A COMPARISON OF THE CLINICOPATHOLOGICAL PRESENTATION AND TREATMENT OUTCOMES OFVULVAR CANCER PATIENTS BETWEEN HIV INFECTED AND NON-INFECTED PATIENTS MANAGED AT THE KENYATTA NATIONAL HOSPITAL BETWEEN, 2012 TO 2019

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PROJECT DISSERTATION SUBMITTED AS PARTIAL FULFILMENT FOR FELLOWSHIP IN GYNECOLOGIC ONCOLOGY, 2021

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This work has been dedicated to all the Gynaecologic oncology patients, past, present and future, I will strive to improve lives through compassionate care.

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LIST OF ABBREVIATIONS

ACOG	American college of Obstetrics and Gynaecology
CT – Scan	Computed Tomography Scan
d – VIN	Differentiated Vulvar Intraepithelial Neoplasia
FIGO	Federation of Gynecology and Obstetrics
GOG	Gynaecologic Oncology Group
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HR – HPV	High Risk HPV
HR-HPV	High-Risk Human Papillomavirus
HSIL	High risk squamous Intra-epithelial lesion
KNH	Kenyatta National Hospital
MOH	Ministry of Health
MRI	Magnetic Resonant Imaging
PET- Scan	Positron Emission Tomography Scan
QOL	Quality of Live
RCOG	Royal College of Obstetrics and Gynaecology
SCC	Squamous cell carcinoma
SGO	Society of Gynecologic Oncology
SLN	Sentinel Lymph Nodes
UK	United Kingdom
USA	United States of America
VC	Vulvar Cancer
VIN	Vulvar Intraepithelial Neoplasia
WHO	World Health Organization
WIHS	Women's Interagency HIV Study

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ABSTRACT

Introduction: Vulvar carcinoma is one of the rarest female genital malignancies with an incidence of 2.5 to 4.0 per 100,000 women, accounting for 3% to 5% of all female genital tract malignancies. It has traditionally been considered as a disease of the elderly, occurring at the age of 64 to 69 years. However, recently young age groups are getting vulvar cancer and this is associated with infection with human immunodeficiency virus (HIV).

Broad Objective: To compare the clinicopathological presentation and treatment outcomes for cancer of the vulvar among HIV infected and non-infected patients managed at the Kenyatta National Hospital from 2012 to 2019.

Methodology

Study design:A retrospective cohort study

Study site and setting:Kenyatta National Hospital

Study population:All patients with a histological diagnosis of vulvar cancer and documented HIV status managed in KNH from 2012 to 2019, where the exposed group were patients with cancer of the vulvar and co-existing HIV infection while those in the non-exposed group were patients with cancer of the vulvar but negative for HIV infection.

Sample size:138, (n=90 HIV positive and n=48 HIV negative)

Data collection:Data for the records were collected using a specially designed data extraction tool, entered into excel sheet and analyzed using SPSS version 24 software.

Data analysis:Categorical variables were compared between HIV positive and the HIV negative group using chi square test while comparison of means were tested using Student's t test. Odds ratios were calculated to estimate relative risks associated with independent variables. Kaplan-Meier curve was plotted to illustrate the 2-year and 5-year survival rates of the patients following treatment in both HIV positive and the HIV negative groups. Statistical significance were interpreted at 5% level (p value less or equal to 0.05 was considered statistically significant).

Results: The mean (SD) age for HIV positive patients was 42(10%) Compared to HIV negative patients which was 63(15%). On gross anatomical types, HIV positive patients had more fungating (39%) than ulcerative (51%) types, while HIV negative patients had more ulcerative (73%) than fungating (21%) types. Almost all HIV positive patients had squamous cell carcinoma (97%) unlike the HIV negative patients (81%). Lymphovascular space invasion occurred more in the HIV negative (31%) group than the HIV positive (16%). Majority of the HIV positive patients were of good immune status with Median (IQR) CD4 count of 419 (330 – 603) cells /mm3, and most were on ART. There was no difference in the cancer treatment offered to both groups of patients. There was no difference in 2 year survival between HIV positive and negative patients. At five years few (13%) of the HIV positive patients were still alive compare to 34% in the HIV negative group.

Conclusion: Cancer of the vulvar at Kenyatta National Hospital is more common among HIV positive patients, who are younger than the HIV negative counterparts. Squamous cell carcinoma is the commonest histologic type in both groups though more in the HIV positive group. The HIV positive group are of good immunity and were all on ART. There was no difference in treatment modality between the two groups. There is no difference in the two year survival. At five years 13% and 34% are alive in the HIV positive and negative group respectively. There is a need to explore the reasons for poor survival in the HIV positive group.

CHAPER 1: INTRODUCTION AND LITERATURE REVIEW

INTRODUCTION

Epidemiology

Vulvar cancer (VC) is a rare malignancy, representing 3%–5% of female genital tract cancers in developed countries(1). The incidence ranges from 2.5–4.0/100,000 worldwide with the United Kingdom (UK) having 1.3/100,000 (2)and North America with an incidence of 0.19%(3).Vulvar cancer has a mortality rateof 0.5–1.9/100 000 worldwide.

The average age of women with invasive tumors ranges from 64 to 69 years(4). The incidence of vulvarcarcinoma has increased in the past 30 years. This increase is attributed to the higher prevalence of high-risk human papillomavirus (HR-HPV) in younger women, the increasing lifespan of humans in the developed world, and human immunodeficiency virus (HIV) infection in the developing world. In Kenya,vulvarcarcinoma makes up less than 1% of all cancers with 119 new cases and 32 deaths every year(5).

Aetiology/Risk Factors for Cancer of the Vulvar

The risk factors for vulvar carcinoma (squamous cell carcinoma as the commonest histologic type) include Lichen Sclerosis and infection with high risk HPV. Vulvar cancer can also result as a progression of vulvar intraepithelial neoplastic changes (VIN).The intraepithelial stage can either be seen first as differentiated VIN when associated with Lichen sclerosis (d- VIN) or undifferentiated when associated with HPV infection. The HPV disease is usually seen in younger age groups and can be multifocal while women with lichen sclerosis are mostly elderly and have a 4% risk of developing invasive vulvarcarcinoma (2).

Cigarette smoking has also been implicated as one of the risk factors associated with differentiated vulvar carcinoma and the risk vulvar SIL and vulvar cancer recurrence is said to be increased in cigarette smokers(6).

Clinical Presentation

Symptoms of vulvar cancer include vulvar irritation, pruritis, dysuria, pain, bleeding or discharge due to ulceration(2). It can also present as vulvar swelling.Vulvarsquamous cell carcinoma is differentiated from other benign conditions by the observation of itchiness which is not relieved by steroids or antifungal drugs and pain which can be burning in nature.

Diagnosis of vulvar cancer

The diagnosis of vulvar cancer starts with visual assessment of any vulvar mass/lesion. Biopsy for histologic confirmation of any suspicious warts is mandatory in postmenopausal women and in all ages with Condylomatous lesions not responding to topical treatment (4). Colposcopy is recommended in cases with persistent focal pruritis but with no obvious mass or in lesions which are not well demarcated. Most vulvar cancer lesions are associated with rapid increase in size of previously smaller lesions, change in colour, raised margins and ulcerations.

Histologic Types of vulvar Carcinoma

Approximately 90% of carcinomas of the vulvarare squamous cell type, the remaining 10% comprises of melanomas, adenocarcinomas, basal cell carcinomas,and sarcomas (WHO classification of tumours (2003), pathology and genetics – attached in the Appendix (3)(25).

Clinical staging of Vulvar Carcinoma

Staging of vulvar carcinoma is based on the International Federation of Gynaecology and Obstetrics (FIGO) classification system, which was updated in 2010(7).

Box 1: FIGO staging of carcinoma of the vulvar

FIGO stage	Description I Tumor confined to the vulvar
I	Tumor confined to the vulvar
IA	Lesions ≤2 cm in size, confined to the vulvar or perineum and with stromal invasion* ≤1.0 mm, no nodal metastasis
IB	Lesions >2 cm in size or with stromal invasion*>1.0 mm, confined to the vulvar or perineum, with negative nodes
II	Tumor of any size with extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with negative nodes
III	Tumor of any size with or without extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with positive inguinofemoral nodes
IIIA	1. With 1 lymph node metastasis (≥5 mm), or 2. With 1–2 lymph node metastasis(es) (<5mm)
IIIB	1. With 2 or more lymph node metastases (≥5 mm), or 2. With 3 or more lymph node metastases (<5mm)
IIIC	With positive nodes with extracapsular spread
IV	Tumor invades other regional (upper 2/3 urethra, upper 2/3 vagina), or distant structures
IVA	Tumor invades any of the following: 1. upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, orfixed or ulcerated inguinofemoral lymph nodes
IVB	Any distant metastasis including pelvic lymph nodes

* The depth of invasion is defined as the measurement of the tumor from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

LITERATURE REVIEW

Association of Gynaecological Cancers and HIV Infection

Human Immune-Deficiency Virus (HIV) infection affects women's reproductive health in all aspects ranging from simple recurrent candida vaginitis, to abnormal cervical cytology and cervical cancer (5). The HIV infected individuals are generally at high risk of developing malignancies which might have an aggressive clinical course and outcome as compared to the general population. This contributes to high mortality in patients who are HIV infected but can be reduced by the use of potent antiretroviral therapy (ART) (6).

Human Papilloma Virus (HPV) is the main risk factor for cervical dysplasia and neoplasia in HIV infected patients as well as undifferentiated (type one) vulvar cancer due to their common etiology. The immunosuppressive effect of HIV virus prevents infected patients from clearing oncogenic HPV virus from their body (10), thus increasing their risks for low and high grade squamous intra-epithelial lesions (LSIL and (HSIL), atypia (ASCUS), and carcinoma in situ. An American study of 309,365 patients infected with HIV virus or have AIDs illustrated an increased risk of cervical intraepithelial lesion with the period of HIV infection (10).

In a prospective study involving 650 women followed up for a period of 3 years, 8.3% of those who were HIV positive developed SIL compared to 1.8% for the HIV negative women(11). The same study also revealed persistence of HPV DNA as a result of infection with multiple types in younger age.The Women Interagency HIV Study (WIHS) concluded that there is increased prevalence in infection with HPV oncogenic types, abnormal Pap test and cervical precancerous lesions among HIV infected women which contributed to their high risk of developing invasive cervical cancer (12).Women with HIV infection are three times more likely to develop cervical cancer with worst outcomes and have high risk of dying from cancer than women who are not HIV infected (13–15).

