CLINICO-PATHOLOGICAL CHARACTERISTICS, MANAGEMENT, AND SURVIVAL OF PATIENTS TREATED FOR CANCER OF THE VULVA AT KENYATTA NATIONAL HOSPITAL, KENYA; 2012- 2017

INVESTIGATOR

DR. INNOCENT ORORA MARANGA

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DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

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DECLARATION

This dissertation is my original work and references made to others' work has been clearly referenced accordingly.

DR. INNOCENT ORORA MARANGA,MBChB,PGD(STI/HIV),MMed (Obs/Gyn), MPH, PhD

SIGNATURE..DATE...**15th February 2021**

APPROVAL OF SUPERVISORS

This dissertation has been submitted with the approval of my supervisors.

Signature .... Date ...15/11/2021...

PROFESSOR S.B.O OJWANG

MD, MMed, (Obs/Gyn), Higher Dip Gynecologic Oncology (Umea University and Karolinska Institute, Sweden), Professor of Gynecologic Oncology,

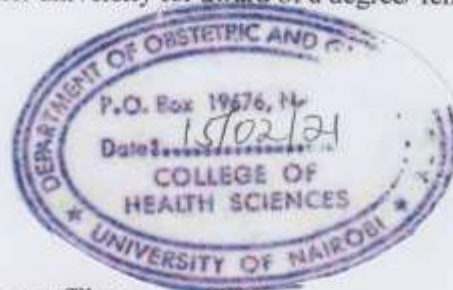Department of Obstetrics and Gynaecology

University of Nairobi

Signature   Date: **15th February 2021**

DR. GEORGE GWAKO, MBChB, MMed (Obs/Gyn), PhD

Lecturer, Department of Obstetrics and Gynaecology,

University of Nairobi.

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CERTIFICATE OF AUTHENTICITY

This is to certify that this dissertation is the original work of Dr Innocent Orora Maranga, Fellow in Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Nairobi, registration number H117/27792/2019. The study was carried out in the Department of Obstetrics and Gynecology, School of Medicine, College of Health Sciences/ Kenyatta National Hospital. It has not been presented in any other university for award of a degree/ fellowship.

Signature _____ Date 15TH February 2021

PROF. OMONDI OGUTU ,MBChB, M.Med (OBS&GYN), PGDRM,FCOG (ECSA)

Associate Professor and Chairman Department of Obstetrics and Gynaecology, University of Nairobi.

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DEDICATION

In memory of the late Dr Medhat Mohamed Amin, the finest Gynaecologic oncology surgeon, whom I had the privilege of calling my mentor. You positively impacted on so many students, residents, fellows, colleagues and patients alike. Your memory will live on forever.

LIST OF ABBREVIATIONS

AJCC	American Joint Committee on Cancer
ART	Anti-retroviral Therapy
BCC	Basal Cell Carcinoma
CRT	Chemo Radiotherapy
CV	Cancer of the Vulva
FIGO	International Federation of Gynecology and Obstetrics
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSIL	High Grade Squamous Intraepithelial Lesion
ILND	Inguinal Lymphnode Dissection
IFLND	Inguino-Femoral Lymphnode Dissection
KMTC	Kenya Medical Training College
KNH	Kenyatta National Hospital
LSIL	Low-grade Squamous Intraepithelial Lesions
LVSI	Lymphovascular Space Invasion
PLND	Pelvic Lymph Node Dissection
SCC	Squamous Cell Carcinoma
SEER	Surveillance, Epidemiology and End Results Program
TNM	Tumour, Node, Metastasis Staging System
UICC	International Union Against Cancer
UoN	University of Nairobi
VIN	Vulvar Intraepithelial Neoplasia
VC	Vulvar Cancer
WLE	Wide Lesion Excision

OPERATIONAL DEFINITIONS

Vulvar LSIL lesions –are benign manifestations of the skin's reaction to an HPV infection; they are often self-limited.

