June 26, 2022

Dear Editorial Board of Gynecologic Oncology,

On behalf of our research group, we would like to submit our Original Report **"Stage and outcomes of invasive cervical cancer patients in Botswana: A prospective cohort study from 2013-2020**" for publication in Gynecologic Oncology as a manuscript.

To date, there exists extensive data on stage distribution and survival outcomes of CC patients in high-income regions (HICs) such as the United States and European countries. However, there remains a shortage of comprehensive stage distribution and outcomes data for CC cases in LMICs, particularly in SSA. Prior studies presenting the stage distribution for women diagnosed with CC in Botswana either included patients treated with chemoradiotherapy (CRT) alone or assessed survival by HIV status and treatment only. Hence, there is a lack of comprehensive data on stage distribution and survival outcomes by stage of CC patients in Botswana. This article presents comprehensive stage distribution, patterns of care, and survival outcomes for CC patients in Botswana and evaluates the impact of stage at presentation on survival. We look forward to your commentary on our work.

Breakdown of roles for all authors who contributed to this paper is as follows:

- Surbhi Grover: Conceptualization, data curation, analysis, writing, funding acquisition, investigation, original draft writing, review and editing
- Jessica George and Shawna Tuli: Analysis, writing, review and editing
- Katie Lichter, Ganen Chinniah, and Rohini Bhatia: Figures/Tables, review and editing
- Barati Monare, Lisa Bazzett-Matabele, Memory, Bvochora-Nsingo, Sebathu Chiyapo, Dawn Balang, Tlotlo Ralefala, Peter Vuylsteke, and Rebecca Luckett: Review and editing
- Sanghyuk Shin and Nicola Zetola: Methodology, supervision, review and editing
- Doreen Ramogola-Masire: Supervision, review and editing

Accompanying this letter is the manuscript formatted for Gynecologic Oncology. Authors who have conflicts of interest are disclosed. Please do not hesitate to contact us for further information as needed.

Sincerely,

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Stage and outcomes of invasive cervical cancer patients in Botswana: A prospective cohort study from 2013-2020

Short Title: Stage and Outcomes of Cervical Cancer

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Data Availability: Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Abstract

Objective
To present the stage distribution, patterns of care, and outcomes of patients from Botswana with invasive cervical cancer (CC), living with or without HIV.

Methods
Between 2013 and 2020, women with CC were prospectively enrolled in an observational cohort study.

Results
A total of 1,043 patients were enrolled; 69% were women living with HIV (WLWH). The median age of the cohort was 47 years (IQR 40-58), with WLWH presenting at a younger age compared to women without HIV (44 vs. 61, $p<0.001$). Among WLWH, the median CD4 count at the time of cancer diagnosis was 429.5 cells/μL (IQR 240-619.5), 13% had a detectable viral load, and 95% were on antiretroviral (ART) treatment. In regard to treatment, 6% (n=58) underwent surgery, 33% (n=341) received radiation therapy (RT), 51% (n=531) received chemoradiation (CRT), and 7% (n=76) did not receive treatment. Stage distribution in the cohort was as follows: I 17% (n=173), II 37% (n=388), III 35% (n=368), and IV 8% (n=88). For all patients, 2-year OS was 67%. In multivariable cox regression, worse OS was associated with stage: II (HR 1.91, $p=0.007$), III (HR 3.99, $p<0.001$), and IV (HR 5.06, $p<0.001$). Improved OS was associated with Hb >10 g/dL (HR 0.51, $p<0.001$).

Conclusions
Among women in Botswana with CC, most patients presented with stage II or III disease warranting RT or CRT. While a third of CC patients were WLWH, HIV did not impact OS.

Introduction

Cervical cancer (CC) is the fourth most common cancer in women worldwide.[1] In 2020, there were 604,000 new cases of CC and 342,000 deaths from the disease.[1] CC is disproportionately prevalent in low-and middle-income countries (LMICs), where 84-90% of new cases occur.[1]

Most CC cases are attributed to human papillomavirus (HPV) infection.[1] Additionally, women infected with human immunodeficiency virus (HIV) have been found to exhibit high rates of chronic HPV infection, further increasing their risk of developing CC over time.[2] In Botswana, a LMIC in Sub-Saharan Africa (SSA) with a high prevalence of HIV infection, CC is the most common cancer and the leading cause of cancer death in women.[1] As of 2019, 25.1% of women in Botswana aged 15-49 were living with HIV, and two-thirds of CC cases occurred among women living with HIV (WLWH).[3] Further, financial constraints and the resource-limited health system hindered appropriate CC screening among women with or without HIV who have CC.[4]

To date, there exists extensive data on stage distribution and survival outcomes of CC patients in high-income regions (HICs) such as the United States and European countries.[5,6] However, there remains a shortage of comprehensive stage distribution and outcomes data for CC cases in LMICs, particularly in SSA.[7] Prior studies presenting the stage distribution for women diagnosed with CC in Botswana either included patients treated with chemoradiotherapy (CRT) alone or assessed survival by HIV status and treatment only.[8,9] Hence, there is a lack of comprehensive data on stage distribution and survival outcomes by stage of CC patients in Botswana. This

article presents comprehensive stage distribution, patterns of care, and survival outcomes for CC patients in Botswana and evaluates the impact of stage at presentation on survival.

Methods

Study site and population

Patients with CC stages I-IV, between April 2013 and November 2020 were prospectively enrolled in the Botswana Prospective Cancer Cohort (BPCC) at Gaborone Private Hospital (GPH), the only radiation facility in Botswana, and gynecological multi-disciplinary team (MDT) clinic at Princess Marina Hospital (PMH), the only multidisciplinary clinic for management of CC in the country. PMH is a tertiary public hospital in Gaborone that provides free care including oncology care to all the citizens of Botswana. The BPCC is an observational cohort study of patients receiving cancer treatment in Botswana.[10]

Data collection

Data were collected using pre-designed electronic forms hosted on the University of Pennsylvania's Research Electronic Data Capture (REDCap) database management system. Patients were followed prospectively every three months until death or last follow-up and data were recorded for each patient via interviews, clinic visits, and medical records. Information was gathered about patient demographics, clinical history, initial presenting symptoms, and history of HIV and HIV-related clinical data including antiretroviral therapy (ART) treatment, CD4 count (cells/μL) and viral load (VL) (cells/μL) at the time of cancer diagnosis. Additional patient baseline information was collected about performance status using the Karnofsky performance status score (KPS) and laboratory values including hemoglobin (Hb) (g/dL), creatinine (Cr)

(μmol/L), absolute neutrophil count (ANC) ($\times 10^9$/L), white blood cells (WBC) ($\times 10^9$/L) and albumin (Alb) (g/dL).[11] Disease characteristics recorded included histology, treatment prescribed and received, and time to treatment which was defined as the time from biopsy to treatment initiation. The treatment dates, regimen, and number of chemotherapy cycles received were recorded for patients who received CRT. The total radiation dose received to point A was calculated using the radiobiological equivalent dose (EQD2) formula.[12]

The Institutional Review Boards of the Ministry of Health of Botswana, Princess Marina Hospital, and the University of Pennsylvania (820159) approved the study. Written consent was obtained from all participants prior to enrollment.

