluster of differentiation 4 (CD4 [T-cell)] count history, and ART history were collected through a review of medical records. Disease stage was determined according to International Federation of Gynecology and Obstetrics (FIGO) guidelines. The Karnofsky performance status (KPS) scale was used to evaluate functional impairment caused by disease.[20]

Main Outcome

The primary objective of this study was to determine the predictors of initiating concurrent CRT with curative intent. After appropriate disease staging, patients were prescribed treatment with curative intent or noncurative treatment. Patients who initiated curative treatment received at least 1 cycle of chemotherapy. Patients who initiated noncurative CRT did not receive any chemotherapy, which includes those who received high-dose RT alone and palliative RT with or without brachytherapy.

Cervical Cancer Treatment

Government-funded cervical cancer care is provided by GPH, which is the only clinical center in the country with the capability to provide RT. Cervical cancer was staged according to FIGO guidelines.[21] Before treatment began, patients underwent a chest x-ray and abdominal ultrasound studies to assess for hydronephrosis. Basic laboratory studies, such as complete blood counts, liver function tests, and renal function tests, also were obtained. Patients received transfusions to a hemoglobin level of 10 g/dL when possible. Curative CRT included from 45 to 50 grays (Gy) of whole-pelvis RT, weekly concurrent cisplatin (35-40 mg/m^2) for 5 cycles, and high-dose-rate brachytherapy (7 Gy in 3-4 fractions or 6 Gy in 4-5 fractions) using either a tandem-and-ring applicator or a tandem-and-ovoid applicator. Details of RT planning at GPH for cervical cancer have been previously described.[15]

Antiretroviral Treatment

HIV status was determined by patients' health records. Patients without HIV infection or with unknown status who had not received an HIV test within the past 6 months were offered an HIV test on site. All WLWH with CD4 counts ≤350 cells/μL, a diagnosis of cervical cancer, or any other HIV-associated condition[22] were eligible to receive free ART from the Botswana National ART Program from 2013 to 2015.[4,6,23] As of 2016, a test-and-treat policy was implemented, such that all patients who had positive HIV results were eligible for free ART at the time of HIV testing and subsequent diagnosis.

First-line ART included tenofovir, emtricitabine, and efavirenz from 2013 to 2016.[5] Regimens that included dolutegravir, tenofovir, and emtricitabine also were first-line options from 2016 and later.[24] Any WLWH who were not already receiving treatment at the time of their cervical cancer diagnosis were referred for ART initiation.

Statistical Analysis

The primary outcome of this study was the initiation of curative CRT. Independent predictors that we evaluated included HIV status, baseline CD4 cell count (>200 and ≤200 cells/μL), age (>61 and ≤61 years), marital status, disease stage, baseline hemoglobin (<10 vs ≥10 g/dL), baseline creatinine level, KPS performance status, and distance from the patient's home to the treatment center. Baseline values represent laboratory results that were obtained before treatment initiation. On the basis of knowledge of clinical practice, we explored older age thresholds for reduced CRT. Age >61 years was identified as be predictive of reduced CRT receipt and was used to dichotomize the age variable for our primary analysis. An additional analysis with continuous CD4 counts and age has been included in Supporting Table 1.

Bivariate associations between independent variables and the initiation of curative CRT were assessed using logistic regression analysis. A multivariable logistic regression model was fitted with CRT initiation as the dependent variable. Independent covariates for inclusion in the final logistic model were selected based on a priori knowledge, which included HIV status, baseline CD4 cell count, age, marital status, disease stage, baseline hemoglobin, baseline creatinine, and performance status.

To understand the role of HIV infection and CD4 count on the initiation of curative CRT, models that included all patients and only patients with HIV were explored. Model 1A compares patients with and without HIV regardless of CD4 count in the population with HIV. Model 1B incorporates information about the CD4 count in patients with HIV infection and compares CD4 counts >200 and ≤200 cells/μL versus counts in HIV-uninfected patients. Model 2 includes only patients with HIV and compares those with CD4 counts ≤200 cells/μL versus >200 cells/μL. Independent variables that had a statistical association with the outcome in bivariate analyses also were included in the multivariate models.