Vulvar HSIL —is often multifocal. The interlabial grooves, posterior fourchette, and perineum are most frequently affected by multifocal lesions; more extensive disease is often confluent, involving the labia majora, minora, and perianal skin. Confluent or multifocal lesions exist in up to two-thirds of women with VIN. HSIL lesion can exist as warty or basaloid VIN or mixture of both.

Differentiated VIN — Differentiated VIN comprises less than 5 percent of VIN and typically occurs in postmenopausal women. It is usually unifocal and unicentric and is often associated with lichen sclerosis, but not with HPV infection.

Simple Vulvectomy — Simple, or total, vulvectomy refers to removal of the entire vulva together with perineal tissues, as indicated, and usually includes some subcutaneous tissue.It may be performed for benign and premalignant conditions of the vulva that are extensive or multifocal.

Radical Vulvectomy – this includes removal of skin and deep subcutaneous tissue up to the perineal fascia. An inguinofemoral lymphadenectomy may be performed ipsilaterally or bilaterally.

Wide Local Excision — is defined as excision of an individual lesion with a 1 cm margin followed by reapproximation of the defect generally provides satisfactory cosmetic results.Regarding depth of excision, removal of the epidermis provides sufficient depth for treatment of VIN as long as the margins are clear.

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ABSTRACT

Introduction: Cancer of the vulva (CV) is the fourth most common gynecologic cancer in high economic countries and it causes about 5-6% of the all the female genital tract malignancies. Among the types of histologic vulvar cancer, squamous cell carcinoma is the most common representing almost 90% of all the cases. Clinical presentation includes vulvar itchiness, vulvar growth, ulceration and inguinal lymphadenopathy. Most women with vulvar cancer are diagnosed at an early stage. Traditional management includes radical vulvectomy with inguinal nodedissection, adjuvantradiotherapy and chemotherapy. The reported cumulative overall 5-year survival rate in the high resource countries is 72% while the 2-year survival rate in low resource countries is 51%, with a median survival of 33 months. Due to paucity of data in African region, this study aimed at describing the clinic-pathological characteristics, management and survival of patients suffering from cancer of the vulva at the Kenyatta National Hospital, Kenya.

Objectives of the Study: To determine the clinico-pathological characteristics, management and 2- and 5-year survival of patients with cancer of the vulva at the Kenyatta National Hospital Gynecologic Oncology Unit between 2012- 2017.

Methodology: Data was collected using the Data Abstraction tool, entered into excel sheet and analyzed using STATA ver.16 software. Descriptive statistics for the socio demographic characteristics and clinico-pathological presentation including management modalities were done and presented using means, variance and standard deviation. Kaplan Myer curve were used to present 2- and 5-year survival rates, taking a p value of less than 0.05 to be significant statistically.

Results: Secondary data and phone calls on clinico-pathological characteristics, the management and Survival of 104 patients treated for cancer of the vulva at the KNH between 2012 to 2017 were reviewed. The median age for the participants was 47 years (IQR 38.0 – 58.5); 78.5% were diagnosed with stage III or Stage IV cancer; data on FIGO staging of half of the patients (53/104) were not available; (60.5%) were HIV positive and 96.2% of these were on ART; 93.3% patients had vulvar lesions/swelling; 23.1% had vulvar itch; 25.0% had inguinal lymph node on the left side and a similar percentage had on the right side; 89.2% had squamous cell carcinoma. A minority of the patients had LVSI (17.3%) and nodal invasion (17.2%); 85.6% (89/104) of pathologist reports had no grading done; more than two-thirds (68.0%) had involvement in the vagina, 38% in the anus and 18% in the clitoris. The most common type of tumor was the ulcerative type (71.2%), followed by fungating type (23.1%) and infiltrative type (8.7%). Almost all patients (98.0%) were examined under anesthesia and over half (52.0%) were determined to be at stage III (i.e. stages 3, 3A and 3B). The primary treatment was radiotherapy in 75.5%; 27%received chemotherapy. By the end of the study period, 29.8% of the patients had died, 26.0% were still alive while the 44.2%were lost to follow-up. Two- year survival rate was 71% while the five-year survival rate was 45%. Patients with FIGO stage 4 appear to have the worst survival experience (i.e. highest failure rate). The results from log-rank test revealed that there was no significant difference in the Survival of the patients by FIGO stage (P-value=0.200)

