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Vulvar cancer in Botswana in women with and without HIV infection: patterns of treatment and survival outcomes

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Abstract

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Contributors Study conception and design: SG, NMZ. Acquisition of data: SS, BM, LB-M, TM, TR, BM, SG. Analysis and interpretation of data: QW, SSS, EM, SS, SG, NMZ. Drafting of manuscript: EM, SS. Critical revision: RL, DRM, NMZ, SG. All authors approved the manuscript before submission.

EM and SS contributed equally.

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Objectives—Vulvar cancer is a rare gynecological malignancy. However, the incidence of human papillomavirus (HPV)-associated vulvar disease is increasing, particularly in low-and middle-income countries. HIV infection is associated with an increased risk of HPV-associated vulvar cancer. We evaluated treatment patterns and survival outcomes in a cohort of vulvar cancer patients in Botswana. The primary objective of this study was to determine overall survival and the impact of treatment modality, stage, and HIV status on overall survival.

Methods—Women with vulvar cancer who presented to oncology care in Botswana from January 2015 through August 2019 were prospectively enrolled in this observational cohort study. Demographics, clinical characteristics, treatment, and survival data were collected. Factors associated with survival including age, HIV status, stage, and treatment were evaluated.

Results—Our cohort included 120 women with vulvar cancer. Median age was 42 (IQR 38–47) years. The majority of patients were living with HIV (89%, n=107) that was well-controlled on antiretroviral treatment. Among women with HIV, 54.2% (n=58) were early stage (FIGO stage I/II). In those without HIV, 46.2% (n=6) were early stage (stage I/II). Of the 95 (79%) patients who received treatment, 20.8% (n=25) received surgery, 67.5% (n=81) received radiation therapy, and 24.2% (n=29) received chemotherapy, either alone or in combination. Median follow-up time of all patients was 24.7 (IQR 14.2–39.1) months and 2-year overall survival for all patients was 74%. Multivariate analysis demonstrated improved survival for those who received surgery (HR 0.26; 95% CI 0.08 to 0.86) and poor survival was associated with advanced stage (HR 2.56; 95% CI 1.30 to 5.02). Survival was not associated with HIV status.

Conclusions—The majority of women with vulvar cancer in Botswana are young and living with HIV infection. Just under half of patients present with advanced stage, which was associated with worse survival. Improved survival was seen for those who received surgery.

INTRODUCTION

Vulvar cancer is the fourth most common gynecological cancer worldwide, representing 4% of all malignancies of the female genital tract.[1] Despite its relative infrequency, the incidence of vulvar cancer is increasing, and the age of patients with invasive vulvar cancer is declining, particularly in low- and middle-income countries with a high burden of human papillomavirus (HPV) infection.[2]

Two distinct etiologies of squamous cell vulvar cancer have been identified: cancers associated with keratinizing vulvar dermatoses and those associated with HPV infection presenting as warty or basaloid lesions.[3] Women with HPV-associated vulvar cancer usually present at a younger age and have risk factors similar to those associated with cervical cancer.[4] Regions such as sub-Saharan Africa also carry a disproportionately higher burden of HIV infection. Co-infection of HIV with HPV can promote chronic HPV carriage, a known risk factor for development of vulvar cancer.[5–7] Due to relatively the low incidence of vulvar cancer, very few prospective studies examining treatment and outcomes in women living with HIV have been published in the literature.

Botswana is a nation of 2.3 million people where the prevalence of HIV infection in 2019 was 25.1% in women aged 15 to 49 years.[8] In women aged 30 to 49 years, this rate was over 40% in 2013.[9] A well-established antiretroviral program covers 87% of

patients living with HIV infection and all-cause mortality has steadily decreased over the past 20 years.[1011] However, as this population lives longer, the timeframe to develop HPV-associated malignancies increases. Botswana is well positioned to provide valuable information about the presentation, treatment, and outcomes of vulvar cancer in women living with well-controlled HIV infection.

Standards for vulvar cancer treatment were created based on evidence gathered in high-resource healthcare systems. Descriptions of current treatment patters and survival outcomes of patients in low-resource settings with high HPV and HIV co-infection rates are limited. In this prospective study, we sought to describe current patient characteristics, treatment patterns, and survival outcomes for patients with vulvar cancer in Botswana.

METHODS

Participants with histologically confirmed vulvar cancer were recruited prospectively from Princess Marina Hospital and Gaborone Private Hospital in Gaborone, Botswana between January 2015 and August 2019. Participants were followed through December 2020.