Work-up and Treatment

Patients were clinically staged according to the 2009 (majority of patients included in the study) and then, starting in 2019, the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging criteria.[10,13] Diagnostic work-up included basic laboratory studies (i.e., complete blood count and renal function test), a chest x-ray, and an abdominal ultrasound before treatment.[8]

Treatment for patients presenting with FIGO stage 2009 I-IV CC was prescribed according to National Comprehensive Cancer Network guidelines.[14] For patients with early-stage (FIGO stage IA-IB1) CC, the standard treatment was surgery and/or radiation therapy (RT) with or without cisplatin-based chemotherapy.[14] For patients with locally advanced CC (FIGO stage IB2-IVA), the standard treatment was a combination of external beam radiotherapy with concurrent cisplatin-based chemotherapy (CRT) and brachytherapy.[14] Patients were treated with RT alone if they were observed to be a poor candidate for chemotherapy based on baseline laboratory values

or performance status. Patients requiring RT or CRT were referred to GPH from the MDT clinic. All costs associated with RT or CRT at GPH are covered through the publicly funded healthcare system.[10]

All WLWH were started on ART, if not already on HIV treatment. Patients accessed ART therapy through the Botswana National ART program, which provides ART free-of-charge to all.[3] Participants with unknown HIV status or previous negative HIV test results were re-tested prior to initiation of cancer treatment.

Primary outcome and exposure

The primary reported exposures were stage of disease at presentation and patterns of care, and the primary outcome was overall survival (OS) by stage. Time-to-death was defined as the time from diagnosis until death, or censorship at the most recent follow-up. If a patient or their next of kin could not be reached by telephone, medical records were searched to determine vital status or the date of the patient's last visit to a health care facility. The patient was censored, at that point, if vital status was not available.

Secondary objectives were to identify baseline demographic and clinical factors associated with overall survival. Main exposures of interest were age at cancer diagnosis, marital status, distance to clinic, HIV status, baseline (at time of treatment) Cr, baseline Hb, baseline ANC, baseline WBC, baseline Alb, baseline KPS, and stage.

Statistical analysis

Descriptive statistics were used to highlight patient, tumor, and treatment characteristics for the entire cohort and compare between patient subgroups divided by HIV status and treatment received.

Categorical variables (age, marital status, previous CC screening, distance from clinic, disease stage, Hb, KPS, HIV status, CD4, VL, ARV received, and treatment type [surgery, CRT, RT, chemotherapy, surgery + chemotherapy, surgery + RT, surgery + CRT, no treatment]) were compared via $\chi 2$ tests and continuous variables (Cr, ANC, WBC, Alb) were compared with the t-test, as appropriate.

Descriptive statistics were used to describe stages of presentation and patterns of care defined as treatment type.

Survival by stage was investigated via the Kaplan-Meier method, with log-rank tests used to compare survival among subgroups. The Cox Hazards Regression model was used to evaluate factors associated with OS and survival by stage in all patients, in patients who received any treatment, and in RT/CRT eligible patients (stages IB2 and above). Statistical analysis was performed using RStudio 2020 (RStudio Team, Boston, MA) and statistical significance was ascertained with the threshold of $p<0.05$.

Results

Patient and clinical characteristics

A total of 1,043 patients were included with a median follow-up of 2.2 years (interquartile range [IQR] 0.03-9.13 years) and 3.4 years for living patients (IQR 0.2-9.13 years) (Table 1). Among the cohort, 714 (68.5%) were WLWH versus 311 (29.8%) women without HIV. Median age among women in the cohort was 47 years (IQR 40-58). WLWH were significantly younger than women without HIV (44 vs. 61 years, respectively, $p<0.001$) (Supplemental Table A). The

median CD4 count for WLWH was 429.5 cells/μL (IQR 240-619.5). Of the 714 WLWH, 396 (55.5%) had a VL <400 cells/μL and the majority, 676 women (94.7%), were receiving ART at the time of CC diagnosis.

Stage distribution

Among the 1,043 patients diagnosed with CC between 2013 and 2020, stage distribution was: 4.3% (n=45) Stage IA (IA, IA1, IA2); 12.3% (n=128) Stage IB (IB, IB1, IB2, IB3); 37.2% (n=388) Stage II (IIA, IIB); 35.3% (n=368) Stage III (IIIA, IIIB, IIIC); 8.4% (n=88) Stage IV (IVA, IVB) (Table 1).

Patterns of care

A total of 967 patients (92.7%) received treatment. The distribution among those who were treated was: surgery alone (5.6%), RT alone (32.7%), chemotherapy alone (1.2%), CRT (50.9%), surgery and RT (0.7%), surgery and chemotherapy (0.8%), and surgery and CRT (1.0%). There were no significant differences in treatment characteristics between WLWH and women without HIV.

Of the 902 RT/CRT eligible CC patients (stages IB2 and above), 63.1% (n=569) received brachytherapy; 52.1% (n=470) received EQD2 ≥ 75 Gy; 57% (n=514) received concurrent cisplatin ≥ 1 cycle. The median treatment duration, as defined as the time from treatment start-date to treatment completion, was 44 days (IQR 36-51 days). Breakdown of stage and treatment is described (Supplemental Table B).

Overall Survival by stage

Survival based on stage is summarized (Figure 1**)**. The median OS was 2.98 years (95% CI 2.61-3.33 years) for Stage I, 2.79 years (95% CI 2.49-3.20 years) for Stage II, 1.57 years (95%

CI 1.45-1.81 years) for Stage III, and 1.27 years (95% CI 0.89-1.60 years) for Stage IV (log-rank, p<0.001). Stage was inversely proportional to patients' 2-year OS rates among the entire cohort: Stage I 88.0% (95% CI 83.0-93.4%), Stage II 77.5% (95% CI 73.3-81.9%), Stage III 54.3% (95% CI 49.2-59.9%), and Stage IV 40% (95% CI 30.8-52.2%) (log rank, p<0.001).

Factors associated with Overall Survival

The median follow-up for the study population was 2.2 years (95% CI 2.1-2.4 years) and 3.4 years for those alive. Among the entire cohort, the 2-year OS rate was 67.5%. On univariate cox regression analysis, OS was associated with: Stage II (HR 2.19, p<0.001), Stage III (HR 5.09, p<0.001), and Stage IV disease (HR 7.23, p<0.001) vs. Stage I; Cr (HR 1.001, p<0.001); Hb >10 g/dL (HR 0.37, p<0.001) vs. Hb ≤10 g/dL; Alb (HR 0.96, p<0.001); and KPS <90 (HR 1.89, p<0.001) vs. KPS ≥90. On multivariable cox regression analysis including all patients considering age, HIV status, disease stage, Cr, Hb, and KPS, OS was associated with: Stage II (HR 1.91, p=0.007), Stage III (HR 3.99, p<0.001), and Stage IV (HR 5.06, p<0.001) vs. Stage I; Cr (HR 1.001, p<0.001); Hb >10 g/dL (HR 0.51, p<0.001) vs. Hb ≤10 g/dL; KPS <90 (HR 1.53, p<0.001) vs. KPS ≥90. HIV was not associated with OS on univariate or multivariate analysis (Table 2).