Conclusion: In patients present in late stage with a diagnosis of cancer of the vulva, majority are treated using radiotherapy and though not significant statistically, tumor stage and size influenced survival with a 2- and 5-year survival rate of 71% and 45% respectively.

Recommendations: Efforts be put in place to enhance early diagnosis of vulva cancer, early initiation of effective treatment and follow up.

Key Words: Cancer of the Vulva, Staging, Clinico-pathological Characteristics, Management, Survival.

CHAPTER ONE: INTRODUCTION

1.0 Background

Cancer of the vulva (CV), mostly occurs in elderly women, is an uncommon tumor representing less than 1% of all the cancers in women and only about 5% of all the gynecologic malignancies(1). Vulvar cancer can be seen in both old and young women due to its bimodal age distribution. Those women tend to have certain risk factors such as vulvar skin infection (lichen sclerosis), smoking, and HPV infection. Cancer of the vulva can be present in the patient even with certain subtle symptoms such as dysuria or pruritus. Therefore, it is necessary that there is enough recognition and awareness surrounding the disease since it can be treated successfully when diagnosed early. Likewise, the treatment morbidity and mortality are correlated with the clinico-pathological presentation at diagnosis(2).

Vulvar carcinoma is surgically staged, and in 2009 there was an update to the prognostic factors (2). Treatment of vulvar cancer has continued to evolve through the years to improve the rate of cures through techniques that are more conservative emphasizing minimal morbidity (2).

1.2 Etiology and Pathophysiology

Squamous cell carcinoma contributes to over 90% of vulvar cancers, althoughbasal cell carcinoma, Bartholin gland adenocarcinoma,melanoma,Paget disease, and sarcoma can occur(2). Associated risk factors that leads to the development of vulvar cancer are lichen sclerosis, smoking, HPV infection, cervical neoplasia, immunosuppression, and ancestry from northern Europe. Squamous cell carcinomas (SCC) can either be seen in keratinizing or HPV infected younger women as a basaloid or warty type carcinomas, or as associated in skin diseases found in older people such as lichen sclerosus(3).

Other risk factors of vulvar cancer (VC) include genital warts, cervical neoplasm, shorter education, lower household income, low social economic status, high number of sexual partner, early age at first sexual intercourse and cigarette smoking (4).

1.3 Clinical Presentation and Assessment

Most vulvar cancers present as a mass on the vulva that can either have discharge or dysuria, or as a palpable lump(5). The labial agglutinations from surrounding dystrophy may however make it difficult to visualize the lesions(2). In another study vulvar pruritis dominated the symptomatology(48.7%) and the tumor size was in average size 3.96cm(6). The mean age of the study diagnosis was 67.1 years. Rarely, vulvar cancers are asymptomatic(2).

Prior to treatment, the patient must be evaluated on their history, a physical exam, and a functional status. Vulvar cancer tends to spread into the surrounding direct tissues and also through the tumor emboli which first spreads into the lymph nodes. There needs to be a size evaluation of the tumor relative to the position of other sensitive organs such as the anus, vagina, urethra, and its bone fixation. Coexistent neoplasia should be looked for in the perianal skin, the vagina, and the cervix.

The patients that experience a significant discomfort should be subjected to an examination under anesthesia (EUA). In case the cancer is at an advanced age, a proctoscopy or cystoscopy should be used to determine the disease extent. Multiple biopsies are necessary in the determination of the boundaries of the tumor since vulvar cancer is multifocal and it tends to arise due to infections of the skin, HPV, and intraepithelial neoplasia (VIN) in order to plan for the correct treatment plan.