Association between VulvarCancerand HIV Infection

About 10% of vulvar squamous cell carcinoma (SCC) occur under the age of 40 years (16) but this has changed due to immunosuppressive infections. The youngest patient diagnosed with invasive vulvar cancer was a 12 year old girl who was a

victim of vertical transmission of HIV (17). The number of invasive vulvar cancer has doubled in the last three decades with four times increase in younger patients due to infection with HIV and high risk HPV (18).

A retrospective study done in South Africa has confirmed a median age of vulvar cancer in HIV positive as 31 years and 51 years for non-HIV infected patients (19). Coinfection with moderate and high risk HPV genotype in HIV positive patients reduce host cutaneous immune response to clear HPV leading to development of vulvar intraepithelial neoplasia and thus vulvar cancer as compared to women who are non-HIV infected (20). A prospective cohort study of 1,562 women with HIV and 469 without HIV concluded that there is an increased incidence of genital warts and VIN among those with HIV (21)and thus risk of vulvar cancer.

Two other comparative studies that looked at age at presentation, prognostic variables, and clinical characteristics revealed that younger patients present late but have better treatment outcomes and survival compared to their elderly counterparts who have early presentation but worst prognostic outcomes (22,23). When it comes to disease treatment, older women are more likely to receive radiation therapy as a primary treatment for vulvar cancer than younger patients with the same disease stage and are prone to suffer from the disease and treatment complications (24).

An Ethiopian cohort study that looked into patients' characteristics and disease survival in patients with cancer of the vulvar showed that more than 80% of those with recorded HIV status were positive with a median age of less than 40 years. The study also revealed that majority of the HIV positive presented with WHO stage four disease which might have contributed to their primary treatment with radiotherapy instead of the standard surgical treatment. Their mean period on HAART was more than three years. Majority of the cases of vulvar cancer were between stage one and three and their survival at two years was about 50 % (25).

Management ofVulvarCancer

The management of vulvar cancer starts with clinical assessment of any lesion followed by histologic diagnosis, imaging to determine the extent of metastases and then surgery. The gold standard approach of care is surgical management with or without radiotherapy. Disease surveillance of patients treated for vulvar carcinoma should be done closely during the first five years since recurrence is common after initial treatment(26).

Surgical Management of Vulvar Cancer

The extent of surgery is determined by the stage of the disease and should usually be done in a center with a gynaecological oncologist(1). Individualization of surgical management should be the best practice where minimal surgical intervention should result into cure of the disease with minimal treatment morbidity(27). Stage 1A disease can be managed with wide local excision and stage 1B and above should be managed with modified radical vulvectomy plus lymph nodes dissection (1).

Wide local excision with a 0.5 to 1 cm free margin can be done in women where invasive disease cannot be ruled out even if histologic findings of biopsy is of vulvar HSIL. Modified radical vulvectomy is used to resect primary lesions with a free margin of 2 cm to spare normal tissues. Lesions more than 1 cm from the midline should be managed with wide local excision or modified radical vulvectomy and ipsilateral inguinofemoral lymphadenectomy(26). In some centers inguinofemoral lymphadenectomies are replaced by sentinel lymph nodes (SLN) dissection (1). Lymph nodes dissection is usually done via a separate incision and adjuvant therapy is then considered based on the pathological report.

Radiotherapy

Radiotherapy is used as an adjunct to surgery when the diagnosis of invasive vulvar cancer is confirmed by histology which might show involvement of the margins and positive lymph nodes. Neoadjuvant radiotherapy is an option in locally advanced disease with involvement of vital organs such as the urethral and anal openings (1). Chemoradiation with cisplatin and 5-fluorouracil has been found to be effective by the Gynaecologic Oncology Group (GOG) (27).

Medical Management

There is limited data as to the use of chemotherapy as the primary management, thus it is usually used as part of a salvage therapy or aspart of chemoradiation. Most vulvar cancer patients are elderly thus making them weak to withstand the effects of cytotoxic drugs. Most cases of vulvar cancer achieve remission with surgery and radiation (28).

Surveillance/Follow up

Most patients who have been treated for vulvar carcinoma will develop recurrence within the first year following treatment although some studies confirmed recurrence after five years of treatment in 10% of patients(29). Vulvarcancer can also manifest as a field cancerization effect thus requiring lifetime follow up. There are no standard surveillance strategies for vulvar carcinoma(30).The Society of Gynaecologic Oncology (SGO) has developed the following surveillance guidelines:

1. Review of symptoms and physical examination on every clinic visit. Examination of the skin bridge and inguinal lymph nodes
2. In stages I and II disease, follow up should be every six months for the first two years and then yearly thereafter.
3. For advanced-stage disease, follow up should be three monthly for the first two years then six monthly for from the third to the fifth year then yearly thereafter (30)
4. Cervical cytology or vault smear should be done annually.

Most recurrences are detectable by physical examination; thus, routine imaging is not encouraged but in some cases of suspected recurrence computed tomography (CT-Scan) and/or Positron emission tomography (PET-Scan) can be done as well as vulvar colposcopy and biopsy. Sexual function is of utmost importance and should be considered during follow-up visits. Recurrence of vulvar cancer after primary treatment can be local, regional or distant. Treatment for recurrence depends on the site; if local recurrence then wide local excision can be done with or without radiation and for distant recurrence chemoradiation is appropriate (30).

Survival among Patients with Vulvar Cancer

Vulvarcarcinoma generally has a good prognosis with a median survival time of eight years and a five-year survival rate of up to 62.3% overall. As in all other malignancies, the stage at diagnosis has an impact on individual outcomes. The five-year survival varies deteriorates with advancing staging for squamous cell carcinoma; stage I (93.3%), stage II (78.7%) stage III (52.7%) and stage IV (28.7%). The older the patient the more negative the impact on the disease survival. For all vulvar cancer, those aged below 60 Years had a higher survival rate (96.0%) compared to those over 60 years (68.8%)(26).

The literature has so far confirmed the high survival rate in vulvar cancer but there are few studies done to compare survival among HIV infected patients. Few studies done on vulvar cancer showed increased risk of cancer in HIV infected patients and patients of low social status, but there is no study that clearly compares patients with vulvar cancer, HIV status, age, treatment outcome and survival. The aim of this study is to assess the effect of HIV on vulvar cancer treatment outcome and survival.

CONCEPTUAL FRAMEWORK

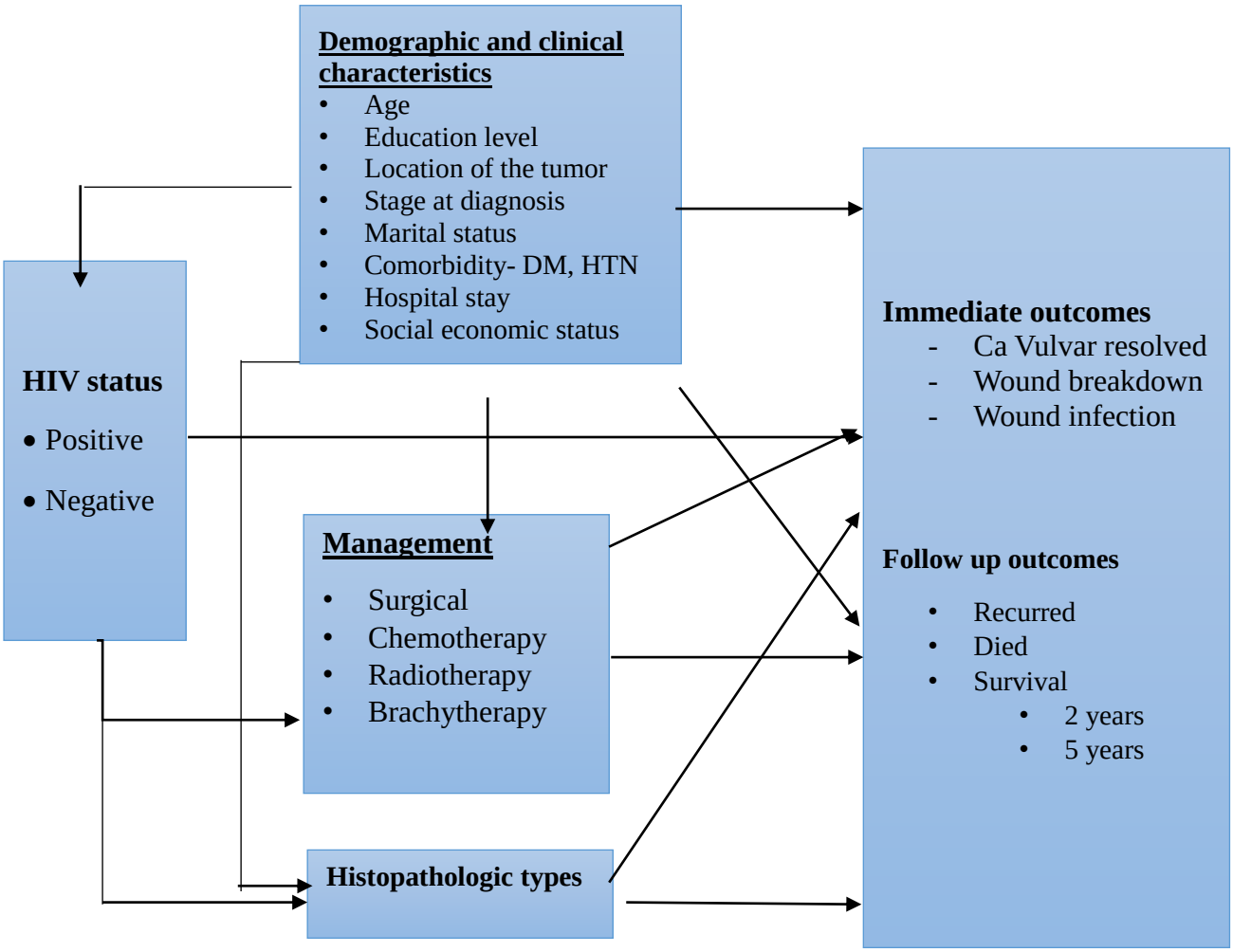

Figure 1: Conceptual Framework

STUDY JUSTIFICATION

Since vulvar cancer has been seen more commonly among HIV infected patients, further understanding of the disease interaction, the patient characteristics and the subsequent survival of patients managed for vulvar cancer is paramount in differential treatment and follow up of these patients.