Recruitment

Enrollment excluded patients aged <18 years and those who declined participation (<1% of all approached patients). After written informed consent was obtained, interviews were conducted by designated research assistants in the participants' preferred language. Patient information regarding demographics, marital status, and distance from their home to the treatment facility was collected during this time. Medical record review collected clinical information including disease stage, pathology treatment received, as well as HIV treatment history. HIV status was confirmed by medical records. During radiation treatment, patients were evaluated weekly for treatment-related side effects. All information was recorded in a REDCap database. Patients were routinely seen at 3-month intervals at the clinic or contacted by telephone. The public hospital electronic medical record was also used to supplement survival data.

Vulvar Cancer Treatment Landscape in Botswana

Gynecological Multidisciplinary Clinic—All patients with biopsy-proven gynecological malignancies at Princess Marina Hospital and from other centers around the country are referred to gynecological multidisciplinary tumor board at Princess Marina Hospital. In multidisciplinary clinic, all patients are evaluated by a gynecologist or a gynecological oncologist and a clinical or radiation oncologist, after which a treatment plan is created. Specifics regarding the characteristics of patients seen in multidisciplinary clinic have been described in detail previously.[12] It should be noted here that 60% of patients seen in multidisciplinary clinic were living with HIV infection.[12]

Work-up Prior to Treatment—Before treatment initiation, patients underwent a physical examination and chest X-ray. Blood tests including complete blood count, liver function tests, and renal function were performed. Patients received transfusion to a hemoglobin level of 10 g/dL when needed. More advanced imaging such as computed tomography

(CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) was not routinely available to assess the extent of primary or nodal disease.

Treatment—The global standard treatment for invasive vulvar cancer currently calls for surgical resection when adequate margins can be achieved, with the addition of radiation therapy and chemotherapy in cases of advanced disease.[13] Disease stages were determined according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines.[14] Treatment of early-stage vulvar cancer in Botswana is ideally surgical, when feasible, and consists of radical local excision of the vulvar tumor and inguinofemoral lymphadenectomy for depth of invasion equal or greater than 1 mm, or size of tumor equal or greater than 2 cm. Patients who were deemed surgical candidates were referred to general gynecologists at Princess Marina Hospital or a private hospital for primary surgery. If histopathology confirmed inguinofemoral lymph node metastases, or if close or positive margins could not be re-resected, adjuvant radiotherapy with or without chemotherapy was typically given after surgery. Tumors considered by gynecologists to be unresectable due to size or location were treated non-surgically with radiation therapy and/or chemoradiation. Staging in these cases did not include pathological evaluation of lymph nodes. Inguinal radiation boost was given to those who were biopsied and found to have positive nodes (pN+) or for cN0 patients who were noted to have groin lymph nodes suspicious for involvement on CT imaging done during radiation planning but were not able to undergo inguinal lymph node biopsy. At the time of this study, Gaborone Private Hospital housed the sole radiation oncology facility in Botswana. The government maintained a public–private partnership to cover the cost of radiation therapy for patients with or without concurrent chemotherapy for patients with vulvar cancer providing that they are citizens of Botswana. All of these patients from Princess Marina Hospital who required chemoradiation or radiation therapy were referred to Gaborone Private Hospital for treatment.

Follow-up

All patients were followed up by office visit (30%), telephone call (50%), or electronic medical records (20%). All patients were followed up every 3 months until time of analysis (December 2020). They were censored at time of death or last contact. If a patient was not reachable at the time of analysis they were classified as lost to follow-up. Because a very limited number of patients were able to present for follow-up office visits, recurrence data are not reliably available.

HIV Antiretroviral Therapy

In 2002, Botswana was the first country in sub-Saharan Africa to provide citizens with free antiretroviral therapy. Eligibility increased over time and starting in 2013 all Batswana with CD4 counts ≤350 cells/μL or any HIV-associated condition were eligible to receive free antiretroviral therapy from the Botswana National Antiretroviral Therapy Program. First-line treatment during this time included tenofovir, emtricitabine, and efavirenz. In 2016, the government implemented a test-and-treat policy that provided free antiretroviral therapy for any individual who tested positive. Dolutegravir has also introduced as first-line treatment in 2016. As of 2019, 82% of Batswana living with HIV infection were receiving antiretroviral therapy.[7] Information regarding HIV status, date of diagnosis, antiretroviral therapy regimen,

most recent CD4 count, and viral load were collected at time of enrollment. According to national guidelines, HIV testing was performed on all patients who had not received testing within the past 6 months of their cancer diagnosis. Patients with a new HIV diagnosis or not already on antiretroviral therapy were referred to an HIV clinic for antiretroviral therapy initiation prior to treatment.