In a sub-group analysis of patients receiving treatment, the baseline factors associated with survival were similar to those above in the entire cohort of patients (Supplemental Table C).

Overall Survival by HIV status

For WLWH, the median OS was 2.2 years (95% CI 2.0-2.4 years) versus 2.3 years (95% CI 2.1-2.7 years) for women without HIV. There was no significant difference in 2-year OS rates between women without HIV and WLWH (log rank, p=0.2) (Supplemental Figure A).

Overall survival by treatment

Median OS was 2.3 years (95% CI 2.2-2.5 years) for patients who received any form of treatment as compared to 0.5 years (95% CI 0.3-0.9 years) for patients who did not receive treatment (Supplemental Figure B).

Among patients with stage IB2 disease and above who were eligible for RT/CRT, multivariate analysis adjusting for age, HIV status, Cr, Hb, KPS, disease stage, pathology response, dose of radiation, and chemotherapy, factors associated with improved survival included baseline Hb >10 g/dL (HR 0.57, p<0.001). Worsened survival outcomes were associated with disease stage: Stage III (HR 2.59, p=0.026), response to treatment at the end of RT: partial response (HR 1.58, p=0.005), dose of radiation: EQD2 <79 Gy (HR 1.47, p=0.015), and amount of chemotherapy: chemotherapy <4 cycles (HR 1.63, p=0.004) (Supplemental Table D).

Discussion

In this prospective cohort study of patients with CC in Botswana, most patients presented with locally advanced CC, with the majority of patients presenting with stage II-III disease. WLWH did not present with earlier stage CC despite screening encouragement being incorporated into routine HIV care in Botswana.[15] Among the cohort, 2-year OS by stage was 88.0% for stage I, 77.5% for stage II, 54% for stage III, and 40% for stage IV. Overall survival was largely associated with patients' disease stage. Given that most women in our cohort were found to have locally advanced CC, this demonstrates the importance of cervical cancer screening and early, aggressive intervention to prevent progression of disease and improve overall survival.

Recent studies have presented FIGO data on the stage distribution of women diagnosed with CC

in Ethiopia, Ghana, Kenya, Malawi, Nigeria, Sudan, and Tanzania.[16-25] A 2019 registry study presented stage distribution and survival outcomes of CC patients across 11 SSA countries, however, the study did not include Botswana and provided less granular staging, classifying stage at diagnosis as stage I-II or stage III-IV.[7] Within the study's findings, the 2-year survival outcomes varied by region and were inversely related to stage in the SSA countries.[17,20,23] In an Ethiopian study, 2-year OS was found to be inversely related to stage: 84.8% for patients presenting with stage I–II and 55.8% for stage III–IV.[17] A Nigerian study reported worse outcomes for 2-year OS by stage: about 50% for patients presenting with stage IIA and below and about 15% for IIB and above.[23] Neither the Ethiopian nor Nigerian study provide detailed staging and there still exist differences in survival outcomes in Botswana and other LMICs compared to HICs. In comparison, a HIC study reported a 3-year OS of 74% for stage IB, 79% for stage IIB, 45% for stage IIIB, and 33% for stage IVA.[26] The difference in survival between this HIC study compared to the studies in LMICs could be a result of higher overall EQD2 receipt due to the use of MRI guided adaptive brachytherapy or a result of overall smaller tumors, even for the same stage.

In evaluation of RT/CRT eligible patients, baseline factors associated with survival such as Hb >10 g/dL were consistent with our prior studies in patients treated with curative intent.[8,27,28] This suggests the significance of Hb in indicating overall performance status of the patient and ability to receive adequate treatment. Additionally, some studies have suggested that low Hb may be associated with impaired tumor oxygenation, resulting in relative radioresistance.[29] Elevated creatinine level was previously found to be associated with radiation dose <80 Gy and withholding of chemotherapy.[27]

HIV was not found to be associated with OS in this cohort of CC patients receiving ART treatment. Although prior studies from this region have reported worse survival among women with HIV, our current data aligns with our findings from previous studies which found no difference in OS by HIV status.[8,27,28] We hypothesize that the WLWH in our cohort have well-managed HIV which likely contributes to both their ability to tolerate treatment and their overall survival. However, given that WLWH presents with cervical cancer at significantly younger ages, it underlines the importance of aggressive cervical cancer screening implementation efforts at even earlier ages than women without HIV.

The present analysis yields the most extensive stage distribution and survival data to date for CC patients in Botswana and SSA and is the first to assess factors associated with OS at presentation in Botswana for all cervical cancer patients. The current findings remain subject to limitations. Patients among this cohort were primarily staged according to 2009 FIGO staging criteria due to limited diagnostic capacity in Botswana. As per 2018 FIGO staging criteria, it has been found that the inclusion of surgical pathologic and image findings resulted in upward stage migration for the majority of patients and improved survival discriminatory ability for stages I and IV patients.[10] Additionally, OS evaluated limited baseline patient characteristics and did not assess the impact of treatment characteristics on survival in early-stage patients treated with surgery. Future studies should assess whether treatment characteristics such as surgical quality or extent of surgery are associated with OS in early-stage patients.

In summary, most women enrolled among the cohort presented with locally advanced CC and

2-year OS was found to be 67%, which was inversely proportional to the stage of disease at presentation. Within the cohort, OS was associated with disease stage, Cr, Hb, and performance status regardless of HIV status. Given the prevalence of late-stage disease among this cohort in Botswana, it is imperative to optimize women's access to screening to allow for early detection and treatment of cervical disease.

Conflict of Interest Statement

Surbhi Grover: Research grant from Varian Medical Systems; Consultant for GenesisCare

Author Contribution Statement

Breakdown of roles for all authors who contributed to this paper is as follows:

- Surbhi Grover: Conceptualization, data curation, analysis, writing, funding acquisition, investigation, original draft writing, review and editing
- Jessica George and Shawna Tuli: Analysis, writing, review and editing
- Katie Lichter, Ganen Chinniah, and Rohini Bhatia: Figures/Tables, review and editing
- Barati Monare, Lisa Bazzett-Matabele, Memory, Bvochora-Nsingo, Sebathu Chiyapo, Dawn Balang, Tlotlo Ralefala, Peter Vuylsteke, and Rebecca Luckett: Review and editing
- Sanghyuk Shin and Nicola Zetola: Methodology, supervision, review and editing
- Doreen Ramogola-Masire: Supervision, review and editing

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Table / Figure Legend

Table 1: Baseline demographic characteristics of cervical cancer patients in Botswana 2013-2020

Table 2: Factors associated with overall survival in CC patients in Botswana: univariate and multivariable analyses [N=1043]

Figure 1: Survival outcomes by stage

ST1- Table A: Baseline demographic and treatment characteristics by HIV status of CC patients in Botswana

ST2- Table B1: Treatment characteristics by FIGO stage groups in CC patients in Botswana