Despite the comparable survival and life expectancy among HIV infected patients and the general population, largely due to the highly active anti-retroviral agents, there is paucity of data in the developing countries on whether co-existing conditions such as HIV infection can influence the clinicopathological and survival among patients with cancer of the vulvar. In essence, there are no guidelines on the management of these patients, who more often present in late stages of both HIV and vulvar cancer.

The findings of this study will therefore provide further insight into the differential clinicopathological presentation of patients with cancer of the vulvar, comparing those with and without HIV infection. Any significant differences between the two groups will help inform policy and guideline development for the management of these patients at the Kenyatta National Hospital (KNH) and the region.

RESEARCH QUESTION

Is there difference in the clinicopathological presentation and outcomes of treatment for cancer of the vulvaramong patients with and without HIV infection managed at the Kenyatta National Hospital?

NULL HYPOTHESIS

There is no difference in clinicopathological presentation and treatment outcomes of cancer of the vulvar between patients with and without HIV infection managed at Kenyatta National Hospital.

STUDY OBJECTIVES

Broad Objective

To compare the clinicopathological presentation and treatment outcomes of vulvar cancer among HIV infected and non-infected patients managed at the Kenyatta National Hospital from 2012 to 2019.

Specific Objectives

Among patients managed for cancer of the vulvar at the Kenyatta National Hospital from 2012 to 2019, to compare:

1. The clinical - pathological presentation between HIV infected and non-infected patients
2. The primary treatment outcomes (remission, complications such as organ failure, wound sepsis) between HIV infected and non-infected patients
3. The two- and five-years survival between HIV infected and non-infected patients

CHAPTER 2: STUDY METHODOLOGY

Study Design

This wasa retrospective cohort study. The exposure group were HIV infected patients and the unexposed group were patients without HIV infection treated for cancer of the vulvarat the Kenyatta National Hospital (KNH) between the year 2012 and 2019. All the collected eligible data was analyzed.The outcomes of interest included sociodemographic characteristics, clinical presentation, pathological findings, the immune status of the HIV infected patients, treatment modality and outcome, and survival. Because cancer of the vulvar is a rare disease, a prospective cohort design would have required a long period of time to accumulate the desired number of cases. In addition, one of the outcomes assessed was survival post-diagnosis which would have further increased the waiting time.

Study Setting

This study was carried in Kenyatta National Hospital (KNH) at the medical records department in Nairobi Kenya. KNH is the largest referral hospital in Kenya, and had been the only hospital for a long period of time that manages gynaecological cancers in Kenya before the Moi Teaching and Referral Hospital (MTRH) started offering similar services. KNH also serves as the teaching hospital for the University of Nairobi and the Kenya Medical Training College. Its catchment population is drawn from all over the country. The whole hospital has a bed capacity of 2,500 patients. The Gynecologic-oncology unit at KNH has high attendance by women seeking management of oncological conditions being referred from all parts of the country, on average it manages 974 reproductive tract cancer patients per year out of which 41 are vulvar cancer (which is 4.2 %)(32). It also has a well-kept and complete records which was essential for data collection for this study. Majority of vulvar cancer patients were managed in ward 1B where all records of their file number and diagnosis are kept in a registry book. The KNH Department of research keeps

Research Electronic Data Capture (REDCap) software for reproductive cancers since 2009.

Patients diagnosed with vulvar cancer were managed in the Gynecologic Oncology unit and post-operative follow up were done at the outpatient clinic 18. Some Gynecologic oncology patients were also managed in ward 1D and others who require radiation therapy were referred to the Radiotherapy Department. In the outpatient clinic (clinic 18), management plans for new patients were being made and follow up for discharged patients is carried out. A multidisciplinary team approach is usually involved in the management of most of these patients and these can include departments of General Surgery, Plastic Surgery, Urology, Uro-gynaecology, Pathology, Nutrition and Psychosocial support. The staff compliment of the unit comprised of one Gynaecologic Oncologists, eight Gynaecologic Oncology Fellows, and Obstetrics and Gynecology Residents.

Study Population

The study population comprisedof all patients with a histological diagnosis of vulvar cancerand documented HIV statusmanaged in KNH from 2012 to 2019, where the exposed group were patients with vulvar cancerand co-existing HIV infection while those in the non-exposed group were patients with cancer of the vulvarcancer but negative for HIV infection.

Inclusion Criteria

Exposed group

1. Patients who had histological diagnosis of cancer of the vulvar
2. Patients who are confirmed and documented diagnosis of HIV infection

Unexposed group

3. Patients with a histological diagnosis ofvulvarcancer
4. Patients with documentation of HIV status as negative

Exclusion Criteria

The following were excluded from the study:

1. Patients with metastatic cancers to the vulvar (secondary tumors)
2. Patients who were not primarily managed at the Kenyatta National Hospital Gynecology Oncology unit

Sample Size Determination

According to hospital records in KNH, 200 patients were managed forvulvar cancer between 2012 and 2019. A pilot study showed that 60% of the patients were HIV positive, meaning approximately 120 of the patients were HIV positive and 80 were HIV negative. The assumption was that all patients were tested for HIV and have the results documented in the files. In addition, it was hypothesized that mortality is 2 times higher among HIV positive patients compared to the HIV negative.Sample size was thencalculated using the formula for comparing proportions in two groups as follows:

$$n = \frac{2\left(Z_{1-\propto/2} + Z_{1-\beta}\right)^2 P_{av}(1 - P_{av})}{(P_0 - P_1)^2}$$

Where

n – The minimum sample size required

$Z_{1-\propto/2}$ – Standard normal at 95% confidence interval = 1.96

$Z_{1-\beta}$ – Standard normal at 80% power = 0.84

P_0 – The overallmortality rate in patients with cancer of the vulvar regardless of HIV status = 20%(25).

P_1 - The mortality rate in HIV positive patients with cancer of the vulvar= 40% (Hypothetical).

P_{av} = $\frac{P_0+P_1}{2}$ = 30%

When substituted,

The minimum sample size, n was then determined to be 82 in each group, giving a minimum total of 164 patients. However, given that, the sample size approximates the total number of records for the patients managed over the study period, all available patient records of 167 fileswere included in the study. Due to missing data, only 138 patients were eligible for analysis in this study, out of which 90 were HIV positive and 48 HIV negative.The reduced original sample size by almost 15% has under powered the study which could mean exclusion of more HIV positive or negative from the study.

Selection of Study Participants/ Sampling Procedure/Screening

All records with diagnostic code for vulvar cancer as outlined in study site and setting were retrieved. Using the KNH information management system, IP numbers were identified for all records meeting the diagnostic criterial for the period 2012 - 2019 for retrieval.

Retrieval of patient files started with screening all records that met the eligibility criteria as described in study population. Given the calculated sample size approximates the total number of available records for patients managed over the targeted period, all the available files were selected to reach our estimated sample size.

Study Variables

Box 2: Study Variables per objectives

Specific objectives	**Indicator definition**	**Indicator classification**	**Sources of data**
Social-demographic characteristics	Age, Smoking, Marital status, Socio-economic status	Intermediate	File, call patient
HIV Status	Positive history of HIV infection	Independent	
Obs/Gyn characteristics	Parity, Age at Menarche, Age at menopause, Contraceptive use, Family history of cancer, Personal history of other Cancer, Pap smear done	Intermediate	
Clinico-pathological characteristics	– Surgical stage – Time of first symptoms – Time at hospital presentation	Dependent	
Treatment options	– Surgery – Chemotherapy – Radiation – Palliative Care	Dependent	
Treatment outcomes	Time of discharge after surgery, Wound break down (specify site), wound infection, Status of wound at discharge	Dependent	
Survival analysis	2- and 5-years survival	Dependent	

Data Collection procedure

Research assistants who were mainly nurses and clinical officers retrieved all the patients' files with a diagnosis of vulvar carcinoma at the KNH registry for the period of the study. All files for patients managed for vulvar cancer from 2012 to 2019 with available recorded HIV infection status were included in the study.

In order to improve on the quality of collected data on survival for patients whose follow up status was not clear in the file, phone calls were made for the eligible patients using recorded phone numbers of patients/next of kin to ascertain information on patient's survival. Data was captured in a structured data abstraction tool (**Appendix 1**) that was used to collect patients' information on socio-demographic characteristics, clinical features, outcomes of treatment and the 2-year and 5-year survival.

Quality Assurance Procedures

Data collection was done by the principal investigator and three research assistants who were qualified clinical officers and nurses with training in data collection.

The data capture tools for patients at KNH which is a globally accepted standardised instruments that capture accurate data was used. Our data collection tool was pretested to ascertain its reliability before the start of data collection and face validity technique was used to ascertain the validity of our data capture tool. The data abstraction tool was shared with colleagues and lecturers in the department of obstetrics and gynaecology and its suitability for data collection was gauged and all their suggestions were factored into the final copy of the tool.Data were checked daily for completeness and accuracy and corrected accordingly.

Data Management and Analysis

Data for the records were collected using a specially designed data extraction tool, entered into excel sheet and analyzed using SPSS version 24 software. The clinic-pathological presentation for the patients including age, parity, signs and symptoms were summarized into means and percentages for continuous and categorical data respectively. Similarly, treatment outcomes and mortality were presented as percentages out of the population studied. Categorical variables were compared between HIV positive and the HIV negative group using chi square test while comparison of means were tested using Student's t test. Odds ratios were calculated

to estimate relative risks associated with independent variables. Kaplan-Meier curve wasplotted to illustrate the 2-year and 5-year survival rates of the patients following treatment in both HIV positive and the HIV negative groups. Statistical significance were interpreted at 5% level (p value less or equal to 0.05 wasconsidered statistically significant).

Ethical Considerations

This study was submitted to the Kenyatta National Hospital/ University of Nairobi Ethics and Research Committeefor approval. The study then commenced after approval was given. Permission to carry out the study was sought from both the KNH research program center and the Obstetrics and Gynaecology departments.