Primary Outcome

The primary objective of this study was to determine overall survival and the impact of treatment modality, stage, and HIV status on overall survival. Overall survival was defined as the time from date of cancer diagnosis as represented in the pathology report for vulvar cancer or, if pathology date was unavailable (n=3), date of presentation to multidisciplinary clinic, until death or censored at date of last contact as determined by office visit, telephone call, or electronic medical record.

Statistical Analysis

Overall survival probabilities were estimated using the nonparametric Kaplan–Meier method and compared by the log-rank test. This comparison was not done between HIV-positive and HIV-negative patients due to the small sample size of patients without HIV infection. Next, Cox proportional hazard models were used to assess the associations between survival and the following variables: age, stage, HIV status, receipt of surgery, and receipt of chemotherapy. The proportional hazard assumptions were examined graphically by inspecting the Kaplan–Meier curves, and by plotting −log(S(T)), that is, the negative log of survival at time T, against follow-up time on the log scale for the specified groups. The curves did not cross mostly, which suggested that the assumption of proportional hazard was reasonable. A multivariable Cox proportional hazard model was then constructed that included all coavariates; these variables were selected based on a priori knowledge of their clinical significance related to survival, or based on an observed p values of less than 0.10 in the bivariate analyses. Receipt of radiation was not included due to the small number of patients in the radiation group who had died. Statistical comparison of groups with and without HIV in Table 1 was not performed due to the small number of patients without HIV infection. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

Ethics

This study was conducted with the approval of the Health Research Development Committee of the Botswana Ministry of Health and the Institutional Review Board of the University of Pennsylvania.

RESULTS

Demographics and Clinical Characteristics

We enrolled 126 patients with vulvar cancer between January 2015 and August 2019. Two patients were excluded due to missing demographic data. Four patients were excluded due to a diagnosis of vulval intraepithelial neoplasia III. Of the remaining 120 patients, 89% (n=107) were women living with HIV infection (Table 1). The median age for women living

with and without HIV was 41 (IQR 38–45) years and 49 (IQR 47–71) years, respectively. In women living with HIV, 54.2% (n=58) were early stage (FIGO stage I/II) and 45.8% (n=49) were advanced stage (FIGO stage III/IV). For those without HIV infection, 46.2% (n=6) were early stage (stage I/II) and 53.8% (n=7) were advanced stage (stage III/IV). Women living with HIV had a baseline median CD4 count of 461 cells/μL (IQR 300.5–684.5) and median viral load less than 400 copies/mL at the time of diagnosis. Of the 98 women living with HIV who had information about antiretroviral therapy, 91% (n=89) were on an antiretroviral therapy at the time of enrollment. The median time on antiretroviral therapy was 9 (IQR 5–12) years. Of all 120 patients, 51.7% (n=62) self-reported receiving cervical cancer screening.

Vulvar Cancer Treatment

Of the 120 patients enrolled, 79.2% (n=95) of patients received treatment. In the cohort of 95 treated patients, 20.8% (n=25) received surgery, 67.5% (n=81) received radiation therapy, and 24.2% (n=29) received chemotherapy, either alone or in combination with surgery or radiation therapy. Online supplemental table 1 outlines treatment received by stage.

Survival Data

The overall median follow-up time of the cohort of 120 patients was 24.7 (IQR 14.2–39.1) months. At the time of analysis, 30.8% (n=37) were deceased, 61.7% (n=74) were alive, and 7.5% (n=9) were lost to follow-up, but were alive at last contact. For all patients, 2-year overall survival was 74% and 3-year overall survival was 63% (Figure 1). The median survival of women living with HIV was 26.3 (IQR 15.2–39.7) months. For those without HIV, median survival was 10.1 (IQR 9.7–17.6; p=0.094) months. Women with early-stage disease (FIGO I and II) had median survival of 27.4 (IQR 17.2–42.7) months as compared with those with late-stage disease (FIGO III and IV) at 22.8 (IQR 12.9–34.0) months (Figure 2; p=0.005). When comparing women who did and did not receive surgery, the median survival was 28.3 (IQR 19.5–48.4) months and 23.7 (IQR 13.6–35.5) months, respectively (Figure 3; p=0.018). Women who received any treatment had a median survival of 26.3 (IQR 13.9–40.4) months and those who did not receive treatment had a median survival of 21.4 (IQR 15.2–31.9; p=0.029) months.