There may be a need for tumor imaging in the case of a large tumor or when there is a metastasis to the pelvic node. The anatomic extent of the tumors can be defined by using a magnetic resonance imaging (MRI). When there isn't enough evidence available for vulvar carcinoma, there is need forevaluation using a PET scan in the detection of distant spread including lymph node metastases(7).

1.6: Diagnostic Criteria of Cancer of the Vulva

In order to make a diagnosis, suspicious looking lesions should be biopsied; this may necessitate several biopsies on multiple sites or on the same region repeatedly. Repeat biopsy is recommended whenever a clinically suspicious lesion does not correlate with the pathology(2).The initial examination should involve the entire vulva examination since in only 13% of the cases, lower genital tract neoplasia is present. It's therefore vital to look for any multifocal lesions in the vagina and cervix (2).

1.7: Staging of Cancer of the Vulva

The American Joint Committee on Cancer (AJCC) TNM staging system and the International Federation of Gynecology and Obstetrics (FIGO) staging systems are used to stage vulvar cancer. These systems are similar since they classify vulvar cancer using three factors: tumor size (T), spread of the cancer to the lymph nodes (N), and its spread (M, metastasis). The final diagnosis depends on the specimen's histopathologic evaluation.

Prognosis and the treatment options are defined by the assignment of a stage to the vulvar cancer. This process allows the oncologist to be able to communicate effectively with the patients and their family. Surgical staging includes both the nodes involvement and the depth of invasion assessment

Table 1 shows the Staging system adopted by FIGO, AJCC, and UICC(8).

Primary tumor (T)

TNM categories	FIGO stages	Definition	Surgery
TX		Primary tumor cannot be assessed	
T0		No evidence of primary tumor	
Tis		Carcinoma in situ	
T1a	IA	Lesions 2 cm or less in size, confined to the vulva or perineum and with stromal invasion 1.0 mm or less	WLE, no LNE
T1b	IB	Lesions more than 2 cm size or any size with stromal invasion more than 1.0 mm, confined to the vulva or perineum	WLE, LNE ipsilateral
T2	II	Tumor of any size with extension to adjacent perineal structures (lower/distal 1/3 urethra, lower/distal 1/3 vagina, anal involvement)	Modified radical vulvectomy (hemivulvectomy, anterior or posterior vulvectomy), LNE bilateral
T3	IVA	Tumor of any size with extension to any of the following: upper/proximal 2/3 urethra, upper/proximal 2/3 vagina, bladder mucosa, rectal mucosa or fixed to pelvic bone	Neoadjuvant chemoradiation and selected surgery, no LNE
Regional lymph nodes (N)			
NX		Regional lymph nodes cannot be assessed	
N0		No regional lymph node metastasis	
N1		One or two regional lymph nodes with the following features	
N1a	IIIA	One or two node metastases, each 5 mm or less	
N1b	IIIA	One lymph node metastasis 5 mm or greater	
N2	IIIB	Regional lymph node metastasis with the following features	
N2a	IIIB	Three or more lymph node metastases each less than 5 mm	
N2b	IIIB	Two or more lymph node metastases 5 mm or greater	
N2c	IIIC	Lymph node metastasis with extracapsular spread	
N3	IVA	Fixed or ulcerated regional lymph node metastasis	
Distant metastasis (M)			
M0		No distant metastasis	
M1	IVB	Distant metastasis (including pelvic lymph node metastasis)	

Abbreviations: WLE, wide local excision; LNE, lymphonodectomy; FIGO, International Federation of Gynecology and Obstetrics.