This study was considered of minimum risk due to its retrospective nature and no patient identifiers were collected.Throughout the cycle of the study the researchers strived to maintainparticipants' confidentiality through anonymity in the data collection and aggregation data. In addition, the collected data had limited access to only the principal investigator and the statistician.The filled data capture tools werefilled directly in the computer-generatedgoogle form and so there were no hard copies of the form.Databases were password protected.The data and results were kept confidential. Verbal consent for phone calls was sought **(Appendix 2)** from patients/next of Kin for information on follow up clinic survival when there was no clear information in the file on last clinic attendance.

STUDY RESULTS DISSEMINATION PLAN

The results from this study was presented in the department of Obstetrics and Gynaecology of University of Nairobi and Kenyatta National Hospital. These findings will also be published in peer reviewed journals and will be presented in conferences hosted locally by the Ministry of Health (MoH) of Kenya and by regional and international bodies. A summary of the findings will also be given to KNH research resource centre and the department of Obstetrics and Gynaecology and KNH-UoN ERC.

STUDY LIMITATIONS AND STRENGTH

The following are the limitations for this study:

i. The main limitation of this study was of missing files and missing data which actually reduced the number by 15 %. The total number of patients diagnosed with vulvar cancer during the period of the study from KNH records were confirmed to be 180 patients. Thirteen (13) files were missing during the data collection period which could either be at the clinic, ward or with another researcher.So the files used for data collection were 167

ii. Missing data on the HIV status of the patients in the eligible files were also another major study set back, since the study point ofinterest was to compare outcomes between HIV infected and non-HIV infected. Out of 167 eligible files, 29 had missing data on HIV status which is about 17.4%, so only 138 files were eligible for analysis.

iii. Some of the phone numbers used in the file when contacted denied any knowledge of the patient so we considered either the number was given out to a different user by the mobile network or the respondent did not want the memory of a lost loved one so we assumed them dead.

iv. There was no clear guideline on how to document the exact diagnosis of Vulvar cancer so others were documented as labial swelling and even after histology report these were not corrected on discharge, and the coding at the records becomes different. This was minimized by checking first for all the gynaecological cancers, narrowed to cancers of external genitalia and only vulvarcancer was included in the list.

v. Definitive post-surgery outcome were missing since some patients (about 15 to 18 %) were lost to followso only their last documented clinic visit or information through phone callswas included in the analysis.

vi. There is no linkage between the records in the Gynecologic Oncology Unit and the Radiotherapy Unit, most patients have 2 different file numbers.

vii. This is the first study to look into the socio-demographic, clinical, pathological and treatment outcomes of vulvar cancer in relation to their HIV status.

CHAPTER 3: RESULTS

A total of 180 patients were managed in KNH between 2012 and 2019. Out of this 13 files were missing and 29 records had missing data giving a total of 138 records eligible for this analysis. Out of the 138 eligible patients, managed for cancer of the vulvar in KNH between 2012 and 2019, 90 (65%) were HIV positive and 48 (35%) were HIV negativeHIV (**figure1**).

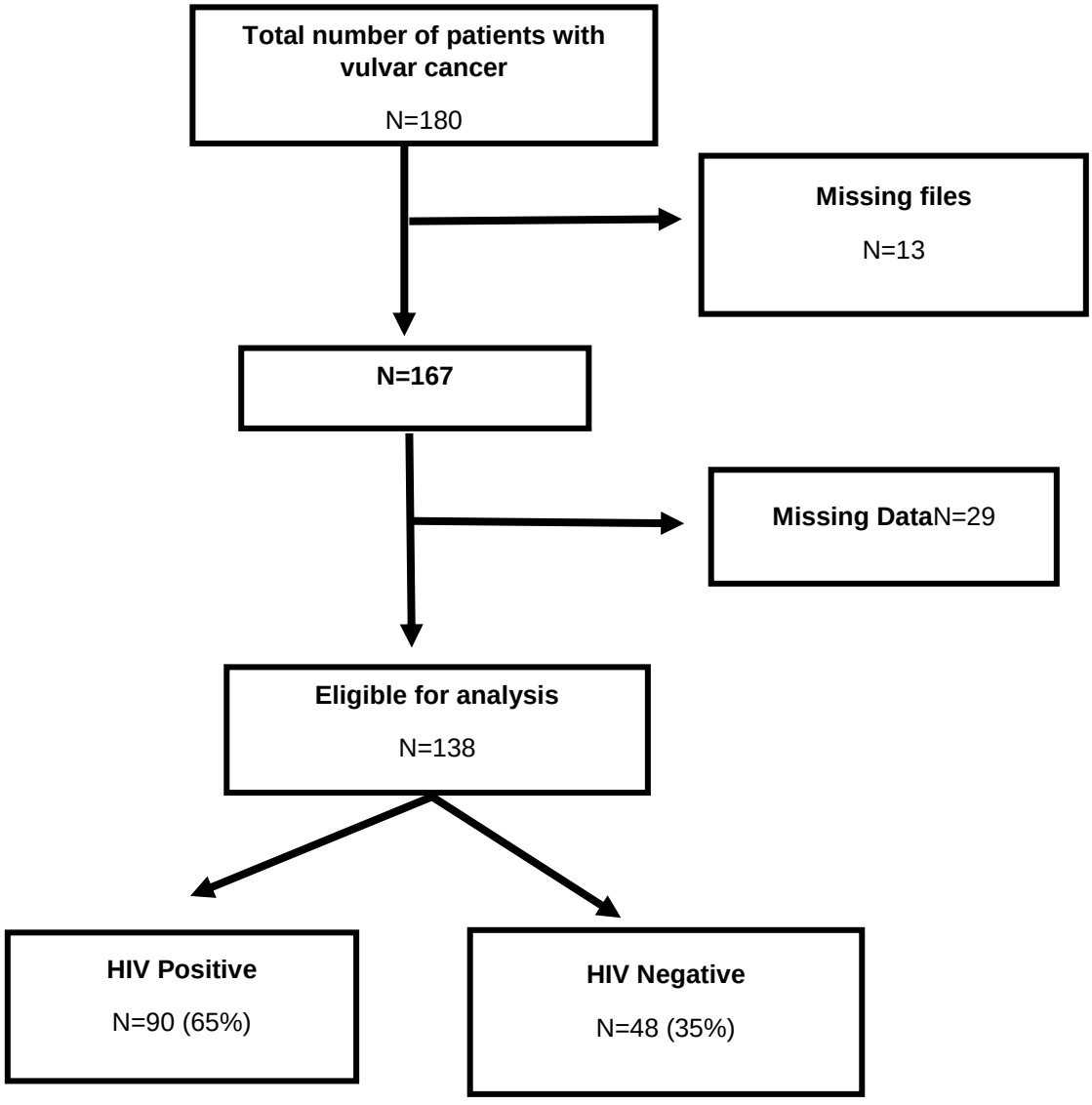

Figure 1: Eligibility flow chart for patients with vulvar cancer at Kenyatta National Hospital (KNH), 2012 to 2019

The demographic and clinical characteristics that were statistically different (p<0.05) between HIV positive and HIV negative vulvar cancer patients are the mean age (SD) 42 (10) and 63(15) respectively; parity and family planning use. There were no difference between HIV positive and negative patients in the following demographic and clinical variables: weight, BMI, family planning method type, smoking, history of prior cancer, genital warts and symptoms (**table 1**)

Table 1: Demographic and clinical characteristics of patients with vulvar cancer by HIV status at Kenyatta National Hospital (KNH), 2012 to 2019

Variable	**HIV Positive N=90**	**HIV Negative N=48**	**P value**
Age in years			
Mean (SD)	**42.0 (10)**	**63.0 (15)**	**<0.001**
Weight (Kg)			
Mean (SD)	60.4 (12)	59.4 (12)	0.737
	N=90 n(%)	**N=48 n(%)**	
BMI			
Normal (<25)	30 (33)	17 (35)	0.500
Overweight (25-29.9)	12 (13)	9 (19)	
Obese (>30)	5 (6)	1 (2)	
MISSING DATA	43 (48)	21(44)	
Para			
0	**3 (4)**	**2 (5)**	**<0.001**
1-3	**50 (62)**	**7 (18)**	
4-6	**23 (28)**	**10 (26)**	
7-8	**4 (5)**	**11 (28)**	
>9	**1 (1)**	**9 (23)**	
Family planning			
Yes	**26 (33)**	**5 (12)**	**0.011**
No	**52 (67)**	**37 (88)**	
FP type			
Hormonal	20 (76)	5 (100)	0.489
Non hormonal	2 (8)	0	
Not indicated	4 (15)	0	
Smoking			
Yes	2 (2)	1 (2)	0.958
No	88 (98)	47 (98)	
History of Prior other cancer			
Yes	4 (4)	0	0.307
No	75 (83)	43 (90)	
Not recorded	11 (12)	5 (10)	
Genital warts			
Yes	15 (17)	6 (13)	0.516
No	75 (83)	42 (88)	
***Symptoms**			
Vulvar Itch	19 (21)	14 (29)	0.291
Vulvar Rashes	1 (1)	0	1.000
Vulvar Bleeding	15 (17)	8 (17)	1.000
Vulvar mass/lesions/ Swellings	67 (74)	36 (75)	0.943
PV Discharge	19 (21)	17 (35)	0.068
Pelvic Pain	10 (11)	8 (17)	0.356
Dysuria	0	1 (2)	0.348
One patient can have more than one occurrences			

Patients with vulvar cancer who are HIV negative hada higher (73%) proportion of ulcerative gross anatomical tumor types compared to HIV negative patients (51%), p=0.013. Fungating gross tumor types were more (39%) in HIV positive patients compared to HIV negative patients (21%), p=0.031. All the other examination findings are not different between the two groups (**table 2**).