The crude Cox regression analysis showed that survival was reduced for advanced stage (stage III/IV) (crude HR (cHR)=2.56; 95% CI 1.30 to 5.02) and improved with receipt of surgery (cHR=0.26; 95% CI 0.08 to 0.86; Table 2). These associations remained robust in the multivariable analysis controlling for age, HIV status, and receipt of chemotherapy (Table 2). Living with HIV infection was not associated with worse survival outcomes (adjusted HR=0.62; 95% CI 0.22 to 1.76) in our cohort of patients, although analysis was limited by the small sample size of patients without HIV.

DISCUSSION

Summary of Main Results

The majority of our patients presented with vulvar cancer at a young age, and most were women living with HIV. Almost half of the patients presented at an advanced stage. As

expected, advanced stage was associated with worse survival. Receipt of surgery was associated with increased survival. Survival did not differ between women with or without HIV infection, although the small number of women without HIV infection limited our analyses.

Results in the Context of Published Literature

This cohort of patients had a very high rate of HIV infection. As mentioned previously, there is a high prevalence of HIV in the general population of Botswana (18.5%) and this prevalence is even higher among sexually active women aged 15–49 years (25.1%).[8] Similar to the cervical cancer cohort in Grover *et al*[15] that demonstrated a high rate of HIV infection, this vulvar cohort had well-controlled HIV infection as demonstrated by high baseline median CD4 count and high proportion with an undetectable viral load. Women with HIV are at an increased risk of developing cancer.[16] A recent study of United States veterans found that women living with HIV were at higher risk of developing genital tract cancers, including vulvar cancer, than their counterparts without HIV infection.[17] The etiology of this discrepancy, whether due to biological differences or social factors, remains unclear. Previously, HIV infection has been associated with a higher risk of cancer-related death in Western populations.[18] We did not find that HIV was associated with reduced survival in our cohort, although our comparative analysis was statistically limited by our small cohort of women without HIV. This is reflected in the short median follow-up time of women without HIV as compared with those with HIV. This difference may reflect the relatively infrequent contact and follow-up women without HIV have with the healthcare system when compared with their counterparts with HIV who have regular engagement with health providers, or may be due to poor sampling. However, our findings are aligned with data from a similar cohort of patients with cervical cancer in Botswana that demonstrated that HIV status is not an independent predictor of survival.[19] Even with its limitations, this study is a significant contribution to the body of data regarding gynecological cancer in women living with well-managed HIV that suggests that treatment regimens may not require modification based solely on HIV status in women with well-controlled HIV.

In our cohort of vulvar cancer patients, women living with HIV trended towards younger age at diagnosis than those without HIV infection. Age at cancer diagnosis across many cancer types has been shown to be lower in patients with HIV.[2021] At 42 years, the overall median age at diagnosis was markedly younger than that observed in high-income countries, where vulvar cancer is often considered a disease of postmenopausal women.[22–25] Low- and middle-income countries such as Botswana have younger populations on average but undoubtedly also have higher rates of HIV and HPV co-infection.[25] Notably, the average age at diagnosis is decreasing in both high- and low-income countries, likely due to earlier detection and increased rates of HPV infection worldwide.[22627] Our observation that women living with HIV tend to be relatively young at diagnosis is consistent with these findings and suggests that clinical suspicion of vulvar lesions should be increased even for women who do not fall into the classic age categories at risk observed in high-income countries.

In this cohort of vulvar cancer patients, 2-year overall survival for all stages was 74% while 3-year overall survival was 63%. These values compare starkly to outcomes in high-income