Statistical analysis was performed using the SAS statistical software package (version 9.4; SAS Institute Inc., Cary, NC). An α cutoff for statistical significance was not defined, as recommended by current statistical guidelines.[25]

Ethics

This study was approved by the Health Research Development Committee of the Botswana Ministry of Health and the Institutional Review Board of the University of Pennsylvania.

RESULTS

Demographic and Clinical Characteristics of the Cohort

We enrolled 532 patients between July 2013 and July 2017. Women with unknown HIV status, marital status, and performance status were excluded from the analysis (n = 13). Of the remaining 519 women, 54.7% (n = 284) initiated curative CRT (Table 1). Of those who initiated curative treatment, 70.4% (n = 200) were WLWH, including 94.9% (n = 187) who were receiving ART at the start of cervical cancer treatment. Of the 235 patients who did not initiate curative CRT, 66.8% (n = 157) were WLWH, including with 92.9% (n = 145) who were receiving ART. The median CD4 count in the curative group was 484.0 cells/μL (interquartile range [IQR], 342.0-611.0 cells/μL) compared with 476.5 cells/μL (IQR, 308.0-649.5 cells/μL) in the noncurative group. Patients who presented with stage I or II disease, stage III or IV disease, or were missing staging information accounted for 64.4% (n = 183), 34.5% (n = 98), and 1.1% (n = 3) of the curative CRT cohort, respectively. In the noncurative cohort, 27.7% (n = 65) presented with stage I or II disease, 54.9% (n = 129) presented with stage III or IV disease, and 17.4% (n = 41) were missing staging information. Tumor histology in the cohort comprised 88.8% (n = 461) squamous cell carcinoma, 6.7% (n = 36) adenocarcinoma, and 3.7% (n = 19) other; 0.6% (n = 3) were missing histologic information. A strong majority of participants in the curative CRT arm (70.1%; n = 199) had hemoglobin counts ≥10 g/dL before starting treatment, and 55.3% (n = 130) of those who received noncurative CRT had comparable hemoglobin levels. The median distance from patients' home towns to Gaborone was 271 kilometers (IQR, 68-410 kilometers) in both groups. The median time from biopsy to treatment initiation for those who did and did not receive curative treatment was 92 days (IQR, 55-141 days) and 77 days (IQR, 43-132 days), respectively (Table 1).

Predictors of Curative CRT

Bivariate analysis

A bivariate analysis of the factors associated with initiating curative CRT in all patients and in HIV-infected patients only is detailed in Table 2. In model 1, the odds

TABLE 1. Characteristics of Study Participants, N = 519

Characteristic	No. of Participants (%)	
	Curative Treatment Initiated, n = 284	Curative Treatment Not Initiated, n = 235
HIV status		
Uninfected	84 (29.6)	78 (33.2)
Infected	200 (70.4)	157 (66.8)
Age: Median [IQR], y	48 [42-57]	49 [42-62]
Age, y		
≤40	58 (20.4)	53 (22.5)
41-50	113 (39.8)	78 (33.2)
51-60	64 (22.5)	39 (16.6)
≥61	49 (17.3)	65 (27.7)
Marital status		
Single	169 (59.5)	152 (64.7)
Married/partnered	78 (27.5)	52 (22.1)
Divorced/widowed	37 (13.0)	31 (13.2)
Disease stage		
I, II	183 (64.4)	65 (27.7)
III, IV	98 (34.5)	129 (54.9)
Missing	3 (1.1)	41 (17.4)
Baseline hemoglobin, g/dL		
<10	85 (29.9)	105 (44.7)
≥10	199 (70.1)	130 (55.3)
Baseline creatinine: Median [IQR], μmol/L	54 [46.5-63]	66.2 [50-87]
Performance status		
≤80	50 (17.6)	61 (26.0)
>80	234 (82.4)	174 (74.0)
Receiving ART[a]		
Yes	187 (94.9)	145 (92.9)
No	10 (5.1)	11 (7.1)
Baseline CD4 cells/μL: Median [IQR][a]	484.0 [342.0-611.0]	476.5 [308.0-649.5]
Baseline CD4 cells/μL[a]		
<200	10 (5.8)	15 (13.9)
200-349	34 (20.0)	20 (18.5)
350-499	45 (26.3)	23 (21.3)
≥500	82 (48.0)	50 (46.3)
Distance from home to treatment facility: Median [IQR], km	271 [68-410]	271 [68-410]