Table 2: Examination findings of patients with vulvar cancer by HIV status at Kenyatta National Hospital (KNH), 2012 to 2019

Variable		HIV Positive N=90n(%)	HIV Negative N=48n(%)	P value
Examination	Under Anesthesia (EUA)	65 (73)	40 (83)	0.174
	Without Anesthesia (EWA)	24 (27)	8 (17)	
***Labial involvement**	Right labia majora	29 (51)	24 (71)	0.065
	Left labia majora	32 (56)	17 (50)	0.570
	Right labia minora	15 (26)	7 (21)	0.537
	Left labia minora	12 (21)	2 (6)	0.052
***Extension to other organs**	Vagina	47 (80)	32 (94)	0.060
	Clitoris	7 (12)	4 (12)	1.000
	Anus	5 (8)	1 (3)	0.410
	Rectum	1 (2)	1 (3)	1.000
Gross tumor types	Ulcerative	**46 (51)**	**35 (73)**	**0.013**
	Fungating	**35 (39)**	**10 (21)**	**0.031**
	Nodular	4 (4)	2 (4)	1.000
	Infiltrative	11 (12)	2 (4)	0.219
Number of lesions	1	31 (72)	15 (63)	
	2	9 (21)	7 (29)	0.391
	3	2 (5)	0(0)	
	>4	1 (2)	2 (8)	
Inguinal LN involvement at presentation	Right side	15 (21)	10 (31)	
	Left Side	21 (30)	9 (28)	0.488
	Both	20 (29)	10 (31)	
	None	14 (20)	3 (9)	
Clinical staging during EWA	IA	0(0)	1 (7)	
	IB	3 (9)	0(0)	
	I	0(0)	1 (7)	
	II	5 (15)	1 (7)	
	IIA	1 (3)	1 (7)	0.360
	IIB	1 (3)	2 (13)	
	III	11 (33)	2 (13)	
	IIIA	2 (6)	2 (13)	
	IIIB	2 (6)	2 (13)	
	IV	4 (12)	1 (7)	
	IVA	1 (3)	1 (7)	
	IVB	2 (6)	0(0)	
	Not indicated	1 (3)	1 (7)	
FIGO clinical staging During EUA	Stage 0	1 (2)	0(0)	
	Stage IA	1 (2)	1 (3)	
	Stage IB	6 (10)	4 (13)	
	Stage IIA	5 (8)	2 (7)	0.727
	Stage IIB	5 (8)	4 (13)	
	Stage III A	16 (26)	4 (13)	
	Stage III B	13 (21)	8 (26)	
	Stage III C	2 (3)	3 (10)	
	Stage IV A	7 (11)	4 (13)	
	Stage IVB	6 (10)	1 (3)	

A patient has more than two occurrences

Almost all (97%) HIV positive patients had squamous cell carcinoma compared to HIV negative patients (81%). Other histologic types (pleomorphic sarcoma, adenocarcinoma, and basal cell carcinoma) occurred in HIV negative patients except small cell carcinoma that occurred in HIV positive patients, **p=0.016**. HIV negative patients have a higher (31%) proportion of lymphovascular space invasion compared to HIV positive patients (16%), **p=0.059** ((**table 3**).

Table 3: Pathology findings of patients with vulvar cancer by HIV status at Kenyatta National Hospital (KNH), 2012 to 2019

Variable	**HIV Positive N=90 n(%)**	**HIV Negative N=48 n(%)**	**P value**
Pathology of EUA/ EWA biopsy			
Yes	86 (96)	38 (79)	0.005
No	4 (4)	10 (21)	
Pathology report			
Yes	49 (54)	19 (40)	0.096
No	41 (46)	29 (60)	
Histology			
Squamous cell carcinoma	87 (97)	39 (81)	**0.016**
Small cell carcinoma	1 (1)	0(0)	
Pleomorphic sarcoma	0(0)	1 (2)	
Adeno squamous	0(0)	1 (2)	
Adenocarcinoma	0(0)	1 (2)	
Anorectal carcinoma	0(0)	1 (2)	
Basal cell carcinoma	0(0)	1 (2)	
Undocumented	2 (2)	4 (8)	
Grade			
1	6 (7)	1 (2)	0.296
2	9 (10)	8 (17)	
3	12 (13)	3 (6)	
Not stated	63 (70)	36 (75)	
Depth of stromal invasion			
1-2 mm	2 (29)	0(0)	0.491
>4mm	5 (71)	4 (100)	
Lymphovascular Space Invasion			
Yes	**14 (16)**	**15 (31)**	**0.059**
No	**58 (64)**	**22 (46)**	
Not documented	**18 (20)**	**11 (23)**	
Nodal invasion			
Yes	15 (17)	11 (23)	0.636
No	49 (54)	23 (48)	
Not documented	26 (29)	14 (29)	

There are no significant differences in the investigations offered to HIV positive and HIV negative patients with vulvar cancer in KNH (**table4**)

Table 4: Other investigations of patients with vulvar cancer by HIV status at Kenyatta National Hospital (KNH), 2012 to 2019				
Variable		**HIV Positive N=90 n(%)**	**HIV Negative N=48 n(%)**	**P value**
Hemoglobin at diagnosis	<6 6-8 8-10 10-12 >12 Not documented	2 (2) 5 (6) 25 (28) 25 (28) 28 (31) 5 (6)	1 (2) 3 (6) 5 (10) 22 (46) 16 (33) 1 (2)	0.111
Imaging done	Ultrasound CXR CT Scan MRI	40 (49) 31 (38) 38 (46) 11 (13)	30 (65) 12 (26) 15 (33) 2 (4)	0.073 0.178 0.130 0.133
CT Scan finding Tumor location	Vulvar Vaginal wall Pelvic side Right labia majora Right inguinal lymph mode Left vulvar labia majora Cervix Anorectal junction Posterior bladder wall	5 (19) 2 (7) 1 (4) 6 (22) 4 (15) 7 (26) 0(0) 0(0) 0(0)	1 (8) 0(0) 1 (8) 2 (15) 1 (8) 3 (23) 1 (8) 1 (8) 1 (8)	0.643 1.000 1.000 1.000 1.000 1.000 0.325 0.325 0.325
Preoperative Full Haemogram	Normal Abnormal	84 (94) 5 (6)	43 (91.5) 4 (8.5)	0.496
Preoperative U/E/C	Normal Abnormal	84 (94) 5 (6)	46 (98) 1 (2)	0.664
Preoperative LFTs	Normal Abnormal	86 (97) 3 (4)	47 (100) 0(0)	0.551

For the HIV positive patients, the median (IQR) CD4 counts (cells/mm^3) is 419(330-603) and 93% of them were on ART. Most HIV positive patients did not have viral load recorded in their files (**table 5**)

Table 5: CD4 counts, Viral load and ART use in HIV positive patients with vulvar cancer at Kenyatta National Hospital (KNH), 2012 to 2019	
Variable	**N=90** **n (%)**
1st CD4 Count at vulvar cancer diagnosis (cells/mm3) Median (IQR)	419.0 (330.0-603.0)
Viral load Undetectable **Not indicated** Negative 94 copies	 10 (11) **78 (87)** 1 (1) 1 (1)
ART Use **Yes** No	 **84 (93)** 6 (7)

More (97%) HIV negative patients received adjuvant radiotherapy compared to HIV positive patients (82%), **p=0.055.** HIV positive patients had a high (66%) percentage of those who received chemotherapy more than HIV negative (38%), **p=0.008** (**table 6**)

Table 6: Cancer treatment of patients with vulvar cancer by HIV status at Kenyatta National Hospital (KNH), 2012 to 2019

Variable	HIV Positive N=90 n(%)	HIV Negative N=48 n(%)	P value
Number of surgeries done			
Median (IQR)	1 (0-1)	1 (1-1)	0.259
Surgery given as primary treatment			
Yes	56 (62)	30 (63)	0.974
No	34 (38)	18 (37)	
Type of surgery			
Inguinal lymphadenectomy	11 (32)	4 (24)	0.514
Biopsy	6 (18)	5 (28)	0.482
Simple vulvectomy	15 (44)	10 (56)	0.432
Radical vulvectomy	15 (44)	5 (28)	0.249
Post-op complication			
Yes	28 (41)	17 (53)	0.238
No	41 (60)	15 (47)	
Type of complication			
Wound breakdown	6 (9)	2 (6)	1.000
Pain	24 (35)	15 (47)	0.246
Infection	3 (4)	1 (3)	1.000
Lymphoedema	0(0)	1 (3)	0.317
DVT	1 (1)	1 (3)	0.535
Inability to walk	1 (1)	0(0)	1.000
Adjuvant radiotherapy			
Yes	**56 (82)**	**32 (97)**	**0.055**
No	**12 (18)**	**1 (3)**	
Reason for radiotherapy			
Treatment	32 (57)	26 (77)	0.063
Palliative	12 (21)	4 (12)	0.245
Neoadjuvant	22 (39)	9 (27)	0.215
Type of radiation therapy			
External beam	41 (75)	24 (83)	0.392
Brachytherapy	14 (26)	5 (17)	
External beam Dose			
Median (IQR)	2.0 (1.8-2.0)	2.0 (1.8-2.0)	0.404
Sessions			
Median (IQR)	30.0 (25.0-33.0)	33.0 (27.0-35.0)	0.093
Chemoradiation given			
Yes	37 (45)	20 (50)	0.749
No	12 (15)	4 (10)	
Not indicated	33 (40)	16 (40)	
Chemotherapy was used			
Cisplatin	**31 (66)**	**11 (38)**	**0.008**
5FU	**3 (6)**	**0(0)**	
Not indicated	**13 (28)**	**18 (62)**	
Treatment interruption			
Yes	9 (12)	2 (5)	0.324
No	69 (89)	41 (95)	
Total days interrupted			
Median (IQR)	10.5 (5.0-24.0)	10.0 (5.0-15.0)	0.857

More (74%) HIV positive patients died compared to HIV negative patients (56%), **p=0.045**. There is no difference in the proportion of those who died at two years between the two groups. Less (13%) HIV positive patients were surviving at five years compared to HIV negative patients (34%), **p=0.012(table 7)**