CHAPTER TWO: LITERATURE REVIEW

2.1 Epidemiology of Cancer of the Vulva

Vulvar cancer has been on the rise throughout the years even though it still remains to be a rare cancer entity (9).An estimated 3500 women in the US were diagnosed with vulvar cancer and 880 of them died in 2007. In 2016, this number increased tremendously to about 5950 and around 1110 deaths (1). Among the East African countries of Malawi, Zimbabwe, and Uganda, incidence rates per 100,000 women was 1.0, 1.1, and 0.6yearly, respectively(5). In Kenya, the incidence of vulvar cancer is not clearly documented.

The median age was found to be 68 years of the diagnosis in the SEER (Survellance, Epidemiology and End Result Program) population between 2009 and 2013 (10). Lai et al reported that there was a significant rise in younger women in England aged between 30-59 years from 1990-2009. This was attributed to the high numbers of cancers that are as a result of HPV (11). The main objective of the study is to look into what constitutes the first insights into vulvar cancer (VC) incidence, the characteristics of the tumor, the demographics of the patients, management, and resulting overall survival in Kenya.

2.2 Clinico-Pathological Characteristics of Patients with Cancer ofthe Vulva

Several studies have been done to describe the clinicopathological presentation of patients with vulvar cancer and the association with treatment and survival outcomes. In a study conducted by Kroeber in Ethiopia, where the median age was 39 years, HIV prevalence was 83% (n=29), while the 1- year survival rate was 80% and the 2-year survival rate was 51% (11).

2.2.1 Age

The vulvar median age for diagnosis has reduced over the years due the growing number of cancer cases related to HPV (12). In a study done by Kroeber in Ethiopia, the median age of the patients was 38 years; the study group was younger than the patients in studies done in developed countries: for example, the United States (SEER) where the median age was 68 years(10) and in Germany showed a median age change from 65.2

years in 1980s to 57.1 years in the early 2000s. People under the age of 50 years who were diagnosed were only 11% but it shot to 41% mainly due to the increase in the high numbers of HPV related cancers (10).

2.2.2 HIV Infection

The infection by HIV has over time been highly associated with the development of vulvar cancer; this is especially for the age group below 40 years and those with weaker immune system (13). In a study done by Kroeger in Ethiopia, where patients with vulvar cancer were assessed, an estimated proportion of 57% were HIV infected(5). This estimate coincides with the data obtained in Cape Town South Africa; where in 2014 the proportion was 50% and 40% in 2015 of the vulva cancer patients testing positive for HIV (5).

There is however a postulated low risk for the development of VC among HIV infected patients in effective ART; neither is there effect on their overall survival(5). Studies conducted in Uganda and Ethiopia showed that there was a low HIV morbidity rate 2 years after ART initiation (14).The patients who are HIV-positive should be checked for vulvar cancer and should be screened for cervical cancer (5).

2.2.3 Disease Stage at Presentation

The clinical stage at presentation varies across different regions. Patients in the more developed countries with better access to health services are likely to present earlier on compared to those in less developed countries. In a study by Kroeger in Ethiopia, only one patient out of the 5 (20%)met the FIGO criteria for stage 1 as compared to 43% of patients in a similar study in Europe that had FIGO stage 1(15).In Ghana, 75% of the patients presented with stage 3 and 4 disease(8).

2.2.4 Other Associated Factors

One major risk factor of vulvar cancer is the **Human Papilloma Virus** infection (HPV) that contributes to almost 67% of all the cases reported (16). The geno-types often involved are 6 & 11. Another major risk is tobacco **Smoking**in women(16) and the **Precancerous conditions** of the vulva. These conditions include

Vulva Intra epithelial Neoplasia (VIN), Paget's disease, Lichen Sclerosus and melanoma and other gynecological cancers such as cervical cancer, vaginal cancer (16)

2.3 Management of Cancer of the Vulva

Vulvar cancer treatment was mostly surgical, but lately, chemotherapy and radiation therapy have been integrated progressively over the last two decades into the treatment protocol (17). Therefore, the management of the cancer has evolved into a multidisciplinary individualizedapproach, andthus they should be referred to a center specialized in management of gynecological cancers with relevant expertise in vulvar cancer(18).