ST3- Table B2: Treatment characteristics by FIGO stage in CC patients in Botswana

ST4- Table C: Factors associated with overall survival in cervical cancer patients who received any treatment
in Botswana: univariate and multivariable analyses [N=967]

ST5- Table D: Factors associated with overall survival in radiation eligible (stages IB2 and above) cervical cancer patients in Botswana: univariate and multivariable analyses [N=902]

SF1- Figure A: Survival outcomes by stage and HIV status

SF2- Figure B: Survival outcomes by treatment receipt

Tables

Table 1: Baseline demographic characteristics of cervical cancer patients in Botswana 2013-2020

Characteristic	Total	All
		N=1043 (100%)
Age (y)	1042	47 (40-58)
21-39		227 (21.8%)
40-59		575 (55.1%)
>60		240 (23.0%)
HIV characteristics		
HIV status	1025	
Seronegative		311 (29.8%)
Seropositive		714 (68.5%)
CD4 (cells/μL)	544/714	429.5 (240.0-619.5)
<200		96 (13.4%)
≥200-<350		125 (17.5%)
≥350-<500		107 (15.0%)
≥500		216 (30.3%)
Viral Load	487/714	
<400 (Undetectable)		96 (55.5%)
≥400 (Detectable)		91 (12.7%)
On ARV	704/714	676 (94.7%)
Treatment characteristics	1043	
Surgery		58 (5.6%)
RT		341 (32.7%)
Chemotherapy		12 (1.2%)
CRT		531 (50.9%)
Surgery + RT		7 (0.7%)
Surgery + Chemotherapy		8 (0.8%)
Surgery + CRT		10 (1.0%)
No Treatment		76 (7.3%)
Disease stage	1017	

I (IA, IA1, IA2)		45 (4.3%)
I (IB, IB1, IB2, IB3)		128 (12.3%)
II (IIA, IIB)		388 (37.2%)
III (IIIA, IIIB, IIIC)		368 (35.3%)
IV (IVA, IVB)		88 (8.4%)
Marital status	1042	
Single		669 (64.1%)
Married/partnered		240 (23.0%)
Divorced/widowed		133 (12.8%)
Previously screened for CC	1003	588 (56.4%)
Distance from treatment facility (km)	1025	
0 km (South-east)		150 (14.4%)
59..2 (Kweneng)		173 (16.6%)
94.6 (Southern)		155 (14.9%)
310 (Central or Boteti)		281 (26.9%)
410 (Kgatleng)		73 (7.0%)
433 (North-east)		109 (10.5%)
517 (Kgalagadi)		49 (4.7%)
668 (Ghanzi)		8 (0.8%)
849 (Ngamiland)		26 (2.5%)
1074 (None above)		1 (0.1%)
Baseline laboratory values		
Creatinine (μmol/L)	962	60 (50-75)
Hemoglobin (g/dL)	974	11.3 (9.5-12.6)
≤10		313 (30%)
>10		661 (63.4%)
ANC ($\times 10^9$/L)	961	3.9 (2.4-6.2)
WBC ($\times 10^9$/L)	962	6.4 (4.7-8.6)
Albumin (g/L)	656	39 (34.3-42.2)
Baseline performance status (KPS)	1011	
≥90		757 (72.6%)

<90		254 (24.4%)

Values are presented as number (percentage) or median (interquartile range).

Abbreviations: CC = Cervical cancer; HIV = human immunodeficiency virus; ARV = antiretoviral; RT = radiation; CRT = chemoradiation; ANC = absolute neutrophil count; WBC = white blood cells; KPS = Karnofsky performance score

Table 2: Factors associated with overall survival in CC patients in Botswana: univariate and multivariable analyses [N=1043]

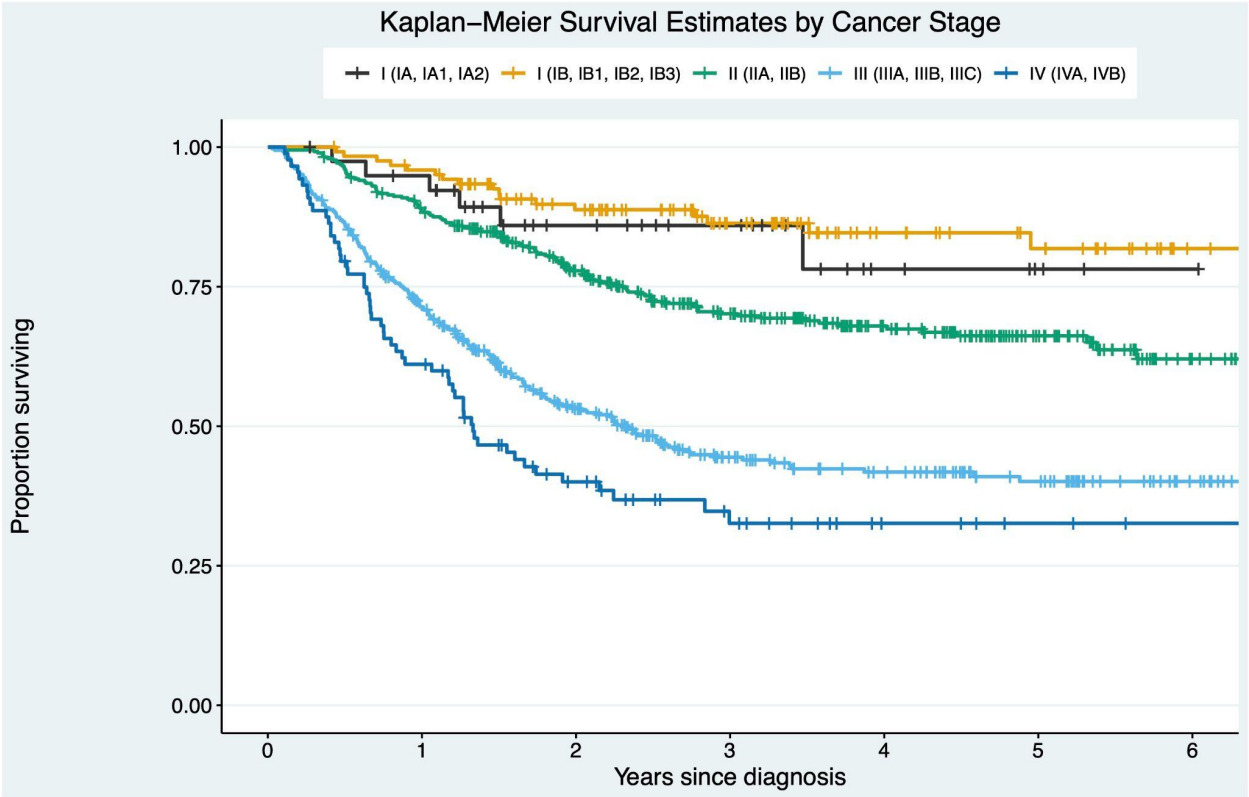
Characteristic	Overall Survival, UVA	p value	Overall Survival, MVA	p value
	HR (95% CI)		HR (95% CI)	
Age (y)				
21-39	1 (ref)	..	1 (ref)	..
40-59	0.81 (0.64-1.04)	0.093	0.86 (0.66-1.11)	0.24
>60	0.91 (0.68-1.21)	0.50	1.07 (0.75-1.52)	0.71
Marital status				
Single	1 (ref)	..	..	..
Married/partnered	0.98 (0.77-1.24)	0.84	..	..
Divorced/widowed	0.94 (0.69-1.27)	0.68	..	..
Distance (km)				
<100 km (South-east, Kweneng, Southern)	1 (ref)	..	..	..
100-500 km (Central or Boteti, Kgatleng, North-east)	1.06 (0.86-1.30)	0.58	..	..
>500 km (Kgalagadi, Ghanzi, Ngamiland, None above)	0.92 (0.62-1.37)	0.68	..	..
Previously screened for CC				
No	1 (ref)	..	..	..
Yes	0.72 (0.59-11.77)	0.0013	..	..
HIV status				
Seronegative	1 (ref)	..	1 (ref)	..
Seropositive	1.17 (0.94-1.46)	0.16	1.28 (0.96-1.70)	0.088
Disease stage				
I (IA, IA1, IA2, IB1, IB2, IB3)	1 (ref)	..	1 (ref)	..
II (IIA, IIB)	2.19 (1.40-3.43)	0.00058	1.91 (1.19-3.06)	0.0074