Table 7: Cancer treatment outcomes of patients with vulvar cancer by HIV status at Kenyatta National Hospital (KNH), 2012 to 2019			
Variable	**HIV Positive N=90 n(%)**	**HIV Negative N=48 n(%)**	**P value**
What is the final treatment outcome			
Died	51 (57)	23 (48)	0.132
Alive	14 (16)	15 (31)	
Lost to follow up	16 (18)	7 (15)	
Palliative care	4 (4)	3 (6)	
Recurrence	5 (6)	0 (0)	
Outcome treatment			
Died	**55 (74)**	**23 (56)**	**0.045**
Alive	**19 (26)**	**18 (44)**	
Surviving at 2 years			
Yes	39 (56)	25 (61)	0.588
No	31 (44)	16 (39)	
Surviving at 5 years			
Yes	**8 (13)**	**12 (34)**	**0.012**
No	**54 (87)**	**23 (66)**	
5 patients had recurrence: ***Mean(SD) in months from last treatment to recurrence:*** *9.5(6.5-29.5)* ***Site of recurrence:*** *Vulvar-3 patients, labia majora-2 patients, labia minora-1 patient* ***Treatment given for recurrence:*** *Surgery-1 patient, Chemoradiation-2 patients, Radiation-2 patients*			

There is no difference in the 2 and 5-year survival between HIV positive and negative patients with vulvar cancer in KNH, log rank test p=0.211 (**Table 8, figure 2 and figure 3**)

Table 8: Two and five-year median survival time of patients with vulvar cancer by HIV status at Kenyatta National Hospital (KNH), 2012 to 2019		
HIV status	**mean survival time (95% CI)**	**Log rank test p value**
Two year mean survival		
Positive	18.3 (16.3-20.3)	0.699
Negative	18.1 (15.7-20.6)	
Five year median survival		
Positive	24.0 (19.6-28.5)	0.064
Negative	31.0 (23.4-38.6)	

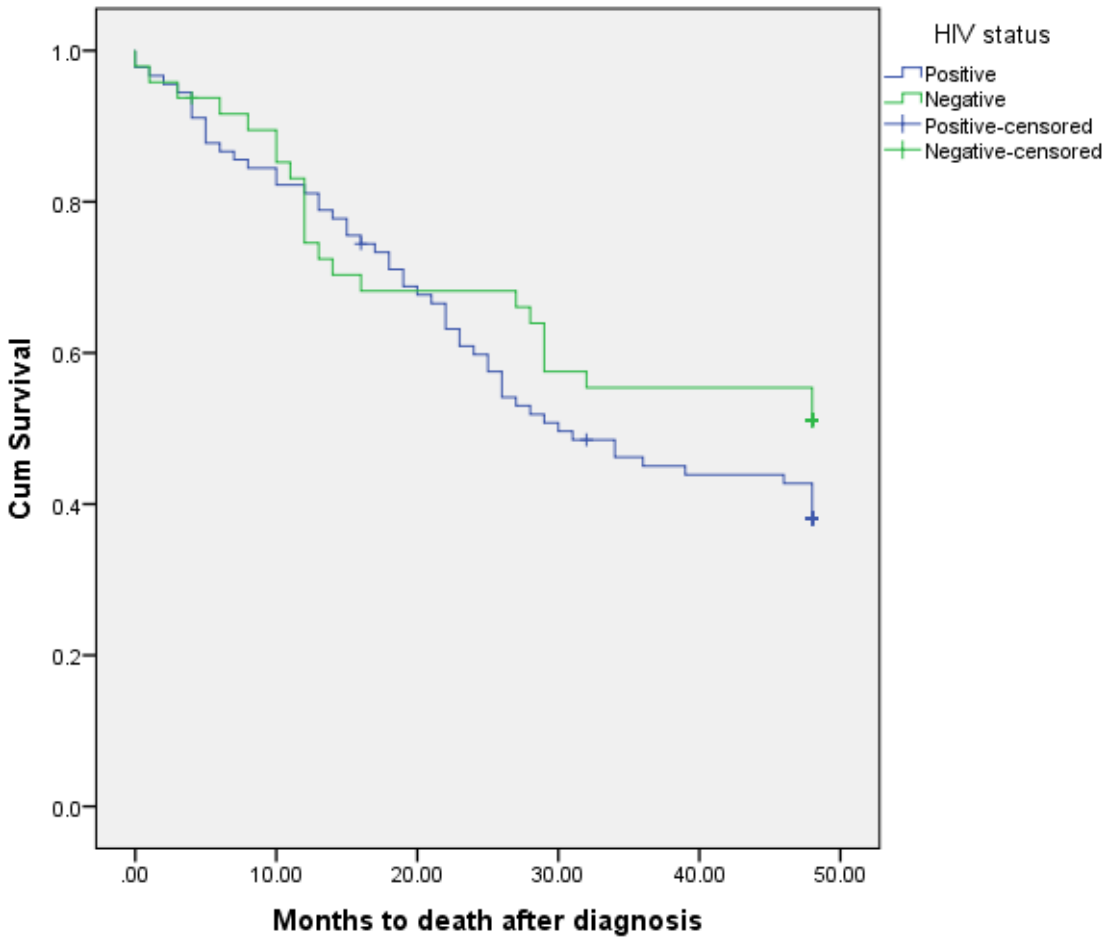

Figure 2: Kaplan Meir two year survival curves for patientswith vulvar cancer by HIV status at Kenyatta National Hospital (KNH), 2012 to 2019

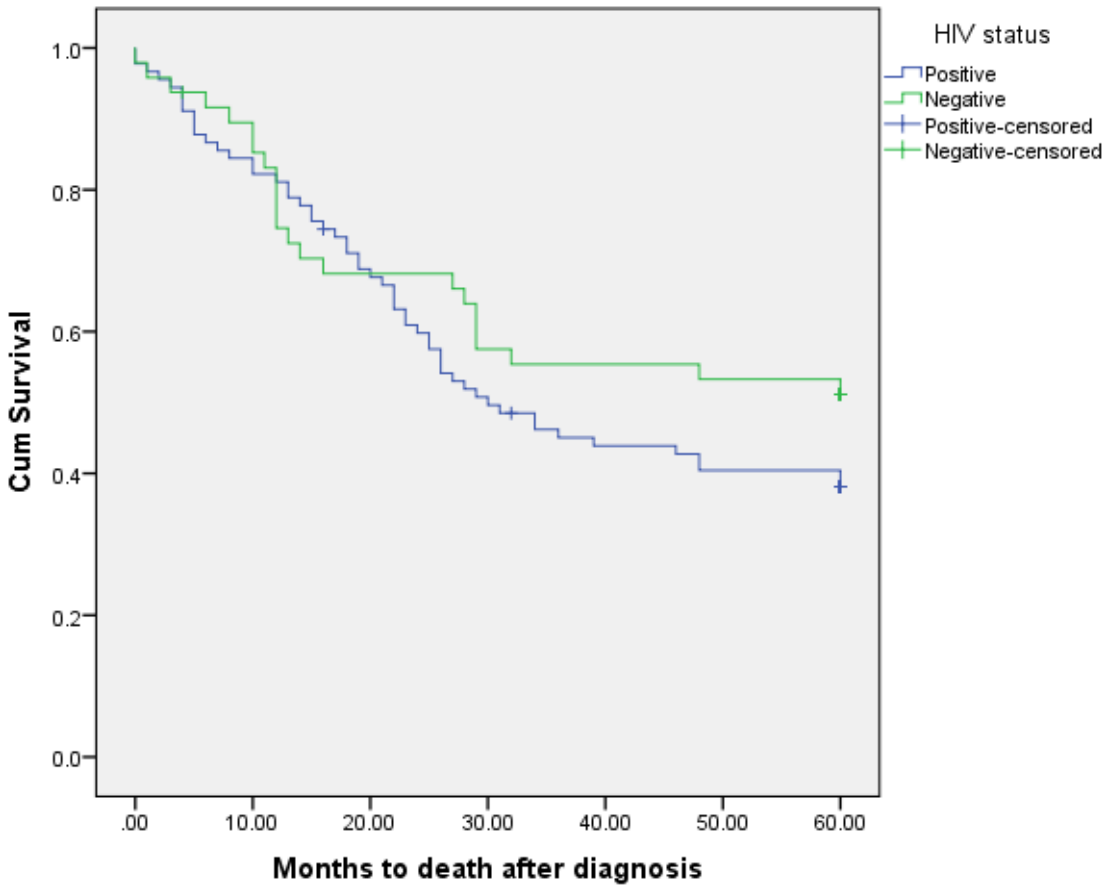

Figure 3: Kaplan Meir five year survival curves for patientswith vulvar cancer by HIV status at Kenyatta National Hospital (KNH), 2012 to 2019

CHAPTER 4: DISCUSSION

The aim for this study was to compare the clinicopathological presentation and treatment outcomes for vulvar cancer among HIV infected and non-infected patients managed at the Kenyatta National Hospital from 2012 to 2019.

There are seven main findings in this study: a) Compared to HIV negative patients, HIV positive patients were younger, less parous and used more family planning methods, b) On gross anatomical tumor types, HIV positive patients had more fungating than ulcerative types, while HIV negative patients had more ulcerative than fungating types, c) Almost all HIV positive patients had squamous cell carcinoma unlike the HIV negative patients, d) Lymphovascular space invasion occurred more in the HIV negative group, e) Majority of the HIV positive patients were of good immune status and most were on ART, f) The same cancer treatment was offered to all patients, and g) More HIV positive patients died. There was no difference in 2 year proportion of surviving patients between HIV positive and negative patients. At five years few (13%) of the HIV positive patients were still alive compare to 34% in the HIV negative group. However the 2 and 5 year survival is not different for the groups.

Compared to HIV negative patients, HIV positive patients were younger, less parous and used more family planning methods. The Mean (SD) age for the HIV positive was 42(10%) as compared to the HIV negative 63(15%). This compares with a study done in Botswana by E.MacDaffie et.al which also found out the median age in HIV positive patients to be 42 years (31).

When considering the gross anatomical tumor types, HIV positive patients had more (39%) fungating than ulcerative types, while HIV negative patients had more (73%)ulcerative than fungating types. This has also been reflected in a study done in Burkina Fuso (Nayi Zongo, et al. BMC journal 2016 – Infectious agents and cancer)of which 66% of HIV positive vulvar cancer patients presenting with ulcero-granulating (Fungating) tumour type(32). Although the stage at presentation in both groups was FIGO stage III and more, there was no statistical difference between them and this was also confirmed at definitive diagnosis as majority (26%) of HIV

positive were categorized as stage IIIA compared to only 13% of HIV negative patients.