countries, where survival at 5 years for all stages is estimated at 71%.[25] Treatment with surgery and early-stage disease were significant positive predictors of survival on univariate and multivariate analysis controlling for age, HIV status, and receipt of chemotherapy. We found that only 21% of our total cohort received surgery. In comparison, surgical intervention for stages I–III in high-income countries ranges between 47% and 80% of cases.[28] Improving survival outcomes for vulvar cancer patients in Botswana will require increasing the relative number of patients presenting at early rather than late stage and subsequently receiving comprehensive surgical intervention. Other low- and middle-income countries have reported relatively high rates of surgery. Studies conducted in South Africa and Ethiopia have recorded receipt of surgery at 67.5% and 37%, respectively.[227] In small cohort studies in Tunisia and Nigeria, all patients were initially treated with surgery.[2930] In Botswana, until recently general gynecologists performed surgical interventions due to the lack of specialty-trained gynecological oncologists at the time of study enrollment. Few of the generalist surgeons had expertize in lymphadenectomy and none in the public system provided radical vulvectomy.[31] Additional barriers to surgery included power outages, equipment, blood product and medicine shortages, and inadequate emergency triage.[31] Ongoing efforts to increase human resource capacity in Botswana, including the introduction of a gynecological oncologist in 2019, a training program in obstetrics and gynecology in 2020, and expanding the multidisciplinary clinic, will improve access to surgical gynecological oncology services.[32]

A relatively large number of patients presented at advanced stage, indicating that there may be a missed opportunity by patients and providers to identify early lesions. Botswana's robust cervical cancer screening program may present such an opportunity to easily screen women for early vulvar cancer lesions, thus increasing the likelihood for early presentation and improved survival.[33] Although vulvar cancer is a rare disease, dedicated visual inspection of the vulva during cervical cancer screening would take little time or effort by examiners and have potential for significant benefit should a suspicious lesion be identified. Prevention measures to curtail all HPV-associated gynecological and anal cancers also include HPV vaccination, for which Botswana is leading an expanding campaign to vaccinate adolescents.[3435]

Study Limitations

Although our study presents the largest cohort of patients with vulvar cancer in sub-Saharan Africa reported in the literature to date, it is not without limitations. This cohort was primarily women living with HIV, which made statistical comparison to women without HIV infection less robust. Staging limitations, namely lack of CT or MRI imaging and obtaining lymph node status from surgical pathology, also reduced our ability to stage patients appropriately. Patients with extensive disease deemed inoperable due to technically challenging genitourinary surgery, for example, requiring flaps or urethral reconstruction, did not have nodal evaluation and were likely understaged. Presumed 'early' stage disease may have been prescribed radiation therapy and/or chemotherapy and experienced worse outcomes than would have been predicted by their initial limited staging. Finally, we were limited in our ability to follow-up with 25 enrolled patients who did not receive any treatment and cannot comment on the reasons they were not treated. As expected, survival

for these women was poorer than for those who were treated. Despite these limitations, we believe this study is an important contribution to the body of literature that aims to understand treatment patterns and outcomes of patients with vulvar cancer in sub-Saharan Africa.

CONCLUSIONS

Our prospective study found that vulvar cancer patients in Botswana are young and largely those living with well-controlled HIV infection. Lower stage at diagnosis and receipt of surgery was associated with improved survival, although overall survial across stages was poor as compared with vulvar cancer patients in high-income countries. The large number of patients presenting at advanced stage represents an opportunity to use existing screening structures for cervical cancer to identify vulvar lesions at an earlier stage. Ongoing efforts to increase HPV vaccination as well as surgical capacity and training should also have positive effects on prevention and treatment of vulvar cancer. We hope that the increasing attention to vulvar cancer at multiple levels of the healthcare spectrum will improve outcomes for all vulvar cancer patients in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement

Data are available upon reasonable request.

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HIGHLIGHTS

- Vulvar cancer patients in Botswana presented with a high rate of HIV infection, young age, and advanced stage.
- Improved survival was seen with early stage and surgery; survival was not associated with HIV status.
- Botswana vulvar cancer patients' overall survival was 74% at 2 years, worse than that of women in high-income countries.

