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ORIGINAL REPORT

HIV Infection and Survival Among Women With Cervical Cancer

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A B S T R A C T

Purpose

Cervical cancer is the leading cause of cancer death among the 20 million women with HIV worldwide. We sought to determine whether HIV infection affected survival in women with invasive cervical cancer.

Patients and Methods

We enrolled sequential patients with cervical cancer in Botswana from 2010 to 2015. Standard treatment included external beam radiation and brachytherapy with concurrent cisplatin chemotherapy. The effect of HIV on survival was estimated by using an inverse probability weighted marginal Cox model.

Results

A total of 348 women with cervical cancer were enrolled, including 231 (66.4%) with HIV and 96 (27.6%) without HIV. The majority (189 [81.8%]) of women with HIV received antiretroviral therapy before cancer diagnosis. The median CD4 cell count for women with HIV was 397 (interquartile range, 264 to 555). After a median follow-up of 19.7 months, 117 (50.7%) women with HIV and 40 (41.7%) without HIV died. One death was attributed to HIV and the remaining to cancer. Three-year survival for the women with HIV was 35% (95% CI, 27% to 44%) and 48% (95% CI, 35% to 60%) for those without HIV. In an adjusted analysis, HIV infection significantly increased the risk for death among all women (hazard ratio, 1.95; 95% CI, 1.20 to 3.17) and in the subset that received guideline-concordant curative treatment (hazard ratio, 2.63; 95% CI, 1.05 to 6.55). The adverse effect of HIV on survival was greater for women with a more-limited stage cancer (P = .035), those treated with curative intent (P = .003), and those with a lower CD4 cell count (P = .036). Advanced stage and poor treatment completion contributed to high mortality overall.

Conclusion

In the context of good access to and use of antiretroviral treatment in Botswana, HIV infection significantly decreases cervical cancer survival.

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INTRODUCTION

Cervical cancer is the most common cause of cancer death among African women,[1] and the HIV epidemic intensifies this burden. Cervical cancer incidence is sixfold greater among women with HIV infection than the general population.[2] Although antiretroviral therapy (ART) for HIV may reduce the frequency and duration of human papillomavirus (HPV) infections that cause cervical cancer,[3] cervical cancer incidence has not decreased since expansion of treatment for HIV.[4] With declining infection-related mortality, cervical cancer has become a leading cause of death for the 16 million women with HIV around the globe.[5]

The impact of HIV on risk of cervical cancer is well described, but the effect of HIV on survival from cervical cancer is poorly understood. In retrospective studies of anal cancer, which is also linked to HPV, outcomes of individuals with and without HIV infection seem to be similar in the context of ART.[6-8] However, observations have suggested that outcomes for cervical cancer may be poorer for women with HIV. Two registry-based

studies[9,10] have suggested possible decreased cervical cancer survival associated with HIV, but trends did not achieve statistical significance, and designs had limited control of possible biases. Treatment of cervical precancers in women with HIV infection is associated with increased relapse or residual disease[11,12] compared with women without HIV.[13] Treatment of locally advanced cervical cancer requires a combination of external beam radiation therapy (EBRT) and brachytherapy and concurrent chemotherapy to maximize survival.[14] In South Africa, women with HIV experience more frequent interruptions of this therapy and lower rates of treatment completion[15] and receive concurrent chemotherapy less often.[16]

With an adult HIV prevalence peaking at 27%, Botswana had the earliest nationwide HIV treatment program in Africa, and its program has achieved HIV treatment coverage and virologic suppression rates higher than even the most successful high-income countries.[17] Despite remarkable corresponding declines in HIV-associated mortality in Botswana,[18] the incidence of cervical cancer remains among the highest in the world (36.6 per 100,000), and nearly two thirds of cases arise in women with HIV.[4] To inform whether novel treatment approaches may be warranted for HIV-associated cervical cancer, we sought to estimate the effect of HIV on survival through a prospective cohort of women with cervical cancer and free access to ART and chemoradiation therapy.

PATIENTS AND METHODS

Study Participants

Women with histologically confirmed invasive cervical cancer treated at Princess Marina Hospital (October 2010 to July 2015), Gaborone Private Hospital (November 2012 to July 2015), and Nyangabgwe Referral Hospital (January 2015 to July 2015) in Botswana were approached for enrollment. Primary therapy for cervical cancer was provided at Gaborone Private Hospital through a public-private partnership with the government of Botswana, which provided the full cost of treatment. Women too ill or unwilling to consent, younger than 18 years, and non-Botswana citizens were excluded. Participants were interviewed and HIV and oncology records abstracted. Cancers were staged on the basis of clinical examination, chest x-ray, and abdominal ultrasound by using the system of the International Federation of Gynecology and Obstetrics. Patients without evidence of HIV infection or a recent test were tested for HIV unless they declined.

After enrollment, participants were contacted every 3 months. Those unable to be contacted by phone were visited in their homes or contacted through the village Kgotla (office of the village chief) or their local clinic. In the event of participant death, families and/or health workers were questioned about the circumstances surrounding the death and causes reported on the death certificate. Cancer treatment details were obtained through review of the electronic radiation treatment planning system (MOSAIQ; Elekta, Stockholm, Sweden) and paper records.

Participants provided written informed consent. The study was reviewed and approved by the ethical review committees of the Harvard T.H. Chan School of Public Health and the Botswana Ministry of Health.

Treatment

Standard treatment of cervical cancer did not vary during the study period and included EBRT of 45 to 50 Gy delivered to the pelvis in 20 to 25 fractions from a single linear accelerator (Elekta Precise). Concurrent cisplatin (35 mg/m^2) was given weekly for four to five cycles during EBRT unless the estimated glomerular filtration rate was $<$ 60 mL/min/1.73 m^2 or poor performance status or hydronephrosis was present. After completion of EBRT, an additional 14 to 26 Gy was delivered through high-dose-rate brachytherapy (Elekta) in two to four fractions of 5 to 7 Gy per fraction. Before brachytherapy was available in Botswana (January 2012), patients were referred to South Africa for brachytherapy. Patients with poor performance status or stage IV disease received palliative radiation, generally 30 to 50 Gy of EBRT (eg, 10 fractions of 3 Gy to 25 fractions of 2 Gy). Concurrent cisplatin was delayed for women with HIV who had not yet started ART; otherwise, the standard treatment approach did not differ between participants with and without HIV infection or by CD4 cell count.