The likelihood of an adequate surgical resection is a dependent choice between radiation and surgery as one of the primary modalities. It also leads to the ability of preserving the function of the bladder, anal, and rectal along with chemo-radiation (2). Available options in the treatment for the disease include chemo-sensitization of radiation therapywith 5-fluorouracil and cisplatinbased chemotherapy in the neoadjuvant set-up, either as being definitive or palliative. However, they require long treatments due to the toxicities that fraught them (8).

2.3.1 Early Disease
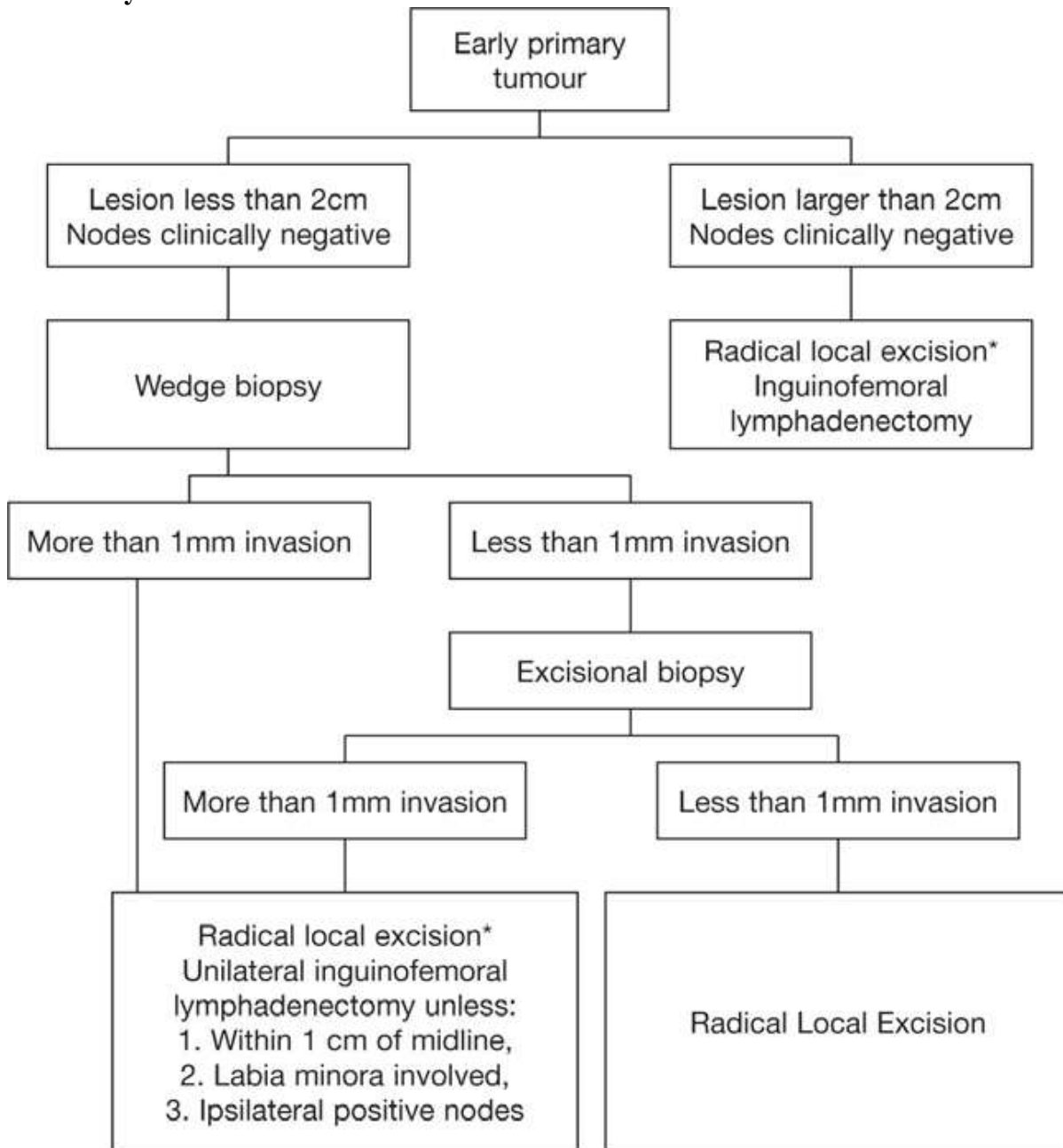
*Figure 1: Management of early vulvar cancer *If there is associated VIN or lichen*