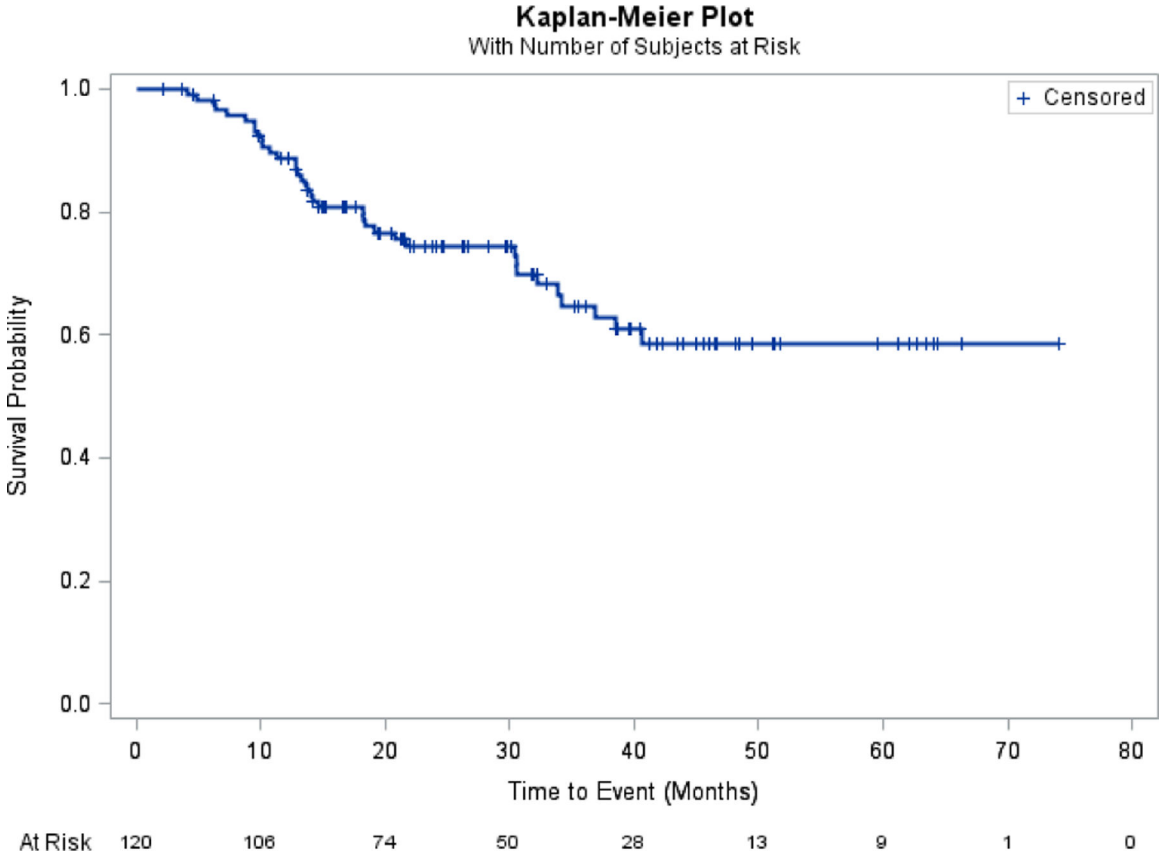

Figure 1.
Kaplan–Meier survival curve of vulvar cancer patients in Botswana 2015–2019.