Toxicities during treatment were noted in the clinical record, and treatment response was assessed by pelvic examination. Follow-up visits are not covered by the public-private partnership, so patients are followed after treatment in their local clinics. Toxicities developing after completion of treatment were not systematically captured.

HIV therapy was provided without cost at government clinics nationwide. During the study period, the CD4 count threshold to initiate ART increased from 250 to 350 cells/μL. Cervical cancer, a World Health Organization HIV stage IV condition, was an absolute indication to start ART irrespective of CD4 count throughout the study period. Standard first-line therapy for HIV was coformulated tenofovir, emtricitabine, and efavirenz. Despite possible additive nephrotoxicity, tenofovir was continued in patients who also received cisplatin.

Analytic Methods

Participants not known to have HIV infection and with negative test results within 1 year of enrollment (or anytime after enrollment) were considered not to have HIV; otherwise, they were considered to have unknown HIV status. Patients were categorized by treatment intent—curative or palliative—as recorded by the treating oncologist. For analytic purposes, women treated with curative intent were considered to have completed the recommended radiation therapy if they received both EBRT and brachytherapy and achieved a combined dose of $>$ 79 Gy in 2 Gy per fraction radiobiologic equivalence (EQD2)[19] as recommended by the American Brachytherapy Society.[20] Those who received less but within the range for international practice (71.2 to 79 Gy)[21] were considered to have received the minimally adequate dose. Those who received $<$ 71.2 Gy were considered to have received an inadequate dose. Participants treated with the recommended radiation therapy and at least one dose of concurrent cisplatin were considered to have received guideline-concordant therapy. Women with unknown HIV status or with $<$ 6 months follow-up were excluded.

The primary analytic objective was to evaluate the effect of HIV infection on survival in women with cervical cancer irrespective of cancer stage, age, and other possible confounding factors. We used inverse probability weighting to develop a Cox marginal structural model[22] to simulate a theoretical trial where chronic HIV infection was randomly assigned in women with cervical cancer.[23] Anticipating strong associations between HIV status and age, cancer stage, and access to treatment (analogous to confounding by indication), this framework enabled adjustment for a robust set of confounders in the context of a limited number of events, avoided assumptions of relationships among potential confounders, and permitted the modeling of HIV infection and subsequent cervical cancer treatment separately. Baseline factors associated ($P < .1$) with HIV infection or survival in univariable logistic and Cox models stratified by HIV status were retained in the final model to determine model weights. The final logistic model that produced inverse probability weights included dichotomized age, use of traditional healers, ordinal cancer stage, education beyond primary school, presence of household electricity, marital status, dichotomized income, and employment status. The model included an updated adjustment for radiation dose received. Significance testing was performed by using robust variance estimators. Sensitivity analyses on the basis of standard multivariable and propensity score-adjusted Cox models were performed. The Appendix (online only) provides more details on the analytic methods used in this study.

Analyses were performed after occurrence of 110 deaths to achieve an estimated 80% power to detect a 70% increased risk of death among women with HIV. Follow-up observations through March 2016 were included in the analysis. Analyses were conducted with SAS 9.3 software (SAS Institute, Cary, NC). All tests were two-tailed, and $P < .05$ was considered statistically significant.

RESULTS

Study Participants

A total of 348 women with a new diagnosis of invasive cervical cancer were enrolled (Fig 1), including 231 (66.4%) with HIV infection, 96 (27.6%) without HIV infection, and 21 (6.0%) with unknown HIV status. Analyses were restricted to 327 with known HIV status. The majority (81.8%) of participants with HIV had started ART before the cervical cancer diagnosis and had received ART for several years (median, 4.8 years; interquartile range [IQR], 1.6 to 8.6 years). Cervical cancer was the initial ART-qualifying condition for 14 (6.1%) participants. Current advanced immunosuppression was uncommon (median CD4 count, 397 cells/μL; IQR, 264 to 554 cells/μL), and only 24 (10.4%) participants had a CD4 count $<$ 200 cells/μL.

Nearly all (96.9%) participants had symptomatic cancer, with 10 (3.1%) cancers detected through screening and 80.8% with parametrial involvement (stage IIB or greater) at the time of diagnosis. No differences were detected in cancer stage at presentation by HIV status (P = .72). Participants with HIV were substantially younger than those without HIV (median, 42 years [IQR, 37 to 48 years] and 57 years [IQR 48 to 68 years], respectively). Reflective of their younger age and the ongoing economic development in Botswana, participants with HIV infection had significantly greater access to education and higher measures of wealth than those without HIV (Table 1).

Follow-Up of Study Participants

During 5,677 person-months of follow-up (median, 19.7 months; minimum, 6.6; maximum, 64.3 months among survivors), 157 (48.0%) participants died. No participants withdrew from the study or were lost to follow-up for $>$ 6 months, for an overall retention of vital status of 100%.

Primary Outcome

One-hundred seventeen (50.7%) participants with HIV infection and 40 (41.7%) without HIV infection died. The majority