III (IIIA, IIIB, IIIC)	5.09 (3.30-7.85)	<0.0001	3.99 (2.52-6.32)	<0.0001
IV (IVA, IVB)	7.23 (4.44-11.77)	<0.0001	5.06 (2.98-8.59)	<0.0001
Baseline laboratory values				
Creatinine (μmol/L)	1.001 (1.001-1.001)	<0.0001	1.001 (1.000-1.001)	0.00020
Hemoglobin (g/dL)				
≤10	1 (ref)	..	1 (ref)	..
>10	0.37 (0.30-0.46)	<0.0001	0.51 (0.40-0.64)	<0.0001
ANC ($\times 10^9$/L)	1.01 (1.00-1.02)	0.084	..	..
WBC ($\times 10^9$/L)	1.002 (0.999-1.006)	0.17	..	..
Albumin (g/L)	0.96 (0.95-0.97)	<0.0001	..	..
Baseline performance status (KPS)				
≥90	1 (ref)	..	1 (ref)	..
<90	1.89 (1.54-2.34)	<0.0001	1.53 (1.21-1.92)	0.00033

Abbreviations: CC = Cervical cancer; HIV = human immunodeficiency virus; ANC = absolute neutrophil count; WBC = white blood cells; KPS = Karnofsky performance score

Figures

Figure 1: Survival outcomes by stage



Number at risk

I (IA, IA1, IA2)	40	36	21	16	6	3	1
I (IB, IB1, IB2, IB3)	123	116	91	65	39	29	13
II (IIA, IIB)	387	337	255	185	122	73	26
III (IIIA, IIIB, IIIC)	367	251	152	92	71	46	20
IV (IVA, IVB)	88	53	28	15	6	3	1

Supplemental Material

Table A: Baseline demographic and treatment characteristics by HIV status of CC patients in Botswana

Characteristic	HIV-infected	HIV-uninfected	All	p value
	N=714 (100%)	**N=311 (100%)**	**N=1025 (100%)**	
Age (y)	44 (39-50)	61 (50.5-69.4)	47 (40-58)	<0.0001
21-39	197 (27.6%)	30 (9.6%)	227 (22.1%)	
40-59	457 (64.0%)	113 (36.3%)	570 (55.6%)	
>60	60 (8.4%)	167 (53.7%)	227 (22.1%)	
HIV characteristics				
CD4 (cells/μL)	429.5 (240.0-619.5)	..	..	..
CD4 category (cells/μL)				
<200	96 (13.4%)	..	..	..
200-<350	125 (17.5%)	..	..	..
350-<500	107 (15.0%)	..	..	..
≥500	216 (30.3%)	..	..	..
Viral Load				
<400 (Undetectable)	396 (55.5%)	..	..	..
≥400 (Detectable)	91 (12.7%)	..	..	..
On ARV	676 (94.7%)	..	..	..
Treatment				
Surgery	43 (6.0%)	14 (4.5%)	57 (5.6%)	0.38

RT	216 (30.3%)	114 (36.7%)	330 (32.2%)	0.11
Chemotherapy	7 (1.0%)	5 (1.6%)	12 (1.2%)	0.36
CRT	380 (53.2%)	150 (48.2%)	530 (51.7%)	0.11
Surgery + Chemotherapy	6 (0.8%)	2 (0.6%)	8 (0.8%)	>0.99
Surgery + RT	2 (0.3%)	5 (1.6%)	7 (0.7%)	0.030
Surgery + CRT	9 (1.3%)	1 (0.3%)	10 (1.0%)	0.30
No Treatment	51 (7.1%)	20 (6.4%)	71 (6.9%)	0.68
Disease stage				0.49
I (IA, IA1, IA2)	36 (5.0%)	8 (2.6%)	44 (4.3%)	
I (IB, IB1, IB2, IB3)	87 (12.2%)	40 (12.9%)	127 (12.4%)	
II (IIA, IIB)	268 (37.5%)	115 (37.0%	383 (37.4%)	
III (IIIA, IIIB, IIIC)	248 (34.7%)	114 (36.7%)	362 (35.3%)	
IV (IVA, IVB)	59 (8.3%)	27 (8.7%)	86 (8.4%)	
Marital status				<0.0001
Single	518 (72.5%)	141 (45.3%)	659 (64.3%)	
Married/partnered	139 (19.5%)	98 (31.5%)	237 (23.1%)	
Divorced/widowed	56 (7.8%)	72 (23.2%)	128 (12.5%)	
Previously screened for CC	438 (61.3%)	146 (46.9%)	584 (57.0%)	<0.0001
Distance from treatment facility (km)				<0.0001
<100 km (South-east, Kweneng, Southern)	295 (41.3%)	174 (55.9%)	469 (45.8%)	
100-500 km (Central or Boteti, Kgatleng, North-east)	338 (47.3%)	118 (37.9%)	456 (44.5%)	
>500 km (Kgalagadi, Ghanzi,	69 (9.7%)	14 (4.5%)	83 (8.1%)	

Ngamiland, None above)				
Baseline laboratory values				
Creatinine (μmol/L)	63 (48.6-73)	58 (53-80)	60 (50-75)	0.0014
Hemoglobin (g/dL)				
≤10	243 (34.0%)	64 (20.6%)	307 (30.0%)	<0.0001
>10	428 (59.9%)	224 (72.0%)	652 (63.6%)	
ANC ($\times 10^9$/L)	4.3 (2.3-6)	3.6 (2.9-6.5)	3.9 (2.4-6.2)	0.00034
WBC ($\times 10^9$/L)	6.8 (5.3-9.1)	6.2 (4.6-8.3)	6.4 (4.7-8.6)	0.0014
Albumin (g/L)	40 (34-42.1)	38.9 (35-42.2)	39 (34.3-42.2)	0.093
Baseline performance status (KPS)				0.31
≥90	528 (73.9%)	222 (71.4%)	750 (73.2%)	
<90	164 (23.0%)	81 (26.0%)	245 (23.9%)	

Values are presented as number (percentage) or median (interquartile range).