Abbreviations: ART, antiretroviral treatment; CD4, cluster of differentiation 4 (T cells); HIV, human immunodeficiency virus; IQR, interquartile range.
[a]ART was applicable only to participants who were positive for HIV.

of initiating curative CRT in all patients were lower for patients aged >61 years (odds ratio [OR], 0.52; 95% confidence interval [CI], 0.33-0.80). Factors that were associated with significantly higher odds of starting curative CRT included a baseline hemoglobin level ≥10 g/dL (OR, 1.89; 95% CI, 1.32-2.71), the presence of stage I or II versus stage III or IV disease (OR, 3.71; 95% CI, 2.52-5.45), a KPS >80 (OR, 1.64; 95% CI, 1.08-2.50), and a CD4 count >200 cells/μL (OR, 1.6; 95% CI, 1.08-2.40).

Subset bivariate analysis of patients with HIV comparing those who had CD4 counts ≤200 cells/μL with those who had CD4 counts >200 cells/μL indicated that CRT initiation is associated with CD4 counts >200 cells/μL in patients with HIV infection (OR, 2.59; 95% CI, 1.12-6.01), baseline hemoglobin levels ≥10 g/dL (OR, 1.74; 95% CI, 1.14-2.67), the presence of stage I or II versus stage III or IV disease (OR, 3.35; 95% CI, 2.11-5.33), and a KPS >80 (OR, 1.75; 95% CI, 1.02-2.98), as indicated in model 2.

Multivariable analysis

Multivariable analysis (Table 2) in model 1A revealed that, after adjusting for HIV status, age, marital status, disease stage, baseline hemoglobin, baseline creatinine, and performance status, the odds of initiating curative CRT were higher among patients with baseline hemoglobin levels ≥10 g/dL (OR, 1.80; 95% CI, 1.18-2.74) and those with stage I or II versus stage III or IV disease (OR, 3.16; 95% CI, 2.10-4.75). Similar to bivariate analysis findings, age >61 years retained its association with lower odds of initiating curative CRT (OR, 0.43; 95% CI, 0.24-0.75). Notably, our findings did not indicate that HIV status was associated with initiating curative CRT (OR, 0.95; 95% CI, 0.58-1.56). Figure 1 also

TABLE 2. Factors Associated With Initiating Curative Treatment Among Study Participants

	Model 1: All Patients, N = 519			Model 2: Patients With HIV Only, n = 357[a]	
		Adjusted OR (95% CI)			
Variable	Crude OR (95% CI)	Model 1A[b]	Model 1B[c]	Crude OR (95% CI)	Adjusted OR (95% CI)
Age, y					
≤61	1.00	1.00	1.00	1.00	1.00
>61	0.52 (0.33-0.80)[d]	0.43 (0.24-0.75)[d]	0.43 (0.24-0.77)[d]	1.02 (0.44-2.40)	0.91 (0.34-2.42)
Marital status					
Single	1.00	1.00	1.00	1.00	1.00
Married/partnered	1.35 (0.89-2.04)	1.52 (0.94-2.45)	1.54 (0.95-2.49)	1.32 (0.78-2.25)	1.28 (0.71-2.31)
Divorced/widowed	1.07 (0.64-1.82)	1.27 (0.68-2.38)	1.34 (0.71-2.54)	1.35 (0.63-2.90)	1.58 (0.65-3.85)
HIV status					
Uninfected	1.00	1.00	NA	NA	NA
Infected		0.91 (0.55-1.49)	NA	NA	NA
Baseline CD4 cells/μL					
≤200	0.62 (0.26-1.46)	NA	0.48 (0.18-1.29)	1.00	1.00
>200	1.61 (1.08-2.40)[d]	NA	1.25 (0.74-2.12)	2.59 (1.12-6.01)[d]	2.84 (1.14-7.09)[d]
Disease stage					
III, IV	1.00	1.00	1.00	1.00	1.00
I, II	3.71 (2.52-5.45)[d]	3.24 (2.15-4.87)[d]	3.36 (2.21-5.11)[d]	3.35 (2.11-5.33)[d]	3.16 (1.92-5.19)[d]
Missing	0.10 (0.03-0.32)[d]	0.08 (0.02-0.26)[d]	0.09 (0.03-0.29)[d]	0.13 (0.04-0.44)[d]	0.13 (0.04-0.47)[d]
Baseline hemoglobin, g/dL					
<10	1.00	1.00	1.00	1.00	1.00
≥10	1.89 (1.32-2.71)[d]	1.75 (1.15-2.65)[d]	1.85 (1.21-2.83)[d]	1.74 (1.14-2.67)[d]	1.63 (0.99-2.69)
Baseline creatinine, μmol/L	0.998 (0.996-1.000)	0.999 (0.997-1.001)	0.999 (0.998-1.001)	0.999 (0.998-1.001)	1.00 (0.999-1.001)
Performance status					
≤80	1.00	1.00	1.00	1.00	1.00
>80	1.64 (1.08-2.50)[d]	1.04 (0.64-1.69)	1.02 (0.62-1.68)	1.75 (1.02-2.98)[d]	1.32 (0.71-2.45)
Distance from home to treatment facility, km	1.000 (0.999-1.001)	Not included in model	Not included in model	1.000 (0.999-1.001)	Not included in model