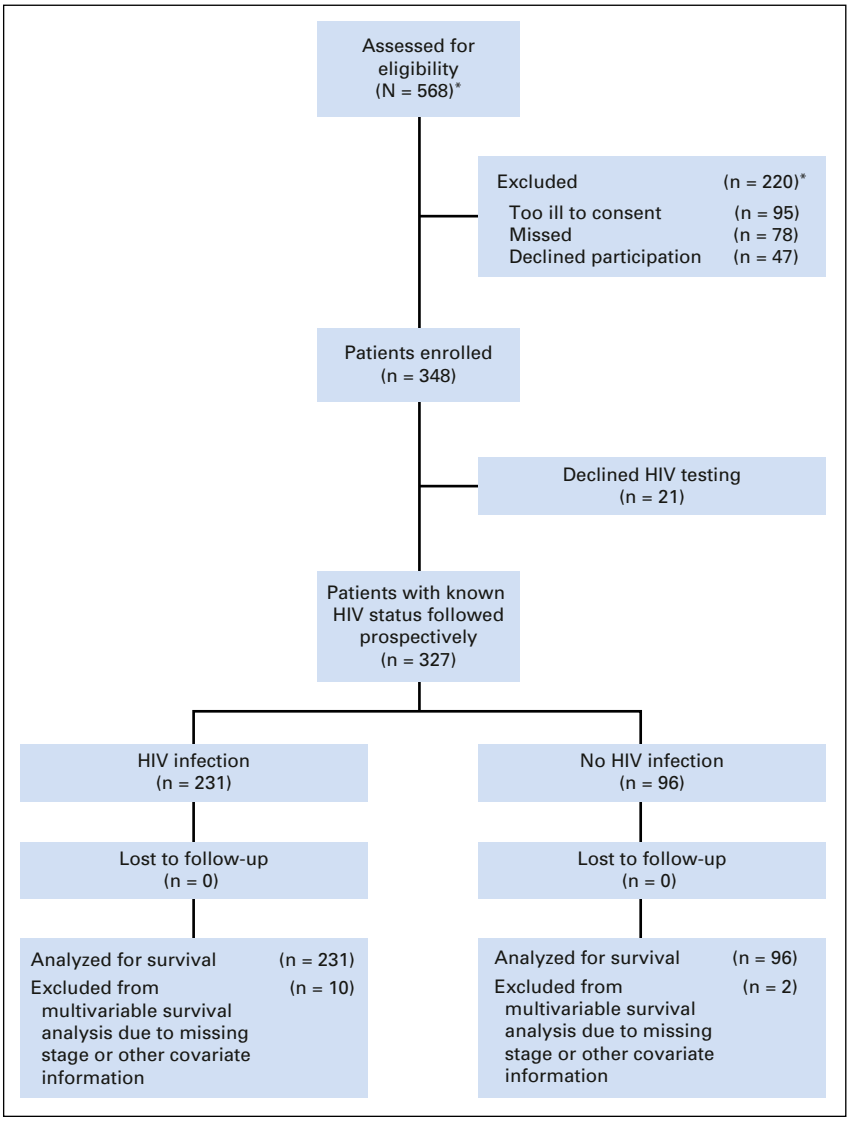

Fig 1. Enrollment and retention. (*)Enrollment registers of the Botswana Prospective Cancer Cohort include all cancers and do not differentiate by cancer site. The number of eligible women with cervical cancer and number excluded were estimated from percentages of the full cohort.

Table 1. Participant Characteristics

Characteristic	Group, No. (%)			*P*
	HIV Infection	No HIV Infection	Overall	
No. of participants	231*	96	327	
Median age (IQR), years	41.5 (37.8-48.4)	57.0 (48.6-67.7)	45.1 (38.8-54.4)	< .001
Occupation				.024
Salaried position	68 (29.7)	20 (20.8)	88 (27.1)	
Other employment or student	27 (11.8)	5 (5.2)	32 (9.9)	
Unemployed	134 (58.5)	71 (74.0)	205 (63.1)	
Education				< .001
Primary school or less	108 (47.2)	74 (77.1)	182 (56.0)	
More than primary school	121 (52.8)	22 (22.9)	129 (42.9)	
Married	70 (30.3)	42 (43.8)	112 (34.3)	.020
Income < $50/month	132 (57.6)	69 (71.8)	201 (61.9)	.016
Indoor toilet in home	60 (26.2)	33 (34.4)	93 (28.6)	.14
Electricity in home	131 (57.2)	61 (63.5)	192 (59.1)	.29
Used traditional medicine	60 (26.2)	35 (36.5)	95 (29.2)	.063
Rural residence	182 (79.5)	83 (86.5)	265 (81.5)	.14
Age at sexual debut				.34
≤ 17 years	62 (26.8)	25 (26.0)	87 (26.6)	
> 17 years	144 (62.3)	55 (57.3)	199 (60.9)	
Declined to answer	25 (10.8)	16 (16.7)	41 (12.5)	
Ever smoker	22 (9.6)	6 (6.3)	28 (8.6)	.33
Initial symptoms leading to diagnosis				.58
Bleeding	142 (62.6)	62 (65.3)	204 (63.4)	
Pain	38 (16.7)	18 (19.0)	56 (17.4)	
Other†	47 (20.7)	15 (15.8)	62 (19.3)	
Histology				.12‡
Squamous cell carcinoma	203 (88.3)	81 (84.4)	284 (87.1)	
Adenocarcinoma	7 (3.0)	8 (8.3)	15 (4.6)	
Adenosquamous	4 (1.7)	3 (3.1)	7 (2.2)	
Other or missing	16 (6.9)	4 (4.2)	20 (6.1)	
Performance status				.16
ECOG 0 or 1	168 (72.7)	77 (80.2)	245 (74.9)	
ECOG 2, 3, or 4	63 (27.3)	19 (19.8)	78 (25.7)	
Cancer stage§				.72‖
IA	4 (1.7)	0 (0)	4 (1.2)	
IX	1 (0.4)	0 (0)	1 (0.3)	
IB	23 (10.0)	9 (9.4)	32 (9.8)	
IIA	18 (7.8)	6 (6.3)	24 (7.3)	
IIX	1 (0.4)	0 (0)	1 (0.3)	
IIB	66 (28.6)	32 (33.0)	98 (30.0)	
IIIA	17 (7.4)	9 (9.4)	26 (8.0)	
IIIX	2 (0.9)	1 (1.0)	3 (0.9)	
IIIB	68 (29.4)	27 (28.1)	95 (29.1)	
IVA	16 (6.9)	7 (7.3)	23 (7.0)	
IVX	4 (1.7)	0 (0)	4 (1.2)	
IVB	3 (1.3)	3 (3.1)	6 (1.8)	
XX	8 (3.5)	2 (2.1)	10 (3.1)	
Advanced stage (III or IV)	110 (49.3)	47 (50.0)	157 (49.5)	.91
Initiated ART before cancer diagnosis	189 (81.8)	—	—	—
Median duration of ART (IQR), years	4.8 (1.6-8.6)	—	—	—
Recent CD4, median cells/μL	397 (264-555)	—	—	—
ART regimen on enrollment				—
TDF/FTC/EFV or NVP	107 (46.3)	—	—	
ZDV/3TC/EFV or NVP	74 (32.0)	—	—	
Second line¶	13 (5.6)	—	—	
Unknown ART	19 (8.2)	—	—	
No ART	18 (7.8)	—	—	
Most recent HIV RNA < 1,000 copies/mL#	133 (97.1)	—	—	—