Almost all (97%) HIV positive patients had squamous cell carcinoma unlike the HIV negative patients who also had other histologic types such as pleomorphic sarcoma, Adeno squamous, Adenocarcinoma and Basal cell carcinoma. This is also comparable to the study done by Nayi Zongo***, et al. (BMC journal2016***) which showed 20 out of 21HIV positive patients diagnosed with vulvar cancer had squamous cell carcinoma as histologictype (32).

HIV negative (31%) patients presented with lymphovascular space invasion as compared to only (16%) of the HIV positive group. This can also be explained in relation to the age of presentation in the latter group who were older and at risk of late presentation. Lymph node involvement was of no significant difference between the two groups though both groups had bilateral inguinal lymph nodes involvement at presentation at 29% and 31% for HIV infected and non-infected respectively. Histologic confirmation of lymph node involvement was at 17 % and 23% for the HIV positive and HIV negative groups respectively. A study by Katharine et.al (Gynaecologic oncology journal, 2021)found out that older women with Vulvar squamous cell carcinoma present with advanced tumour stages at first diagnosis (33). Majority (97%) of the HIV negative patients received adjuvant radiotherapy as compared to 82% from the HIV positive group.

All HIV positive patients diagnosed with vulvar cancer had a Median (IQR) CD4 count of 419 (330 – 603) cells/mm3 and all were on ART. This finding is similar to a study done by E.MacDuffie et al, (international journal of radiation Oncology 2020) in Botswana where majority (n=107, 89%) of patients with vulvar cancer were living with well-controlled HIV infection with a median CD4 count of 461 cell/ul (IQR 300.5-684.5) with high level of viral suppression (95% with viral copies <400)(31).

Though majority of the patients in this study received surgery as primary treatment (>60%), followed by adjuvant radiotherapyin both groups, there was no difference on the treatment modality used between the two groups. A South African study by *J L Butt et al*(The South African Medical Journal 2017) showed that 62.7 % of vulvar cancer patients were treated with primary surgery(34).

When comparing the survival between the two groups, this study found out that there was no difference in 2 year proportion of surviving patients. At five years few (13%) of the HIV positive patients were still alive compare to 34% in the HIV negative group. However the 2 and 5 year survival is not different for the groups, though mortality was higher (74%) in the HIV positive compared to 56% in the HIV negative group. This outcome was also well reflected in a study done by Kroeber, Eric Sven; et al, (Medicine (Baltimore), 03/2018), where the cumulative overall survival rate after 1 and 2 years in patients with vulvar cancer and HIV was 80% and 51%, respectively, with a median survival of 33 months (95% CI: 10–55). (25)

CONCLUSION

Vulvar cancer at the Kenyatta National Hospital is more common among HIV positive patients, who are younger than the HIV negative counterparts. Squamous cell carcinoma is the commonest histologic type in both groups though more in the HIV positive group. The HIV positive group are of good immunity and were all on ART. There was no difference in treatment modality between the two groups. There is no difference in the two year survival. At five years 13% and 34% are alive in the HIV positive and negative group respectively. There is a need to explore the reasons for poor survival in the HIV positive group and to follow up on their quality of live (QOL).

RECOMMENDATIONS

1. All patients with cancer vulvar should be screened for HIV infection, and HIV positive patients to be started on ART
2. All patients with HIV infection, should be evaluated for cancer of the vulvar during cervical cancer screening
3. All HIV positive patients should undergo HPV screening and those found infected be followed closely for any premalignant vulvar dysplasias.
4. Young women should be sensitized to undergo vulvar cancer/ HPV screening and also older women to present earlier for diagnosis

CHAPTER 5: REFERENCES

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CHAPTER 6: APPENDIX

Appendix 1: Data Abstraction Form

DATA ABSTRACTION FORM
A COMPARISON OF THE CLINICOPATHOLOGICAL PRESENTATION AND TREATMENT OUTCOMES OF VULVAR CANCER PATIENTS BETWEEN HIV INFECTED AND NON-INFECTED PATIENTS MANAGED AT THE KENYATTA NATIONAL HOSPITAL BETWEEN 2012 TO 2019
A. STUDY NUMBER AND DATES OF HOSPITAL VISIT AND SURGERY
1. Study number
2. Date of first hospital visit
3. Date of admission for surgery
B. SOCIO_DEMOGRAPHIC CHARACTERISTIC
1. Date of birth
2. Level of education: Primary school [ ] High school [ ] College [ ] University [ ]
3. Occupation
4. Residence
C. CLINICAL CHARACTERISTICS
1. Age in years
2. Weight (Kg)
3. Height (cm)
4. Parity: **Para _____ +_____**
5. Family planning use: YES [ ]NO [ ] **If Yes,Specify type: _____**
6. Hemoglobin (HB) level at diagnosis: **Specify value _____mg/dl**
7. HIV: **a) HIV status:** Positive [ ] Negative [ ] Unknown [ ] **b) If HIV positive:** **1st CD4 Count at Vulvar Cancer diagnosis: _____ cells/mm3** **c) Viral load: _____ copies/ml**

d) ART Use: YES [ ] No [ ] Not recorded [ ]

8. Smoking: Yes [ ] No [ ] Not recorded [ ]

If yes; period of smoking in years _____

9. History of other cancer in the patient: Yes[ ] No [ ] Not recorded [ ]

If yes; specify _____

10. **Family history of cancer:** Yes [ ] No [ ]

If yes; Specify _____

11. History of prior Genital warts in the patient: Yes [ ] No [ ] Not recorded [ ]

D. CLINICAL PRESENTATION

1. Period of onset of symptoms before presentation to hospital

0 to 3 months [ ]

3 to 6 months [ ]

6 to 12 months [ ]

More than 12 months [ ]

2. Presenting Symptoms (tick all that apply)

Irregular vaginal bleeding [ ]

Vulvarl pruritis [ ]

Vulvarl ulcer [ ]

Vulvarl swelling [ ]

Lower abdominal pain [ ]

Vulvar skin discoloration [ ]

Vulvar Bleeding [ ]

Vaginal Discharge [ ]

Dysuria [ ]

Urinary retention [ ]

Dyspareunia [ ]

Inguinal Swelling [ ]

Others [ ] Specify _____

3. Baseline laboratory investigations (record absolute numbers)

a) Full hemogram (FHG)

Hamoglobin (Hb) _____

White blood cells (WBC)_____

Platelets _____

b) Urea Electrolytes Creatinine (UEC)

Urea_____

Creatinine_____

c) Liver Function Tests (LFTs)

Alanine transaminase (ALT)_____

Aspartate aminotransferase (AST) _____

Alkaline phosphatase (ALP)_____

Gamma-glutamyl transferase (GGT) _____

Bilirubin _____

Prothrombin time (PT)_____

Albumin (ALB) _____

4. Imaging done for staging

a) Abdominopelvic Magnetic resonance imaging (MRI)

Yes [ ] No [ ]; Normal [ ] Abnormal [ ]

specify if abnormal; _____

b) Abdominopelvic Computed tomography (CT) scan

Yes [ ] No [ ]; Normal [ ] Abnormal [ ]

specify if abnormal; _____

c) Abdominopelvic Ultrasound scan

Yes [ ] No [ ]; Normal [ ] Abnormal [ ]

specify if abnormal; _____

d) Chest radiograph (CXR)

Yes [ ] No [ ]; Normal [ ] Abnormal [ ]

specify if abnormal; _____

e) Chestcomputed tomography (CT

Yes [ ] No [ ]; Normal [ ] Abnormal [ ]

Specify if abnormal; _____

5. Clinical staging

a) What kind of staging was done:

Examination Under Anesthesia [EUA] [ ]

Examination Without Anesthesia [EWA] [ ]

b) Findings during EUA or Examination without anesthesia (EWA) (tick all that apply)

Tumor location: Labia majora [ ] (Right) (Left) ; Labia Minora [ ] (Right) (Left)

Vaginal involvement: NO [ ] YES [ ] specify:

_____

Clitoris [ ] Anus [ ] Rectum [ ] Vagina [ ] Cervix [ ]

Inguinal LN [ ] Right side [ ] Left Side [ ] Both [ ] Other sites; specify_____

c) Gross tumor types: nodular [ ] fungating [ ] Infiltrative[ ] ulcerative [ ]

Other: Specify _____

d) Number of lesions: 1 [ ], 2 [ ] , 3 [ ], >4 [ ]

e) Size of tumor in cm : <1cm [ ] , 1-2 cm [ ] , 3 – 4 cm [ ], 5 – 6 [ ] , > 6cm [ ]

f) FIGO clinical staging: done : Yes [ ], No [ ]

Stage 0 [ ]

Stage IA [ ]

Stage IB [ ]

Stage II [ ]

Stage III A [ ]

Stage III B [ ]

Stage III C [ ]

Stage IV A [ ]

Stage IVB [ ]

6. Pathology examination under /without anesthesia biopsy

a) Histology report NO [ ] **YES** [ ]

Squamous cell [ ]

Basal cell carcinoma [ ]

Sarcoma [ ]

Adenocarcinoma [ ]

Melanoma [ ]

Pagets disease [ ]

Adeno-squamous [ ]

Bartholins [ ]

Basaloid [ ]

Warty carcinoma [ ]

Verrucous carcinoma [ ]

Other, specify_____

b) Histology Grade: 1 [ ], 2 [ ], 3 [ ], Not stated [ ]

c) Depth of stromal invasion: <1 mm: [ ] 1-2 mm: [ ] 3-4mm: [ ] >4mm [ ], Not stated

d) Lympho vascular space invasion(LVSI): Yes [ ]; No [ ]

e) Nodal invasion : Yes [ ] No [ ]

7. Pathology surgical specimen biopsy

a) Histology report NO [ ] **YES** [ ]

Squamous cell [ ]

Basal cell carcinoma [ ]

Sarcoma [ ]

Adenocarcinoma [ ]

Melanoma [ ]

Pagets disease [ ]

Adeno-squamous [ ]

Bartholins [ ]

Basaloid [ ]

Warty carcinoma [ ]

Verrucous carcinoma [ ]

Other, specify_____

b) Histology Grade: 1 [ ], 2 [ ], 3 [ ], Not stated [ ]

c) Depth of stromal invasion: <1 mm: [ ] 1-2 mm: [ ] 3-4mm: [ ] >4mm [ ], Not stated

d) Lympho vascular space invasion (LVSI): Yes [ ]; No [ ]

e) Nodal invasion : Yes [ ] No [ ]