Abbreviations: CD4, cluster of differentiation 4 (T cells); CI, confidence interval; HIV, human immunodeficiency virus; NA, not applicable; OR, odds ratio.
[a]Model 2 included only HIV-positive individuals with CD4 counts ≤200 vs >200 cells/μL.
[b]Model 1A included HIV-positive and HIV-negative individuals.
[c]Model 1B included HIV-positive and HIV-negative individuals according to CD4 counts ≤200 vs >200 cells/μL.
[d]These values indicate a statistically significant difference.

indicates that there was no variation in the receipt of CRT according to HIV status.

In Model 1B, patients who had HIV were stratified according to the CD4 count (>200 or ≤200 cells/μL) and were compared with patients who did not have HIV. The factors associated with CRT initiation in this model included a CD4 count >200 cells/μL in patients who had HIV (OR, 1.61; 95% CI, 1.08-2.40) compared with those who did not have HIV, age >61 years (OR, 0.43; 95% CI, 0.24-0.77), and the presence of stage I or II versus stage III or IV disease (OR, 3.36; 95% CI, 2.21-5.11).

The multivariable analysis in model 2 included only patients with HIV infection stratified by CD4 count. In this subgroup, the factors associated with initiating CRT included a CD4 count >200 cells/μL (OR, 2.84; 95% CI, 1.14-7.09) and the presence of stage I or II versus stage III or IV disease (OR, 3.16; 95% CI, 1.92-5.19). Figure 2 indicates differences in the percentage of patients with HIV who initiated CRT according to CD4 count.

Age and CD4 count were included as continuous variables in a multivariate analysis, which is provided in Supporting Table 1. Similar to the results described above, the initiation of CRT for all patients had a significant association with early stage I or II disease (OR, 3.16; 95% CI, 2.10-4.75) and the baseline hemoglobin level (OR, 1.80; 95% CI, 1.18-2.74). In an analysis of only patients who had HIV, disease stage (OR, 3.55; 95% CI, 2.03-6.22) and baseline hemoglobin level (OR, 1.82; 95% CI, 1.04-3.17) alone were identified as significant predictors of CRT initiation.

DISCUSSION

In this large, prospective, observational cohort study of women with locally advanced cervical cancer in Botswana, 55% of patients initiated curative CRT. HIV infection was not associated with the initiation of curative treatment. We observed that the odds of initiating CRT were significantly higher for patients who had baseline hemoglobin

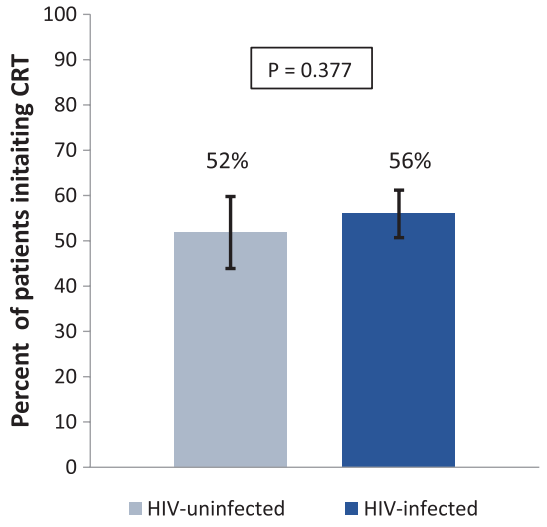

Figure 1. Percent of patients that initiate chemoradiation (CRT) by HIV status. No significant difference in the percent of patients who initiated CRT was found when patients with and without HIV were compared ($P = .377$). Error bars indicate 95% CI.