NOTE. *P* values from Wilcoxon rank sum test for continuous measures and χ^2 test for categorical measures.
Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; ECOG, Eastern Cooperative Oncology Group; EFV, efavirenz; FTC, emtricitabine; IQR, interquartile range; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.
*Baseline demographic information not obtained from two participants with HIV infection.
†Includes 10 cancers (eight in participants with HIV infection and two without HIV infection) detected through Papanicolaou smear or visual inspection with ascetic acid screening.
‡Fisher exact test used due to small cell numbers.
§Cases with inadequate information to completely stage are denoted with an X.
‖Analyzed as ordinal using Wilcoxon rank sum.
¶All second-line regimens included ritonavir-boosted lopinavir in combination with TDF/FTC (n = 7), ZDV/3TC (n = 3), or abacavir/3TC (n = 2).
#Viral load measurements were available for 137 (65.6%) participants with HIV infection who received ART.

of deaths were attributed to cancer (with HIV, 102 [97.1%]; without HIV, 38 [97.4%]; $P = 1.0$). However, the cause of death was not known for 12 (10.3%) participants with HIV and one (2.5%) without HIV ($P = .19$). The death of one woman (0.9%) was attributed to HIV infection by treating clinicians. In unadjusted analysis, participants with HIV had shorter overall survival (median, 21.7 months; 95% CI, 16 to 24 months) than those without HIV (median, 30.5 months; 95% CI, 20 months to not estimable; $P = .020$; Fig 2).

In the primary adjusted model, HIV infection nearly doubled the risk of death (hazard ratio [HR] 1.95; 95% CI, 1.20 to 3.17; $P = .007$). Analysis restricted to participants who received curative intent therapy resulted in similar findings (HR, 2.35; 95% CI, 1.36 to 4.06; $P = .002$). Similarly, analysis restricted to participants with

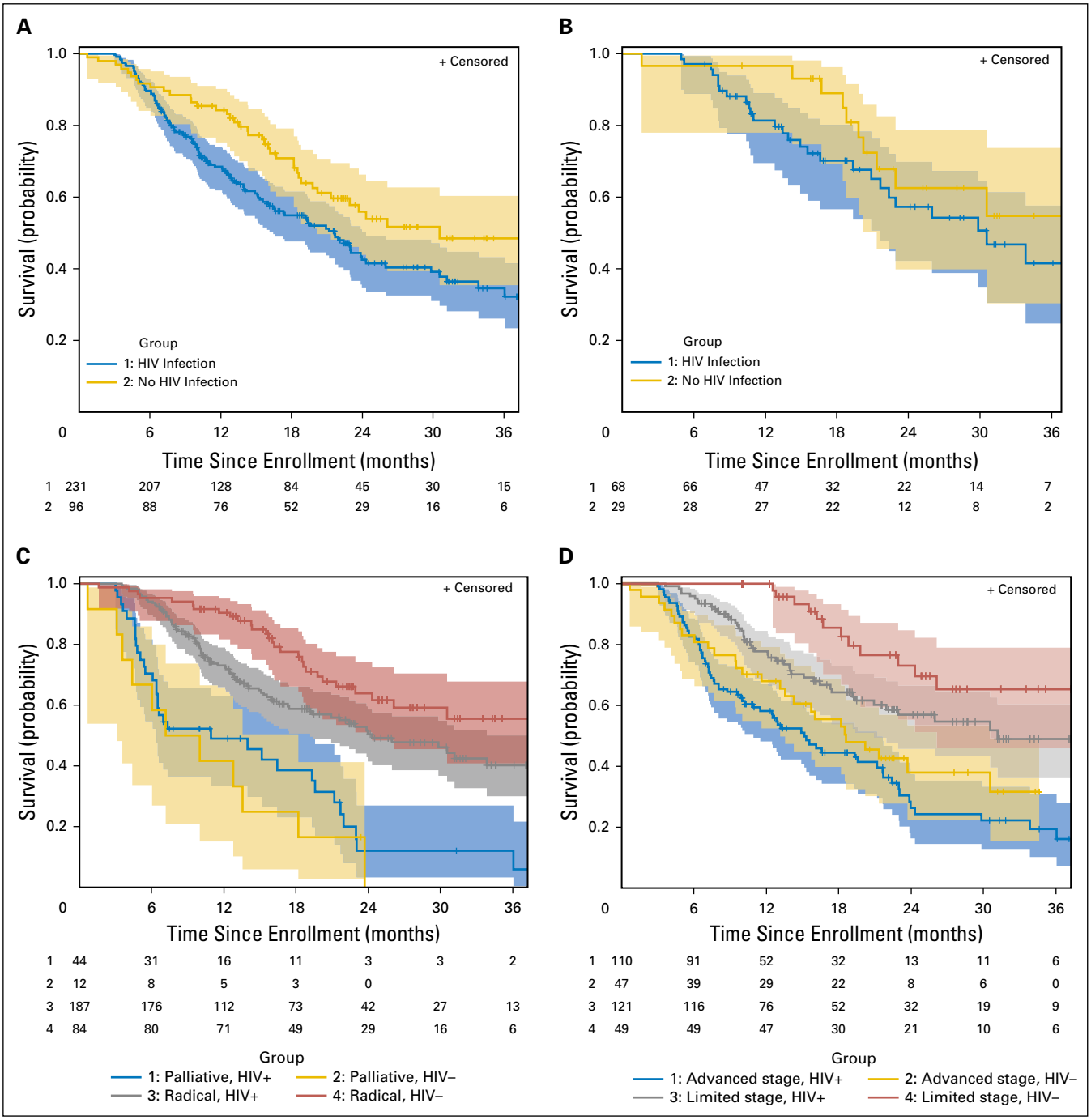

Fig 2. Kaplan-Meier estimated survival by HIV status (A) overall, (B) among participants who received guideline-concordant curative treatment, (C) by treatment intent, and (D) by stage. Number at risk is shown under the curves, and shaded areas indicate 95% confidence bands. Survival significantly differed by HIV status in these univariable analyses among all participants ($P = .022$), among those treated with radical intent ($P = .019$), and among those with limited-stage cancer (stage IA to IIB; $P = .036$). HIV+, with HIV infection; HIV–, without HIV infection.