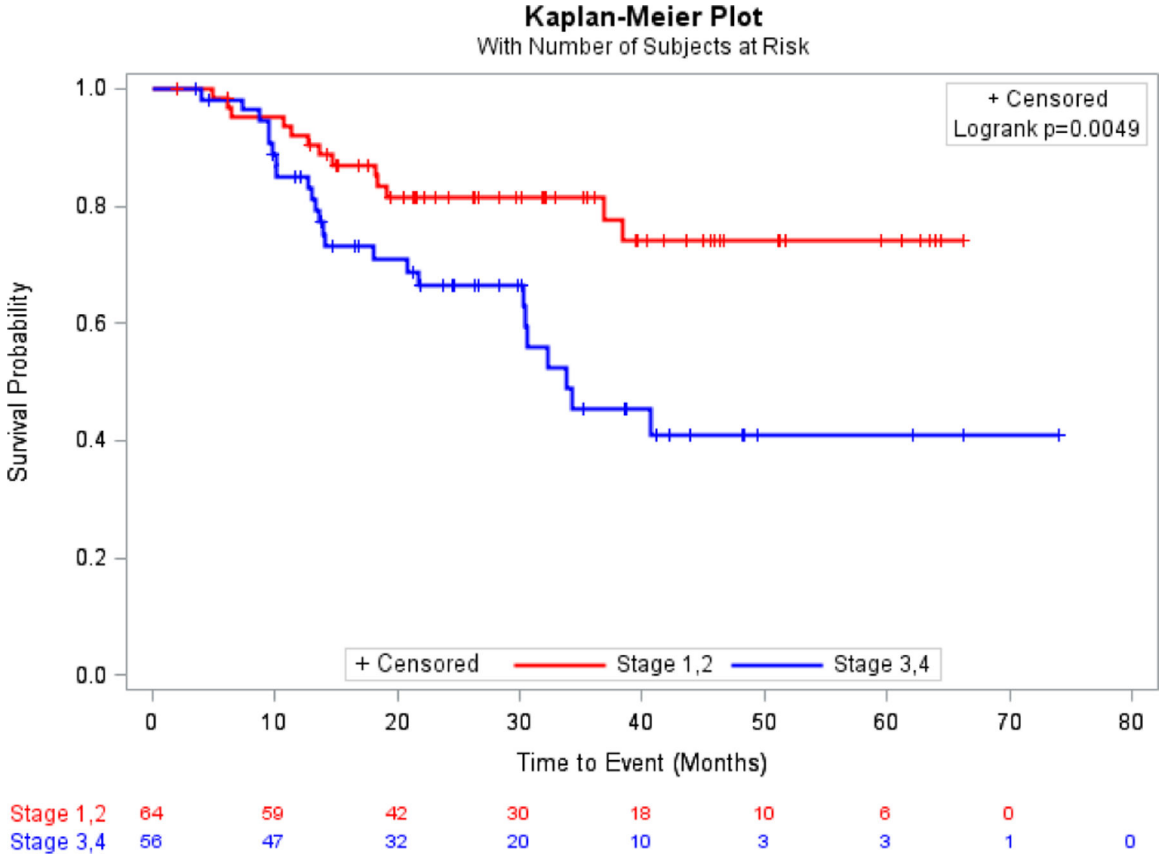

Figure 2.

Kaplan–Meier survival curve of vulvar cancer patients in Botswana 2015–2019 by International Federation of Gynecology and Obstetrics (FIGO) stages I/II versus III/IV.

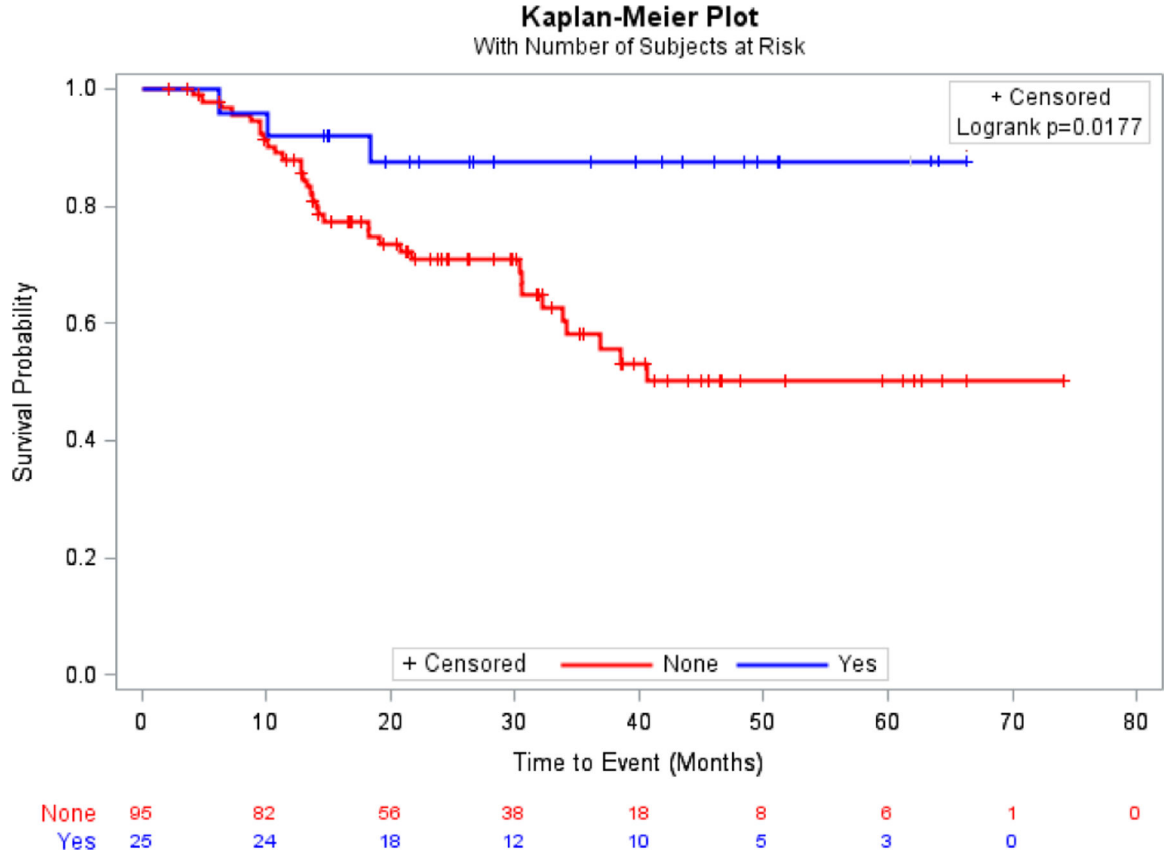

Figure 3.