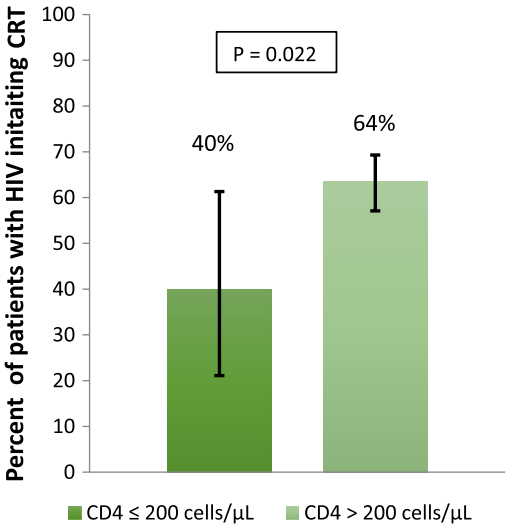

Figure 2. Percent of patients with HIV that initiate chemoradiation (CRT) by CD4 count. Of the subset patients with HIV, the percent of patients who initiated CRT was significantly higher in those with CD4 counts >200 cells/µl as compared to patients with CD4 counts ≤200 ($P = .022$). Error bars indicate 95% CI.

levels ≥10 g/dL and those who had stage I or II versus stage III or IV disease. Furthermore, the odds of treatment initiation were significantly decreased in patients aged >61 years. Among WLWH, CD4 counts >200 cells/µL and stage I or II versus stage III or IV disease were associated with a higher odds of initiating CRT.

Although several studies have reported that HIV is a significant, negative predictor of survival after treatment for cervical cancer,[14,26] our recent findings in Botswana suggest that HIV has no impact on 2-year overall survival among patients who initiate curative CRT.[15] The results from that analysis identified the baseline hemoglobin level, receipt of the total prescribed RT dose, and age as the significant predictors of 2-year overall survival.[15] That study was limited in its ability to determine whether HIV infection was associated with the initiation of curative CRT among patients who were intended to receive it. Results from the current study indicate that, overall, WLWH in Botswana are not preferentially prescribed noncurative treatment over curative treatment compared with women who do not have HIV. This result drives a striking contrast with studies in the United States, which revealed that patients with HIV who had cancer were significantly less likely to be prescribed cancer treatment.[27,28] Taken together, these studies suggest that the disparities that may exist in the treatment of these patients in the United States are not biologic in origin but, rather, are based on inaccurate clinical perceptions of patients with cancer who are living with HIV or a lack of guidelines for the management of patients who are living with HIV. Lack of bias in Botswana may be caused by the higher volume of patients living with HIV relative to those without HIV being treated for cancer compared with those in the United States and by high ART coverage, leading to well managed HIV infection in Botswana.[6] Nevertheless, a certain degree of bias toward the initiation of curative CRT for WLWH who have low CD4 cell counts may remain, even in settings in which WLWH account for the majority of patients with cervical cancer.

We identified the baseline hemoglobin level as a significant predictor of CRT initiation. Previous studies of locally advanced cervical cancer in WLWH, including results from our curative cohort of patients with and without HIV, have demonstrated that a low hemoglobin level at baseline is a significant, negative predictor of overall survival.[14,15,29] Although survival outcomes may be linked to tumor biology, such as hypoxic microenvironments or aggressive phenotypes,[30,31] the determination to initiate curative therapy is a clinical choice. Patients in our study who had low baseline hemoglobin levels routinely received transfusions before they began treatment whenever blood was accessible. Studies have produced conflicting results regarding the clinical utility of this practice,

with some highlighting benefit[32,33] and others cautioning its use.[34,35] Persistently low hemoglobin levels despite transfusion may be a cause for delaying treatment or omitting concurrent chemotherapy.