HIV who received guideline-concordant curative intent treatment showed higher mortality (HR, 2.63; 95% CI, 1.05 to 6.55; $P = .037$). The effect of HIV differed significantly ($P = .035$ for interaction) by cancer stage, with a much greater adverse effect of HIV infection for participants with more localized disease (Fig 3). The effect of HIV was significantly attenuated by increasing CD4 cell count category ($P = .036$ for interaction), but the adverse effect of HIV was apparent even in strata of near-normal CD4 cell counts. Although the survival curves suggest a possibility that the adverse effect of HIV may decline with follow-up time, no significant interaction was observed with time detected ($P = .33$). A similar but smaller estimated effect of HIV was obtained in sensitivity analyses on the basis of multivariable and propensity score–adjusted Cox models that used the same covariates as the primary inverse probability weighted model (HR, 1.57 [95% CI, 1.03 to 2.41; $P = .037$] and 1.54 [95% CI, 1.01 to 2.35; $P = .043$], respectively).

Treatment Delivered and Response

The majority of participants (271 [82.9%]) were candidates for potentially curative therapy, as determined by the treating oncologist, and 47 (14.4%) were treated with palliative intent. No significant differences ($P = .32$) were found in the proportion eligible for definitive therapy by HIV status. Among those treated with curative intent, 85 (48.0%) participants with HIV infection and 40 (48.0%) without HIV infection completed the recommended radiation therapy (> 79 Gy [EQD2]). A sizable minority received an inadequate radiation dose (< 71.2 Gy [EQD2]; 50 [28.3%] *v* 29 [35.8%] for participants with *v* without HIV infection, respectively). Failure to achieve the target dose was the result of inadequately received fractions of brachytherapy (62.2%), EBRT (26.3%), or both (27.8%). No significant differences in radiation treatment completion, dose received, or treatment duration by HIV status were found.

Information on chemotherapy received was available for 198 (76.7%) participants treated with curative intent. A total of 114 (84.4%) participants with HIV infection and 46 (73.0%) without HIV infection received at least one cycle of concurrent cisplatin ($P = .080$). Treatment response was documented for 193 (74.8%) participants treated with curative intent. Among these participants, complete or nearly complete tumor response was seen in 115 (83.9%) with HIV and 54 (88.5%) without HIV ($P = .52$).

Complications

Participants with and without HIV infection commonly experienced cervical stenosis, proctitis, and hyperpigmentation during cervical cancer treatment (Table 2). No significant differences in incidence of any complication or frequency of specific complications by HIV status were found. Because participants received subsequent follow-up care at local facilities, we were unable to reliably ascertain complications that occurred after treatment completion.

DISCUSSION

In this prospective study of women with cervical cancer in Botswana, HIV infection nearly doubled the risk of death. Excess risk

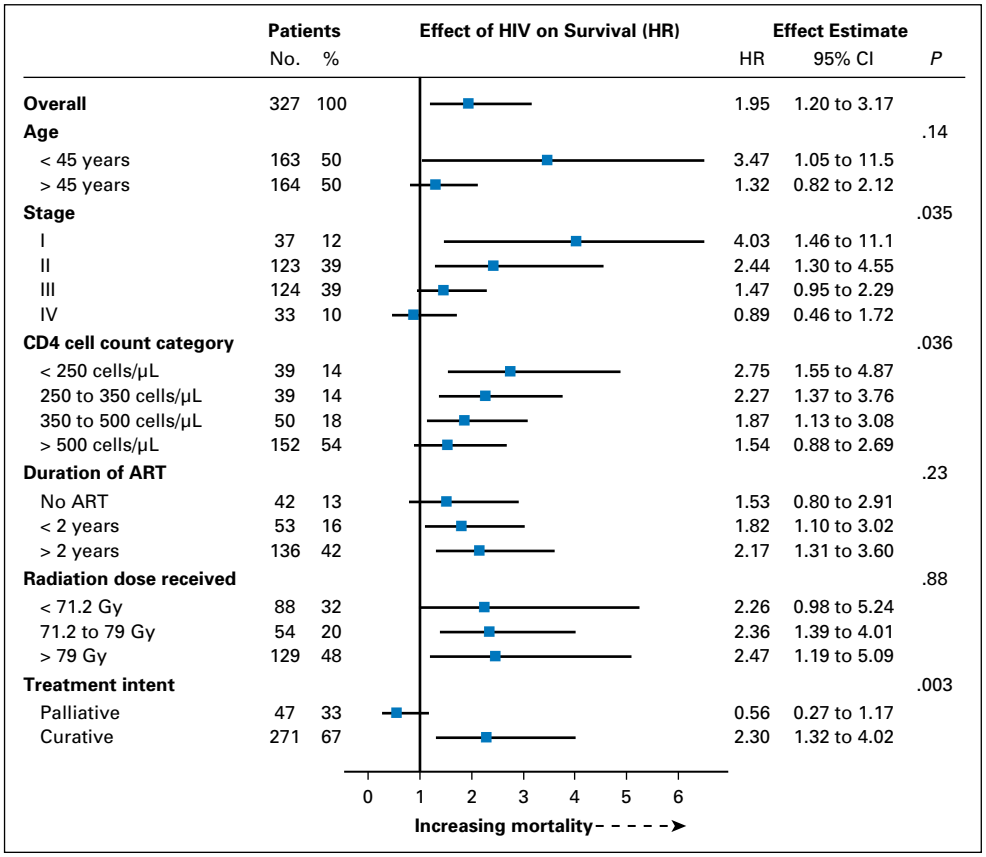

Fig 3. Effect of HIV on overall survival within subgroups. The *P* value is from the statistic for testing the interaction between HIV status and the subgroup variable. Only participants treated with curative intent are included in the comparison of effect of HIV by radiation dose received. ART, antiretroviral therapy; HR, hazard ratio.

for women with HIV infection was greater for those with earlier stage cancer, although survival was poorer for all with HIV infection except those with stage IV cancer. With the exception of one death attributed to HIV, all deaths with available information were attributed to cancer. Treatment completion was a challenge for all participants, with nearly one third of those treated with curative intent receiving less radiation than international norms.[21]

To our knowledge, this study is the first to prospectively compare cervical cancer outcomes by HIV status. Prior clinical cohort studies in anal carcinoma,[6-8] diffuse large B-cell lymphoma,[24] and hepatocellular carcinoma[25] have demonstrated similar survival between patients with and without HIV infection and cancer in the modern ART era. However, potentially related to increased sample size, population-based studies that used US cancer registries or health care systems have documented 1.2- to threefold decreased survival for individuals with HIV for several cancers,[26-28] including an estimated 1.4-fold increased risk of death as a result of cervical cancer in contemporaneous patients.[10] Poorer survival observed in population studies may be related to confounding due to decreased access to treatment and other factors.[29,30] The current study based on prospective observation and improved adjustment for confounding factors and treatment received adds to the existing evidence that suggests an elevated risk due to concurrent HIV infection and extends this evidence to the African setting where the bulk of HIV-associated cancers occur.