E. TREATMENT GIVEN

1. Radiotherapy as primary treatment: Yes [ ] No [ ]

a) Start date of Radiotherapy treatment _____

b) Reason for radiotherapy :

Neoadjuvant [ ], Treatment [ ] , Salvage/emergency [ ], Palliative [ ] , Adjuvant [ ]

c) If salvage/emergency specify reason _____

d) Type of radiation therapy: External beam [ ] Brachytherapy [ ]

e) If external beam: Dose _____ Sessions _____Not indicated [ ]

f) External beam completed: Yes [ ] No [ ], If no give reasons;

_____

g) If brachytherapy: Dose_____ Sessions _____ Not indicated [ ]

h) Brachytherapy completed: Yes [ ] No [ ], If no give reasons;

_____

2) **Surgery given as primary treatment:** NO [ ] YES [ ]

a) **Date when surgery was done** _____

b) **Type of surgery:**

Wide local incision [ ]

Unilateral inguinal lymphadenectomy [ ]

Bilateral inguinal lymphadenectomy [ ]

Radical vulvectomy [ ]

Simple vulvectomy [ ]

Wound flap [ ]

Biopsy [ ]

c) **Post-surgical complication:** Yes [ ]; No [ ]

d) **Type of complication :**Wound breakdown [ ] Infection [ ] Lymphoedema [ ]Contractures [ ], DVT [ ] Others, Specify _____

e) **If wound break down/infection: specify site** _____

3) **Chemoradiation given:** NO [ ] YES [ ] Not indicated [ ] Completed Yes [ ] No [ ]

a) **If chemoradiation, reason for chemoradiation:** Neoadjuvant [ ], Treatment [ ] , Salvage/emergency [ ], Palliative [ ] , Adjuvant [ ]

b) **Which chemotherapy was used:** Cisplatin [ ]5FU [ ]paclitaxel/cisplatin [ ]Others [ ] specify_____ Not indicated [ ]

c) **Was there treatment interruption** YES [ ] No [ ]: If yes specify total days interrupted_____

d) **Reasons for treatment interruptions:** Lack of drugs [ ], Financial [ ], Anemia [ ], Neutropenia [ ], Thrombocytopenia [ ], Poor general condition [ ], Renal failure [ ], Liver failure [ ]Others, Specify; _____

F. TIME TO EVENTS

1. **Date when vulvarl cancer was suspected** _____
2. **Date when examination under/without anesthesia histological Diagnosis was made:** _____
3. **Date when surgery was done** _____
4. **Date of discharge after surgery** _____
5. **Date when radiotherapy was started** _____
6. **Date when radiotherapy was completed** _____
7. **Number of days from surgery to discharge from hospital** _____

8. **Status of wound at discharge from hospital:** Healed [ ], undergoing wound dressings [ ], Septic [ ] Others, specify _____

9. **Date of death** _____ Not indicated [ ]

G. TREATMENT OUTCOME

1. **When was the last date of review** _____**?**
2. **What is the final treatment outcome?:** Alive [ ] Died in hospital [ ] Lost to-follow-up [ ] Remission [ ] Resistance/ Residual [ ] Recurrence [ ] Palliative care [ ]
3. **Recurrence: Yes [ ] No [ ]** If yes, Local [ ] Distant met [ ]
   Date of recurrence diagnosis _____
4. **How long in months did it take from last treatment date to recurrence**
   _____
5. **What was the site of recurrence:** Vulvar[ ]; Clitoral [ ]; Anal [ ]; Urethral [ ] ; Labia Majora (Right) (Left) ; Labia Minora (Right) (Left) Vaginal [ ] Inguinal [ ] Pelvis [ ] Lungs [ ] Distant metastasis [ ], Specify _____
6. **What was the treatment given for recurrence:** Surgery [ ] Radiation alone [ ] Chemotherapy alone [ ], Chemoradiation [ ] Palliative ; colostomy [ ], catheterization [ ]; urinary diversion [ ] Other; specify_____

H. SURVIVAL DATA

1. **At two years after treatment**
   Cancer free [ ]
   Cancer recurrence [ ]
   Cancer persistence [ ]
   Deceased [**]**
   Unknown [**]**
2. **At five years after treatment**
   Cancer free [ ]
   Cancer recurrence [ ]
   Cancer persistence [ ]
   Deceased [**]**
   Unknown [**]**

Appendix 2: Verbal consent

PHONE CALL/VERBAL CONSENT
Management and Survival Of Cancer Of The Vulvar Among Patients With and Without HIV treated At Kenyatta National Hospital, 2012-2019
I am D.r Idyoro Ojukwu, the lead researcher in a study looking at management and follow up of patients with cancer of the vulvar treated at the Kenyatta National Hospital. This study will evaluate 100 patients who have been in care since 2012-2019, and you are one of them. Your phone number is listed in the file within the Hospital. I am calling because I need your assistance to clarify some of the information that is missing or unclear from your file. This information will help us complete the study and understand how to manage patients with cancer of the vulvar. This study has been approved by Kenyatta National Hospital/University of Nairobi Ethics & Research Committee. None of your identifying information will be collected. Information collected will be used only for purposes of this study. Your information will be kept confidential. Please note that the call may be recorded for reference purposes. The phone call will last a maximum of five minutes. Should you choose not to give any information or stop giving information at any point, it will not affect care given to you or your loved one at Kenyatta National Hospital. Do you have any questions/clarifications? I would be happy to answer the questions or clarify any concerns. Would you be willing to participate in the study and answer some questions on phone? Yes [ ] No [ ] THANK YOU FOR YOUR TIME.

KISWAHILI VERSION:

KIBALI KWA SIMU YA RUNUNU
MATIBABU NA MAISHA YA WAGONJWA WALIOTIBIWA SARATANI YA VULVAR/ SEHEMU YA UKE KATIKA HOSIPITALI KUU YA KITAIFA YA KENYATTA, MIAKA YA 2012-2019
Mimi ni Daktari Idyoro Ojukwu, mtafiti anayeongoza katika utafiti akiangalia usimamizi na ufuatiliaji wa wagonjwa walio na saratani ya uke iliyotibiwa katika Hospitali ya Kitaifa ya Kenyatta. Utafiti huu utatathmini wagonjwa 100 ambao wamekuwa katika huduma tangu 2012-2019, na wewe ni mmoja wao. Nambari yako ya simu imeorodheshwa kwenye faili ndani ya Hospitali. Ninapiga simu kwa sababu ninahitaji msaada wako kufafanua baadhi ya habari ambayo haipo au haijulikani wazi kutoka faili yako. Habari hii itatusaidia kumaliza utafiti na kuelewa jinsi ya kusimamia wagonjwa walio na saratani ya uke. Utafiti huu umeidhinishwa na Hospitali ya Kitaifa ya Kenyatta / Kamati ya Maadili na Utafiti ya Chuo Kikuu cha Nairobi. Kamati ya Maadili imetoa idhini ya kufikia faili yako. Hakuna habari yako ya kutambua itakusanywa. Habari iliyokusanywa itatumika tu kwa madhumuni ya utafiti huu. Habari yako itahifadhiwa kwa siri. Tafadhali kumbuka kuwa simu inaweza kurekodiwa kwa sababu za kumbukumbu. Simu itadumu kwa dakika tano. Iwapo utachagua kutotoa habari yoyote au kuacha kutoa habari wakati wowote, haitaathiri utunzaji unaopewa wewe au mpendwa wako katika Hospitali ya Kitaifa ya Kenyatta. Je! Una maswali / ufafanuzi wowote? Ningefurahi kujibu maswali au kufafanua wasiwasi wowote. **Je! Uko tayari kushiriki katika utafiti na kujibu maswali kadhaa kwa simu?** **NDIO ( ) LA ( )** ASANTE SANA KWA MUDA WAKO.

Appendix 3: Study Timelines and Budget

Timelines

Activity	Aug	Sep	Oct	Nov	Nov	Dec
Proposal Development						
Proposal Presentation						
Ethics Committee Review						
Data Collection						
Data Analysis						
Results Presentation						
Publication						

Budget

ACTIVITY	ITEM	KSHS
Proposal Development	Printing of data capture tools	3,000
	Printing copies of proposal	8,000
ERC	Review of proposal	2,000
Data Collection	Two research assistants @5000 per day for 10 days	50,000
	Stationery such as pens and pencils and rubbers	3,000
Data Analysis	Statistician	60,000
Thesis Development	Printing of draft theses	10,000
	Printing of final theses	10,000
	Contingency fund (10% of total budget)	19,600
	TOTAL	**167,600/=**

Appendix 4: Ethics Approval

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
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KNH-UON ERC
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Website: http://www.erc.uonbi.ac.ke
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Ref: KNH-ERC/A/153

6th May 2021

Dr. Idyoro Joseph Ojukwu
Reg. No.H117/27178/2019
(Fellowship in Gynecologic Oncology)
Dept of Obstetrics and Gynaecology
School of Medicine
College of Health Sciences
University of Nairobi

KENYATTA NATIONAL HOSPITAL
APPROVED
06 MAY 2021
KNH/UoN-ERC
P.O. BOX 20723 - 00202 NAIROBI

Dear Dr. Ojukwu

RESEARCH PROPOSAL –A COMPARISON OF THE CLINICOPATHOLOGICAL PRESENTATION AND TREATMENT OUTCOMES OF VULVAR CANCER PATIENTS BETWEEN HIV INFECTED AND NON-INFECTED PATIENTS MANAGED AT THE KENYATTA NATIONAL HOSPITAL BETWEEN 2012 TO 2019 (P607/11/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 6th May 2021 – 5th May 2022.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g. Submission of an *executive summary* report within 90 days upon completion of the study.

Protect to discover

This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website**http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information Dept, KNH
The Dean, School of Medicine, UoN
The Chair, Dept. of Obstetrics and Gynaecology, UoN
Supervisors: Prof. S.B. Ojwang, Dept.of Obstetrics and Gynaecology, UoN
Dr. Alfred Osoti, Dept. of Obstetrics and Gynaecology, UoN
Dr. Jacqueline Chesang, School of Public Health, UoN