Patients with early stage disease were significantly more likely to initiate curative CRT than those with late-stage disease. This is likely because of the better performance status in patients who have early stage disease. Also, urgent palliative RT often is needed in women who have advanced cervical cancer. Patients who present with advanced or metastatic cancers frequently report living with pain, anorexia, and fatigue.[36,37] It has been demonstrated that short-course RT is effective in controlling vaginal bleeding and pelvic pain.[38,39]

The odds of initiating CRT decreased for women aged >61 years in our study. Despite evidence that elderly women tolerate pelvic RT and brachytherapy well,[40,41] studies have indicated that older women are less likely to receive surgery and adjuvant RT for cervical cancer than their younger counterparts.[42,43] This trend may be caused by treatment bias among physicians who worry about the perceived risk associated with curative treatment of an older patient, but it also may take into account older patients' desire to forego cancer treatment in the face of multiple comorbidities.[43,44] More studies are needed to determine the underlying cause of reduced treatment initiation among older women in this population.

Within the subgroup of patients who are infected HIV, CD4 counts >200 cells/μL and stage I or II versus stage III or IV disease were associated with higher odds of initiating CRT after adjusting for hemoglobin level, creatinine level, and performance status. These findings are consistent with those from a previous study, which associated CD4 counts <144 cells/μL and advanced-stage disease with reduced odds of receiving cancer treatment.[27] It is possible that patients with HIV who have CD4 counts ≤200 cells/μL are unable to initiate CRT because of physician discomfort with giving chemotherapy to patients with such low CD4 counts. Although there are limited studies in this area, previous data from South Africa suggested that patients with HIV tolerated chemotherapy poorly, and most patients with HIV had CD4 counts ≤200 cells/μL.[45] Further studies are needed to assess the tolerability of chemotherapy and CRT in patients with HIV who have CD4 counts ≤200 cells/μL.

The current study was noteworthy for its large cohort size, specifically of WLWH who were well controlled with ART. Despite the multiplicity of survival data, few studies have explored biases in clinical judgment regarding HIV status. However, our study was limited by a lack of availability of data from patients who were not able to present for treatment. We were not able to capture information about those who were unable or unwilling to travel, possibly because of HIV-related or cancer-related disability. In addition, although disease stage was a predictor of initiating curative treatment, performance status was not. This may be attributable to different cultural interpretations of KPS questions, resulting in a downward bias, and a potential lack of power to detect such an association. Given Botswana's public funding of ART and high rate of ART adherence, our results may not be generalizable to regions with high rates of untreated HIV. Additional studies in HIV-endemic areas are needed to confirm our conclusions.

In summary, the initiation of curative CRT for women with cervical cancer who present for treatment was predicted by hemoglobin level, disease stage, and age, but not by HIV status. These results demonstrate that women living with well managed HIV infection are not preferentially prescribed noncurative treatment over curative treatment. In concert with our previous findings demonstrating that treatment outcomes in cervical cancer do not depend on HIV status, the current analysis has potential implications for the treatment of patients with cancer who are living with well managed HIV around the globe.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Surbhi Grover: Conceived and designed the study, curated the data, formally analyzed and interpreted the data, and wrote the original draft. **Emily C. MacDuffie:** Curated the data, formally analyzed and interpreted the data, and wrote the original draft. **Qiao Wang:** Formally analyzed and interpreted the data and reviewed and edited the article. **Memory Bvochora-Nsingo:** Curated the data and reviewed and edited the article. **Rohini K. Bhatia:** Curated the data and reviewed and edited the article. **Dawn Balang:** Curated the data and reviewed and edited the article. **Sebathu P. Chiyapo:** Reviewed and edited the article. **Rebecca Luckett:** Reviewed and edited the article. **Doreen Ramogola-Masire:** Reviewed and edited the article. **Scott L. Dryden-Peterson:** Reviewed and edited the article. **Lilie L. Lin:** Reviewed and edited the article. **Sanghyuk S. Shin:** Formally analyzed and interpreted the data and reviewed and edited the article. **Nicola M. Zetola:** Conceived and designed the study and reviewed and edited the article.

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