Table 2. Treatment Delivered and Complications

Treatment or Toxicity	Group, No. (%)			*P*
	HIV Infection	No HIV Infection	Overall	
Treatment intent				.32
Curative	187 (81.0)	84 (87.5)	271 (82.9)	
Palliative	36 (15.6)	11 (11.5)	47 (14.4)	
Not recorded	8 (3.5)	1 (1.0)	9 (2.8)	
Therapy received for participants treated with curative intent*				
Radiotherapy completion				.21
Received recommended dose (> 79 Gy [EQD2])	85 (48.0)	40 (48.0)	125 (48.5)	
Received minimally adequate dose (71.2-79 Gy [EQD2])	42 (23.7)	12 (14.8)	54 (20.9)	
Received inadequate dose (≤ 71.2 Gy [EQD2])	50 (28.3)	29 (35.8)	79 (30.6)	
Median radiation received (IQR), Gy [EQD2]				
Total	78.4 (68.3-79.8)	78.4 (62.9-79.8)	77.4 (67.3-79.8)	.83
External beam	50.0 (45.8-50.0)	50.0 (50.0-50.0)	50.0 (46.0-50.0)	.038
Brachytherapy	29.8 (17.9-29.8)	29.8 (14.2-29.8)	29.8 (16.7-29.8)	.79
Delayed treatment (> 8 weeks)†	14 (11.0)	9 (17.3)	23 (12.8)	.32
Median treatment duration (IQR)†	6.6 (5.9-7.6)	6.6 (6.0-7.6)	6.6 (6.0-7.6)	.77
Received any brachytherapy	144 (81.4)	66 (81.5)	210 (81.4)	1.0
Completed brachytherapy (> 29 Gy EQD2)	110 (62.1)	48 (59.3)	158 (61.2)	.68
Received of concurrent cisplatin‡	114 (84.4)	46 (73.0)	160 (80.8)	.080
Received recommended treatment (> 79 Gy and at least one dose of cisplatin)‡	66 (48.9)	29 (46.0)	95 (48.0)	.76
Received minimally adequate treatment (> 71.2 Gy and at least one dose of cisplatin)‡	94 (69.6)	37 (58.7)	131 (66.2)	.15
Treatment response				.39
Complete or nearly complete	112 (63.3)	52 (64.2)	164 (63.6)	
Residual tumor	22 (12.4)	7 (8.6)	29 (11.2)	
Unknown	43 (24.3)	22 (27.2)	65 (25.2)	
Toxicities among all patients (curative and palliative)				
Reported toxicity during treatment	208 (90.0)	91 (94.8)	299 (91.4)	.16
Type of toxicity reported				
Dry desquamation	17 (7.8)	5 (5.4)	22 (7.1)	.63
Moist desquamation	18 (8.3)	4 (4.4)	22 (7.1)	.33
Excoriation	5 (2.3)	3 (3.3)	8 (2.6)	.70
Hyperpigmentation	58 (26.7)	23 (25.0)	81 (26.2)	.78
Fibrosis	4 (1.8)	3 (3.3)	7 (2.3)	.43
Proctitis	79 (36.4)	37 (40.2)	116 (37.5)	.52
Stenosis	119 (54.8)	56 (60.9)	175 (56.6)	.38
Renal failure	1 (0.4)	0 (0)	1 (0.3)	1.0
Infection	2 (0.9)	0 (0)	2 (0.6)	1.0
Other§	5 (2.2)	9 (9.4)	14 (4.3)	.006

NOTE. *P* values from Wilcoxon rank sum test for continuous measures and Fisher exact test for categorical measures.
Abbreviations: EQD2, 2 Gy per fraction radiobiologic equivalence[19]; IQR, interquartile range.
*Restricted to women treated since February 2012 when brachytherapy became available in Botswana. Twelve women were treated before and referred to South Africa for brachytherapy.
†To avoid misrepresentation of treatment duration through inclusion of women who did not complete therapy, the analysis was restricted to those who received the recommended therapy or the minimally adequate dose.
‡Due to missing data, only includes 121 participants with HIV infection and 61 without HIV infection.
§Recorded toxicity for participants with HIV infection were anemia (n = 1), constipation (n = 1), and unspecified (n = 3), and for those without HIV infection, toxicities included cervical laceration (n = 1), anorexia (n = 2), severe pain (n = 1), tinnitus (n = 1), and unspecified (n = 4).

HIV is believed to increase incident cervical cancer primarily through an increased risk of developing the initial precancerous lesion[31] through impaired clearance of high-risk HPV infections[32-36] and requisite infection of cervical basal cells.[37] However, these mechanisms would not be expected to affect survival after the cancer develops. Regression of intraepithelial lesions seems to be a process mediated by tissue $CD4^+$ and $CD8^+$ lymphocytes, which lead to the killing of infected cells.[38,39] We speculate that immune responses from tissue lymphocytes also contribute to the clearance of residual cancerous cells after treatment. Mucosal $CD4^+$ cells are decimated early in HIV infection and do not recover substantially with ART, despite an increased circulating CD4 cell count.[40,41] The residual deficiency in cellular immunity could contribute to poorer responses to cervical cancer therapy in women with HIV infection. The impact may be larger for those with more localized and more curable cancers, which would account for the striking modification of the effect of HIV by cancer stage. Further investigation into the role of cellular immunity to maintain cervical cancer remission could lead to improvements in cervical cancer survival for women with and without HIV.

Alternatively, ART could affect response to radiation as some infrequently used protease inhibitors potently sensitize cells to radiation.[42-44] In vitro results have suggested that the commonly used combination of tenofovir, emtricitabine, and efavirenz sensitizes tumors to EBRT (< 4 Gy per fraction) but protect tumors from brachytherapy (≥ 4 Gy per fraction).[45] However, early responses to treatment and toxicity were similar between groups, which suggests that these effects are not a major contributor to the observed survival difference.