Abbreviations: CC = Cervical cancer; HIV = human immunodeficiency virus; ARV = antiretoviral; RT = radiation; CRT = chemoradiation; ANC = absolute neutrophil count; WBC = white blood cells; KPS = Karnofsky performance score

Table B1: Treatment characteristics by FIGO stage groups in CC patients in Botswana

	I (IA-IB3)	II (IIA-IIB)	III (IIIA-IIIC)	IV (IVA-IVB)
	N=173 (100%)	**N=388 (100%)**	**N=368 (100%)**	**N=88 (100%)**
Surgery				
N=58 (100%)	50 (86.2, 28.9)	1 (1.7, 0.3)	1 (1.7, 0.3)	0 (0, 0)
RT				
N=341 (100%)	20 (5.9, 11.6)	90 (26.4, 23.2)	162 (47.5, 44)	65 (19.1, 73.9)
Chemotherapy				
N=12 (100%)	1 (8.3, 0.6)	2 (16.7, 0.5)	7 (58.3, 1.9)	1 (8.3, 1.1)
CRT				
N=531 (100%)	79 (14.9, 45.7)	283 (53.3, 72.9)	158 (29.8, 42.9)	9 (1.7, 10.2)
Surgery + RT				
N=7 (100%)	5 (71.4, 2.9)	1 (14.3, 0.3)	1 (14.3, 0.3)	0 (0, 0)
Surgery + Chemotherapy				
N=8 (100%)	6 (75, 3.5)	0 (0, 0)	1 (12.5, 0.3)	1 (12.5, 1.1)
Surgery + CRT				
N=10 (100%)	4 (40, 2.3)	6 (60, 1.5)	0 (0, 0)	0 (0, 0)
No Treatment				
N=76 (100%)	8 (10.5, 4.6)	5 (6.6, 1.3)	38 (50, 10.3)	12 (15.8, 13.6)

Values are presented as number (row percentage, column percentage).
Abbreviations: CC = Cervical cancer; RT = radiation; CRT = chemoradiation

Table B2: Treatment characteristics by FIGO stage groups in CC patients in Botswana

	Surgery	RT	Chemotherapy	CRT	Surgery + RT	Surgery + CRT	Surgery + Chemotherapy	No Treatment
	N=58 (100%)	N=341 (100%)	N=12 (100%)	N=531 (100%)	N=7 (100%)	N=10 (100%)	N=8 (100%)	N=76 (100%)
IA								
N=8 (100%)	3 (37.5, 5.2)	2 (25, 0.6)	0 (0, 0)	1 (12.5, 0.2)	0 (0, 0)	1 (12.5, 10)	0 (0, 0)	1 (12.5, 1.3)
IA1								
N=33 (100%)	26 (78.8, 44.8)	2 (6.1, 0.6)	0 (0, 0)	3 (9.1, 0.5)	1 (3, 14.3)	0 (0, 0)	0 (0, 0)	1 (3, 1.3)
IA2								
N=4 (100%)	2 (50, 3.5)	2 (50, 0.6)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
IB								
N=15 (100%)	4 (26.7, 6.9)	4 (26.7, 1.2)	1 (6.7, 8.3)	5 (33.3, 0.9)	0 (0, 0)	0 (0, 0)	0 (0, 0)	1 (6.7, 1.3)
IB1								
N=55 (100%)	13 (23.6, 22.4)	5 (9.1, 1.5)	0 (0, 0)	26 (47.3, 4.9)	4 (7.3, 57.1)	2 (3.6, 20)	5 (9.1, 62.5)	0 (0, 0)
IB2								
N=52 (100%)	2 (3.8, 3.5)	3 (5.8, 0.9)	0 (0, 0)	41 (78.8, 7.7)	0 (0, 0)	1 (1.9, 10)	1 (1.9, 12.5)	4 (7.7, 5.3)
IB3								
N=6 (100%)	0 (0, 0)	2 (33.3, 0.6)	0 (0, 0)	3 (50, 0.6)	0 (0, 0)	0 (0, 0)	0 (0, 0)	1 (16.7, 1.3)
IIA								
N=56 (100%)	0 (0, 0)	12 (21.4, 3.5)	0 (0, 0)	44 (78.6, 8.3)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
IIB								
N=332 (100%)	1 (0.3, 1.7)	78 (23.5, 22.9)	2 (0.6, 16.7)	239 (72, 45)	1 (0.3, 14.3)	6 (1.8, 60.0)	0 (0, 0)	5 (1.5, 6.6)
IIIA								
N=61 (100%)	1 (1.6, 1.7)	19 (31.1, 5.6)	0 (0, 0)	44 (72.1, 8.3)	0 (0, 0)	0 (0, 0)	1 (1.6, 12.5)	5 (8.2, 6.6)
IIIB								
N=305 (100%)	0 (0, 0)	142 (46.6, 41.6)	6 (2, 50)	123 (40.3, 23.2)	1 (0.3, 14.3)	0 (0, 0)	0 (0, 0)	33 (10.8, 43.4)

IIIC								
N=2 (100%)	0 (0, 0)	1 (50, 0.3)	1 (50, 8.3)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
IVA								
N=73 (100%)	0 (0, 0)	56 (76.7, 16.4)	0 (0, 0)	9 (12.3, 1.7)	0 (0, 0)	0 (0, 0)	1 (1.4, 12.5)	7 (9.6, 9.2)
IVB								
N=15 (100%)	0 (0, 0)	9 (60, 2.6)	1 (6.7, 8.3)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	5 (33.3, 6.6)

Values are presented as number (row percentage, column percentage).
Abbreviations: CC = Cervical cancer; RT = radiation; CRT = chemoradiation

Table C: Factors associated with overall survival in cervical cancer patients who received any treatment in Botswana: univariate and multivariable analyses [N=967]

Characteristic	Overall Survival, UVA	p value	Overall Survival, MVA	p value
	HR (95% CI)		HR (95% CI)	
Age (y)				
21-39	1 (ref)	..	1 (ref)	..
40-59	0.83 (0.64-1.08)	0.17	0.88 (0.66-1.16)	0.36
>60	0.93 (0.68-1.26)	0.63	1.04 (0.71-1.53)	0.83
Marital status				
Single	1 (ref)	..	..	..
Married/partnered	1.09 (0.85-1.40)	0.50	..	..
Divorced/widowed	1.02 (0.74-1.42)	0.88	..	..
Distance (km)				
<100 km (South-east, Kweneng, Southern)	1 (ref)	..	..	..
100-500 km (Central or Boteti, Kgatleng, North-east)	1.20 (0.96-1.50)	0.11	..	..
>500 km (Kgalagadi, Ghanzi, Ngamiland, None above)	0.98 (0.64-1.52)	0.94	..	..
Previously screened for CC				
No	1 (ref)	..	..	..
Yes	0.71 (0.57-0.88)	0.0017	..	..
HIV status				
Seronegative	1 (ref)	..	1 (ref)	..
Seropositive	1.14 (0.90-1.45)	0.28	1.25 (0.92-1.70)	0.15
Disease stage				
I (IA, IA1, IA2, IB1, IB2, IB3)	1 (ref)	..	1 (ref)	..
II (IIA, IIB)	2.47 (1.52-4.02)	0.00027	2.07 (1.25-3.44)	0.0047