Kaplan–Meier survival curve of vulvar cancer patients in Botswana 2015–2019 by receipt of surgery.

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Table 1

Characteristics of participants with vulvar cancer in Botswana 2015–2019 by HIV status

Characteristic		HIV-positive (n=107)	HIV-negative (n=13)	Total (n=120)
Age in years, median (IQR)		41 (38–45)	49 (47–71)	42 (38–47)
Marital status, n (%)	Divorced/widowed	8 (7.5)	3 (23.1)	11 (9.2)
	Married	11 (10.3)	1 (7.7)	12 (10.0)
	Single	88 (82.2)	9 (69.2)	97 (80.8)
FIGO vulvar stage, n (%)	I	37 (34.6)	3 (23.1)	40 (33.3)
	II	21 (19.6)	3 (23.1)	24 (20.0)
	III	29 (27.1)	2 (15.4)	31 (25.8)
	IV	20 (18.7)	5 (38.5)	25 (20.8)
Surgery, n (%)	No	85 (79.4)	10 (76.9)	95 (79.2)
	Yes	22 (20.6)	3 (23.1)	25 (20.8)
Radiation, n (%)	No	35 (32.7)	4 (30.8)	39 (32.5)
	Yes	72 (67.3)	9 (69.2)	81 (67.5)
Chemotherapy, n (%)	No	79 (73.8)	12 (92.3)	91 (75.8)
	Yes	28 (26.2)	1 (7.7)	29 (24.2)
Have you ever been screened for cervical cancer?, n (%)	No	49 (45.8)	2 (15.4)	51 (42.5)
	Yes	54 (50.5)	8 (61.5)	62 (51.7)
	Missing	4 (3.7)	3 (23.1)	7 (5.8)
Baseline creatinine, median (IQR)		59.0 (48.0–68.0)	54.0 (42.0–85.8)	58.5 (48.0–68.8)
Baseline hemoglobin, median (IQR)		11.7 (10.0–12.6)	11.9 (10.5–13.4)	11.7 (10.0–12.8)
Baseline albumin, median (IQR)		38.0 (32.3–42.3)	38.5 (36.5–41.7)	38.0 (33.1–42.1)
Radiation dose, median (IQR)		5800 (4910–6100)	4500 (2000–6100)	5800 (4600–6100)
Time to treatment initiation in months, median (IQR)		3.1 (1.2–5.0)	2.2 (1.0–3.1)	3.0 (1.2–4.9)
Years since HIV diagnosis, median (IQR)		10 (7–13)	N/A	
Years on ART, median (IQR)		9 (5–12)	N/A	
Nadir CD4, median (IQR)		299.5 (289–672)	N/A	
Baseline CD4, median (IQR)		461 (300.5–684.5)	N/A	
Baseline viral load (copies/mL), n (%)	≤400	72 (90.0)	N/A	
	>400	8 (10.0)	N/A	

Characteristic	HIV-positive (n=107)	HIV-negative (n=13)	Total (n=120)
Median follow-up time in months, median (IQR)	26.3 (15.2–39.7)	10.1 (9.7–17.6)	24.7 (14.2–39.1)

ART, antiretroviral therapy; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; N/A, not available.

Table 2

Survival analysis of patients with vulvar cancer in Botswana 2015–2019 (n=120)

Variable		Crude HR (95% CI)	Adjusted HR (95% CI)
Age in years (+1 year)		1.03 (0.99 to 1.06)	1.03 (0.99 to 1.07)
HIV status	Negative	1.00	1.00
	Positive	0.46 (0.18 to 1.17)	0.62 (0.22 to 1.76)
Stage	Stage I, II	1.00	1.00
	Stage III, IV	**2.56 (1.30 to 5.02)**	**2.22 (1.11 to 4.45)**
Surgery	No	1.00	1.00
	Yes	**0.26 (0.08 to 0.86)**	**0.30 (0.09 to 0.99)**
Chemotherapy	No	1.00	1.00
	Yes	0.72 (0.33 to 1.57)	0.63 (0.28 to 1.44)

Bold type denotes statistical significance.

CI, confidence interval; HR, hazard ratio.