This study is strengthened by prospective data collection from the largest cohort of HIV-associated cervical cancers to our knowledge and complete vital status ascertainment. However, the findings should be considered in the context of study limitations. Fewer than half of the participants received guideline-concordant treatment, and although many came close to this target and there were no differences by HIV status, receipt of a suboptimal dose may explain poorer-than-expected survival overall. Further work is needed to better understand barriers to treatment completion. Due to limited documentation, we are unable to determine with confidence that access to and tolerability of cisplatin was not affected by HIV status or to determine the proportion of participants who received guideline-concordant therapy. Further study could determine whether patients with HIV infection receive fewer doses of cisplatin and whether this could partially explain the adverse impact of HIV on survival.[46] Staging evaluation did not include cross-sectional imaging, so analyses did not include tumor volume or nodal involvement. Finally, information about relapses and cause of death was limited, which restricted analysis to overall survival. With an observed annual mortality rate of 0.9% for women with HIV infection in a Botswana cohort with similar CD4 cell counts and access to ART but without cancer,[47,48] only a small portion of the observed 31.6% mortality at 1 year in the current study is expected to be due to noncancer causes.

In conclusion, even in the context of good access to and use of ART, HIV infection more than doubled the risk of death among women who received curative guideline-concordant therapy. Competing mortality from HIV-associated infections seemed to contribute minimally to the excess risk of death; rather, earlier oncologic progression among women with HIV seemed to account for the excess mortality. Challenges in retention and completion of guideline-concordant therapy were observed irrespective of HIV status and likely contributed to overall low survival. Improved treatment approaches for women with HIV-associated cervical cancer and novel retention strategies for all women are urgently needed to address the rising burden of cervical cancer in sub-Saharan Africa and other low-income regions.

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Disclosures provided by the authors are available with this article at www.jco.org.

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Appendix

Statistical Analyses

Objective. The primary objective was to assess the effect of HIV infection on the overall survival among women with cervical cancer irrespective of possible confounders. Secondary objectives were to assess the effect of HIV among women treated with curative intent and those treated with curative intent who received guideline-concordant treatment.

Analytic models. An inverse probability weighted Cox marginal structural model (IPW MSM) was chosen as the primary analytic approach to simulate a theoretical trial where baseline HIV infection was randomly assigned to eliminate bias from confounders. Although less commonly used in cohort studies, we anticipated considerable confounding from age (population with HIV infection younger than that without HIV infection in Botswana), socioeconomic factors (younger citizens have benefited from brisk economic development), cancer stage (possible earlier detection in women with HIV infection due to regular care or more rapid tumor progression in women with HIV), and potential bias in treatment decisions (women with HIV infection observed to be offered less-aggressive care in other settings). The relationship between these key confounders and unmeasured factors were not known. Rather than use a standard conditional approach, we used the IPW MSM approach to break the relationship between HIV and the measured factors without needing to make assumptions of the causal structure.

Model weights were generated from the inverse probability of HIV infection as estimated by a logistic model. All baseline factors associated ($P < .1$) with overall survival in a univariable Cox model stratified by HIV status were included in the logistic model. To further limit confounding, all baseline factors associated with HIV infection ($P < .1$) were included, even if not significantly associated with survival (Table A1). To improve precision, model weights were stabilized by overall probability of HIV infection in the cohort. Where L represents all included covariates (dichotomized age, use of traditional healers, ordinal cancer stage, education beyond primary school, presence of household electricity, marital status, dichotomized income, and three-category employment status), the weights used were as follows:

$$\text{Weights for women with HIV infection: } w_s = \frac{\Pr[\text{HIV} = 1]}{\Pr[\text{HIV} = 1|\text{L}]}$$

$$\text{Weights for women without HIV infection: } w_s = \frac{\Pr[\text{HIV} = 0]}{\Pr[\text{HIV} = 0|\text{L}]}$$

The resulting model weights are summarized in Table A2.

Because women with HIV infection may not be offered the same treatment as those without HIV infection, the final MSM included adjustment for radiation dose received:

$$\text{Log}(\lambda|\text{A}, \text{R}_1, \text{R}_2) = \beta_o + \beta_1 \text{A} + \beta_2 \text{R}_1 + \beta_3 \text{R}_2$$

where A is HIV infection and R_1 and R_2 are two of three radiation dose levels.

Given the marginal association between survival and receipt of cisplatin (Table A3), inclusion of this factor was explored. However, the effect estimate from this model was similar to the model restricted to those with known cisplatin status who received curative therapy (only patients treated with curative intent received standard cisplatin routinely; hazard ratio, 2.57 [95% CI, 1.38 to 4.78] and 2.61 [95% CI, 1.41 to 4.83], respectively). Final models were executed with proc genmod in SAS software (SAS Institute, Cary, NC) by using Anderson-Gill formatted data and robust variance estimators.

Effect modification, including over follow-up time, was assessed by introducing a product term for the possible effect modifier (M) to the model:

$$\text{Log}(\lambda|\text{A}, \text{R}_1, \text{R}_2, \text{M}, \text{M} \times \text{A}) = \beta_o + \beta_1 \text{A} + \beta_2 \text{R}_1 + \beta_3 \text{R}_2 + \beta_4 \text{M} + \beta_5 \text{M} \times \text{A}$$

A propensity score–adjusted Cox model was used for sensitivity analysis. The probability of HIV infection based on the same covariates included in the IPW MSM was used as the propensity score. The model included adjustment for the radiation dose received separate from the propensity score (P):

$$\text{Log}(\lambda|\text{A}, \text{R}_1, \text{R}_2, \text{P}) = \beta_o + \beta_1 \text{A} + \beta_2 \text{R}_1 + \beta_3 \text{R}_2 + \beta_3 \text{P}$$

A standard conditional Cox pLroportional hazards model was also used for sensitivity analysis. The same covariates included in the IPW MSM (L_1 to L_{10}) were used in the model, including radiation dose received:

$$\text{Log}(\lambda|\text{A}, \text{R}_1, \text{R}_2, \text{L}_1\text{-L}_{10}) = \beta_o + \beta_1 \text{A} + \beta_2 \text{R}_1 + \beta_3 \text{R}_2 + \beta_4 \text{L}_1 + \beta_5 \text{L}_2 + \beta_6 \text{L}_3 + \beta_7 \text{L}_4 + \beta_8 \text{L}_5 + \beta_9 \text{L}_6 + \beta_{10} \text{L}_7 + \beta_{11} \text{L}_8 + \beta_{12} \text{L}_9 + \beta_{13} \text{L}_{10}$$