III (IIIA, IIIB, IIIC)	5.17 (3.21-8.33)	<0.0001	3.95 (2.40-6.50)	<0.0001
IV (IVA, IVB)	7.91 (4.63-13.52)	<0.0001	5.76 (3.25-10.20)	<0.0001
Baseline laboratory values				
Creatinine (μmol/L)	1.001 (1.000-1.001)	<0.0001	1.001 (1.000-1.001)	0.0024
Hemoglobin (g/dL)				
≤10	1 (ref)	..	1 (ref)	..
>10	0.40 (0.32-0.50)	<0.0001	0.54 (0.42-0.69)	<0.0001
ANC ($\times 10^9$/L)	1.01 (1.00-1.02)	0.084	..	..
WBC ($\times 10^9$/L)	1.002 (0.99-1.01)	0.68	..	..
Albumin (g/L)	1.002 (0.998-1.01)	0.39	..	..
Baseline performance status (KPS)				
≥90	1 (ref)	..	1 (ref)	..
<90	1.80 (1.43-2.27)	<0.0001	1.49 (1.16-1.92)	0.0018

Abbreviations: CC = Cervical cancer; HIV = human immunodeficiency virus; ANC = absolute neutrophil count; WBC = white blood cells; KPS = Karnofsky performance score

Table D: Factors associated with overall survival in radiation eligible (stages IB2 and above) cervical cancer patients in Botswana: univariate and multivariable analyses [N=902]

Characteristic	Overall Survival, UVA	p value	Overall Survival, MVA	p value
	HR (95% CI)		HR (95% CI)	
Age (y)				
21-39	1 (ref)	..	1 (ref)	..
40-59	0.86 (0.67-1.10)	0.22	0.80 (0.57-1.11)	0.18
>60	0.93 (0.70-1.25)	0.63	0.95 (0.59-1.51)	0.81
Marital status				
Single	1 (ref)	..	..	..
Married/partnered	1.01 (0.79-1.28)	0.95	..	..
Divorced/widowed	1.04 (0.76-1.42)	0.80	..	..
Distance (km)				
<100 km (South-east, Kweneng, Southern)	1 (ref)	..	..	..
100-500 km (Central or Boteti, Kgatleng, North-east)	1.04 (0.84-1.29)	0.70	..	..
>500 km (Kgalagadi, Ghanzi, Ngamiland, None above)	0.82 (0.55-1.23)	0.34	..	..
Previously screened for CC				
No	1 (ref)	..	..	..
Yes	0.75 (0.61-0.92)	0.0060	..	..
HIV status				
Seronegative	1 (ref)	..	1 (ref)	..
Seropositive	1.23 (0.98-1.54)	0.080	1.36 (0.92-2.00)	0.13
Disease stage				
I (IA, IA1, IA2, IB1, IB2, IB3)	1 (ref)	..	1 (ref)	..
II (IIA, IIB)	1.66 (0.87-3.17)	0.12	2.07 (1.25-3.44)	0.0047

III (IIIA, IIIB, IIIC)	3.85 (2.04-7.28)	<0.0001	2.59 (1.12-5.98)	0.026
IV (IVA, IVB)	5.46 (2.78-10.71)	<0.0001	2.28 (0.89-5.87)	0.087
Baseline laboratory values				
Creatinine (μmol/L)	1.001 (1.000-1.001)	<0.0001	1.001 (1.000-1.002)	0.17
Hemoglobin (g/dL)				
≤10	1 (ref)	..	1 (ref)	..
>10	0.42 (0.34-0.52)	<0.0001	0.57 (0.43-0.77)	0.00027
ANC ($\times 10^9$/L)	1.01 (0.99-1.014)	0.16	..	..
WBC ($\times 10^9$/L)	1.002 (0.99-1.01)	0.25	..	..
Albumin (g/L)	0.96 (0.95-0.97)	<0.0001	..	..
Baseline performance status (KPS)				
≥90	1 (ref)	..	1 (ref)	..
<90	1.79 (1.44-2.22)	<0.0001	1.39 (1.01-1.91)	0.043
Pathology response				
Complete	1 (ref)	..	1 (ref)	..
Partial	2.18 (1.68-2.84)	<0.0001	1.58 (1.15-2.17)	0.0046
Not available	3.54 (2.27-5.53)	<0.0001	2.36 (1.39-4.03)	0.0016
EQD2 (Gy)				
≥79	1 (ref)	..	1 (ref)	..
<79	2.38 (1.89-3.01)	<0.0001	1.47 (1.08-2.01)	0.015
Chemotherapy cycles				
≥4	1 (ref)	..	1 (ref)	..
<4	2.48 (1.93-3.19)	<0.0001	1.63 (1.17-2.27)	0.0040
Chemotherapy cycles				
0	1 (ref)	..	..	..
1	0.80 (0.46-1.39)	0.43	..	..
2	0.56 (0.35-0.91)	0.019	..	..

3	0.42 (0.29-0.63)	<0.0001	..	..
≥4	0.31 (0.24-0.41)	<0.0001	..	..

Abbreviations: CC = Cervical cancer; HIV = human immunodeficiency virus; ANC = absolute neutrophil count; WBC = white blood cells; KPS = Karnofsky performance score

Figure A: Survival outcomes by stage and HIV status- Survival outcomes by stage were similar between WLWH and women without HIV: 2-year OS rates, Stage I HIV-positive 91.5%, HIV-negative 81.5%; Stage II HIV-positive 77.3%, HIV-negative 78.1%; Stage III HIV-positive 48.2%, HIV-negative 67.2%; Stage IV HIV-positive 39.9%, and HIV-negative 40.4%.