Table A1. Predictors of Overall Survival and HIV Infection

	Stratified Univariable Analyses				Multivariable Analyses	
	Overall Survival		HIV Infection		Overall Survival	
Factor	HR (95% CI)	*P*	OR (95% CI)	*P*	HR (95% CI)	*P*
HIV infection*	1.53 (1.06 to 2.19)	.022	—	—	1.60 (1.04 to 2.45)	.034
Cancer stage (per increase in half stage [eg, IIA-IIB])	1.44 (1.30 to 1.60)	< .001	0.96 (0.83 to 1.12)	.64	1.40 (1.26 to 1.56)	< .001
Age < 45 years	1.01 (0.72 to 1.42)	.97	7.98 (4.43 to 14.4)	< .001	1.02 (0.69 to 1.51)	.93
Primary school or less education	1.06 (0.76 to 1.48)	.72	0.27 (0.15 to 0.46)	< .001		
Electricity in home	0.76 (0.55 to 1.04)	.088	0.77 (0.47 to1.25)	.29	0.97 (0.64 to 1.46)	.87
Occupation		.006		.024		.058
Unemployed	Reference	—	Reference	—	Reference	—
Other employment or student	0.31 (0.14 to 0.67)	—	2.86 (1.06 to 7.75)	—	0.46 (0.64 to 1.46)	—
Salaried position	0.73 (0.51 to 1.07)	—	1.80 (1.01 to 3.02)	—	1.28 (0.66 to 2.50)	—
Married	0.71 (0.49 to 1.01)	.058	0.56 (0.34 to 0.91)	.020	0.85 (0.58 to 1.23)	.38
Used traditional medicine	0.99 (0.70 to 1.40)	.99	0.62 (0.37 to 1.03)	.063	0.94 (0.66 to 1.34)	.64
Income < $50/month	1.61 (1.13 to 2.28)	.008	0.53 (0.32 to 0.89)	.016	1.42 (0.74 to 2.73)	.29
Rural residence	1.03 (0.69 to 1.56)	.88	0.61 (0.31 to 1.18)	.14	—	—
Age ≤ 17 years at sexual debut	1.27 (0.89 to 1.83)	.19	0.95 (0.52 to 1.66)	.85	—	—
Indoor toilet in home	0.88 (0.61 to 1.27)	.50	0.68 (0.41 to 1.13)	.14	—	—
ECOG 2, 3, or 4†	1.34 (0.94 to 1.92)	.11	1.52 (0.85 to 2.71)	.16	—	—
Ever smoker	0.86 (0.51 to 1.47)	.59	1.59 (0.63 to 4.06)	.33	—	—
Histology		.64		.15	—	—
Squamous cell carcinoma	Reference	—	Reference	—	—	—
Adenocarcinoma	1.27 (0.59 to 2.75)	—	0.35 (0.12 to 0.99)	—	—	—
Adenosquamous	1.57 (0.64 to 3.83)	—	0.53 (0.11 to 2.43)	—	—	—
Other or missing	0.83 (0.42 to 1.62)	—	1.60 (0.52 to 4.92)	—	—	—

NOTE. Univariable analyses of survival are stratified by HIV status. Baseline factors associated with survival or HIV infection ($P < .10$) were included in final models.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OR, odds ratio.
*Not stratified by HIV status.
†Due to strong association with cancer stage, model used to assess performance status included cancer stage.

Table A2. Inverse Probability Model Weights by HIV Status and Selected Covariates

Factor	HIV Infection		No HIV Infection	
	Mean	Minimum, Maximum	Mean	Minimum, Maximum
Overall	1.00	0.72, 3.34	1.07	0.37, 5.85
Advanced cancer stage (III and IV)	0.98	0.72, 2.50	0.77	0.37, 3.47
Age < 45 years	0.79	0.72, 0.96	3.33	0.82, 5.85
Primary school or less education	1.17	0.73, 3.36	0.66	0.37, 4.90
Electricity in home	1.03	0.72, 3.36	1.05	0.37, 5.17
Salaried employment	0.96	0.73, 2.50	1.75	0.42, 4.96
Married	1.09	0.74, 3.36	0.64	0.37, 2.27
Used traditional medicine	1.13	0.73, 3.35	0.83	0.37, 3.47
Income < $50/month	1.05	0.73, 3.35	0.78	0.37, 5.85

Table A3. Treatment and Early Response Factors and Association With Overall Survival and Baseline HIV Status

Factor	Bivariable Analyses				Multivariable Analyss	
	Overall Survival		HIV Infection		Overall Survival	
	HR (95% CI)	*P*	OR (95% CI)	*P*	HR (95% CI)	*P*
Radiotherapy completion		.049		.21		.12
Received recommended dose (> 79 Gy [EQD2])	Reference		Reference		Reference	
Received minimally adequate dose (71.2-79 Gy [EQD2])	1.63 (0.99 to 2.67)	—	1.64 (0.78 to 3.46)	—	1.65 (0.97 to 2.81)	—
Received inadequate dose (≤ 71.2 Gy [EQD2])	1.66 (1.05 to 2.63)	—	0.81 (0.45 to 1.47)	—	0.87 (0.47 to 1.63)	—
Received concurrent cisplatin	0.67 (0.39 to 1.15)	.14	2.01 (0.97 to 4.14)	.060	0.76 (0.43 to 1.32)	.32
Treatment response		.024		.64		.023
Complete or nearly complete	Reference	—	Reference	—	Reference	—
Residual tumor	2.14 (1.20 to 3.82)	—	1.46 (0.59 to 3.63)	—	2.39 (1.28 to 4.82)	—
Unknown	1.50 (0.93 to 2.40)	—	0.91 (0.49 to 1.67)	—	1.10 (0.46 to 2.63)	—

NOTE. Bivariable Cox survival models included cancer stage and were stratified by HIV status. The multivariable model was also stratified by baseline HIV status and included all listed factors and cancer stage. Restricted to women treated with curative intent after February 2012.
Abbreviations: EQD2, 2 Gy per fraction radiobiologic equivalence; HR, hazard ratio; OR, odds ratio.