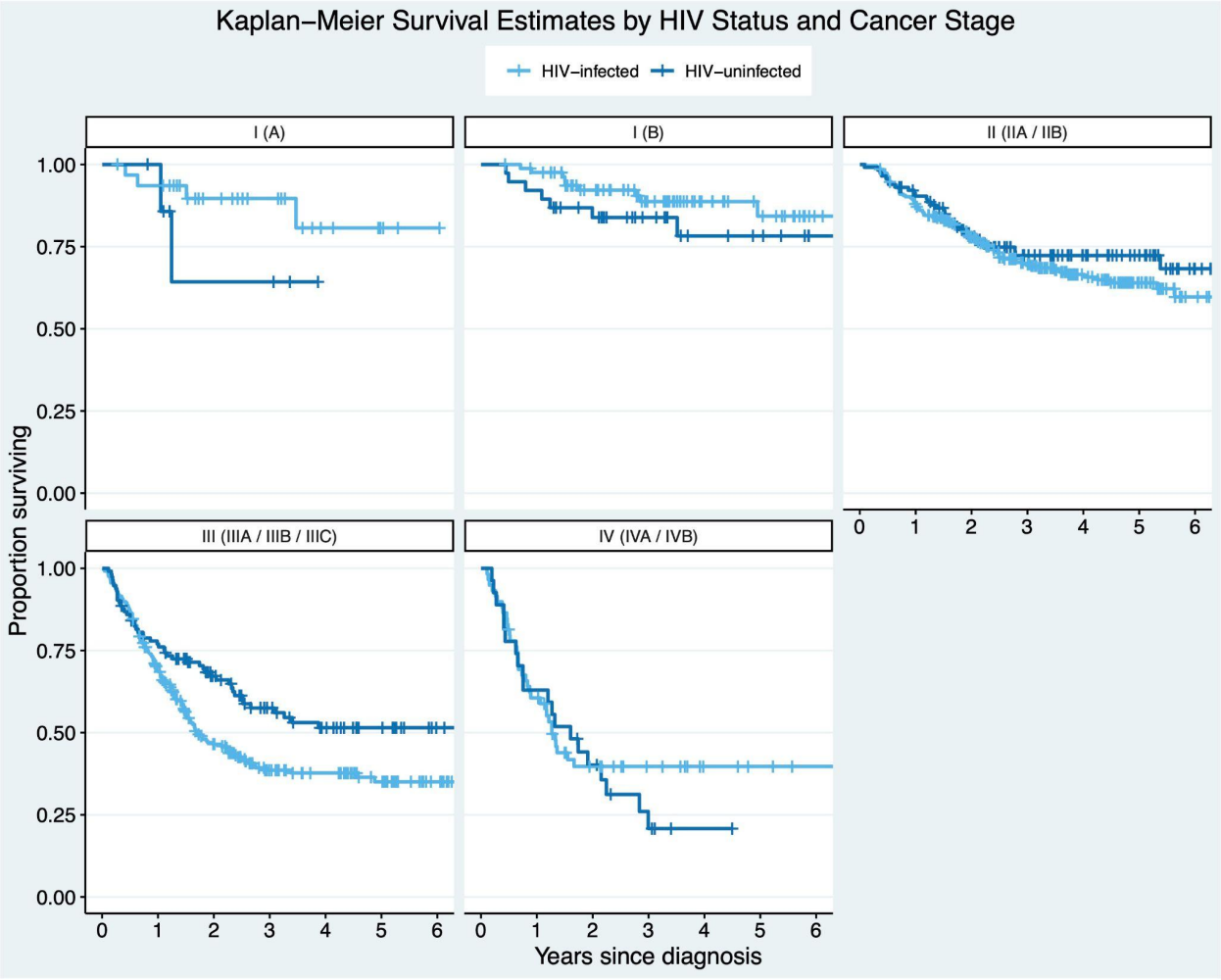
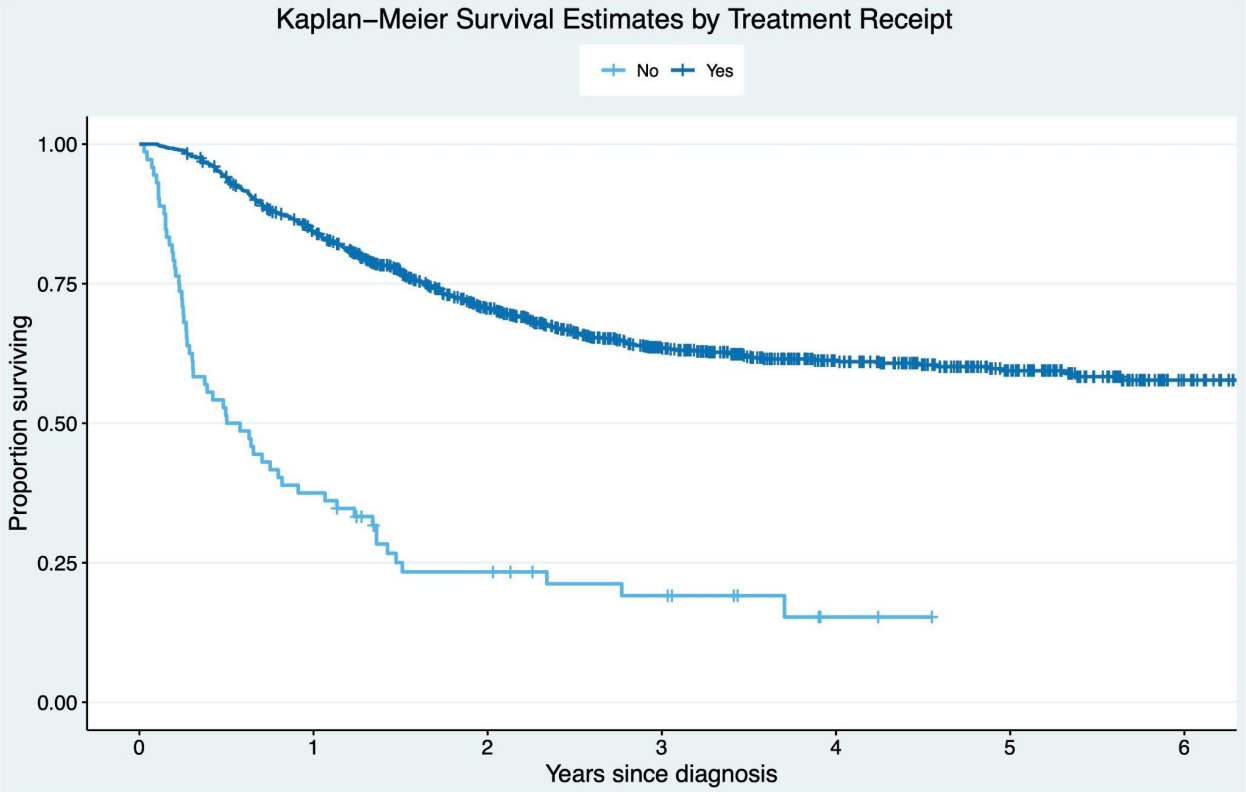


Figure B: Survival outcomes by treatment receipt- Patients who were treated had significantly better survival outcomes compared to those who did not receive treatment: 2-year OS rates, Treated 70.5% vs. Untreated 23.4%.



Number at risk

No	72	27	14	9	2	0	0
Yes	955	782	546	375	246	155	61

Highlights

- To date, there exists extensive data on stage distribution and survival outcomes of CC patients in high-income regions (HICs) such as the United States and European countries.
- However, there remains a shortage of comprehensive stage distribution and outcomes data for CC cases in LMICs, particularly in SSA.
- Prior studies presenting the stage distribution for women diagnosed with CC in Botswana either included patients treated with chemoradiotherapy (CRT) alone or assessed survival by HIV status and treatment only.
- Hence, there is a lack of comprehensive data on stage distribution and survival outcomes by stage of CC patients in Botswana.
- This article presents comprehensive stage distribution, patterns of care, and survival outcomes for CC patients in Botswana and evaluates the impact of stage at presentation on survival. We look forward to your commentary on our work.