The small vulvar tumors with diameter<2cm, tend to have an invasion of 1 mm and have no lympho-vascular space involvement, and hence treated with wide deep excisions. This group of patients have a <1% lymphatic dissemination hence do not require lymph node evaluation (19).

Stage I tumors that have stromal invasion of >1 mm, have treatment that can be accomplished by lymph node assessment and a wide excision. The radical wide excisions involve an incision of 2 cm around the tumor

margin and the subcutaneous fat excision up to the perineal fascial layer. The location of the tumor coupled with positive nodes determine the extent of the assessment of the lymph node. Laterization of the tumor in the midline structures from the clitoris to the urethra means that assessment of the unilateral node will not be sufficient, with the assumption that the removed nodes are negative for tumor. An assessment of the bilateral inguinal nodes should be done if there exists positive ipsilateral nodes or midline structure involvement(2).

2.3.2 Larger Stage I and II tumors

The vulva cancers that are >2 cm or the tumors that are adjacent to the midline vulvar structures, the treatment that was used was a radical vulvectomy and inguinal node dissection that included a "butterfly" incision. The cancer has to be removed en bloc hence the need to totally remove the skin in the adjacent areas surrounding the vulva, the perineal fascia, and the pubic rami. Although this approach led to many individuals being cured, it also has increased morbidity including infections, loss of sexual function, and wound breakdowns (2).

The radical approach used may fail to control the disease if there are inadequate margins around the disease. Surgical excision is done when there is comparison of the en bloc approach to the radical local resection, with lateral margins 1 cm deep and having not showed any considerable treatment outcome through the radical resection (20).

2.3.3 Sentinel Lymph Node Dissection

There is a probability that around 30-40% of patients are at risk of infection due to inguinofemoral lymphadenectomy being highly morbid and a 30% risk of chronic lymphedema(21). There is a 25-30% probability that for women in Stage I or II cancer, they will develop lymph node metastases. However, the standard care used is inguinofemoral lymphadenectomy since the unrecognized groin metastases are usually fatal (22).

In order to optimize the detection of sentinel lymph nodes, lymphatic mapping is performed with lymphoscintigraphy and intraoperatively with blue dye as well as radio-localization (23).Blue dye injections and radionuclide are used when doing biopsies on the sentinel lymph node prior tothe primary tumor resection (23).

The Gynecologic Oncology Group (GOG) 173 reported a sensitivity of 92% after comparing sentinel lymph node biopsy with full lymphadenectomy with a 96% negative predictive value mostly in women having a unifocal and lateral tumors less than 4cm. Therefore, in patients that are well-selected and in expertise centers specializing in biopsy of the sentinel lymph node, the procedure becomes a good alternative due to its less morbidity as compared to a full inguinal lymphadenectomy(2).

2.3.4 Advanced Vulvar Cancers: Clinical Stage III/IV

Following an inguinofemoral dissection, the patient can be diagnosed withStage III of vulvar cancer. The number of positive nodes will determine the treatment. The treatment may be either a local groin radiation or observation. Observation is done when the patients present fewer than two nodes or those that contain a metastasis less than 5mm needing no additional treatment since they have a low risk of pelvic modal metastasis (2).
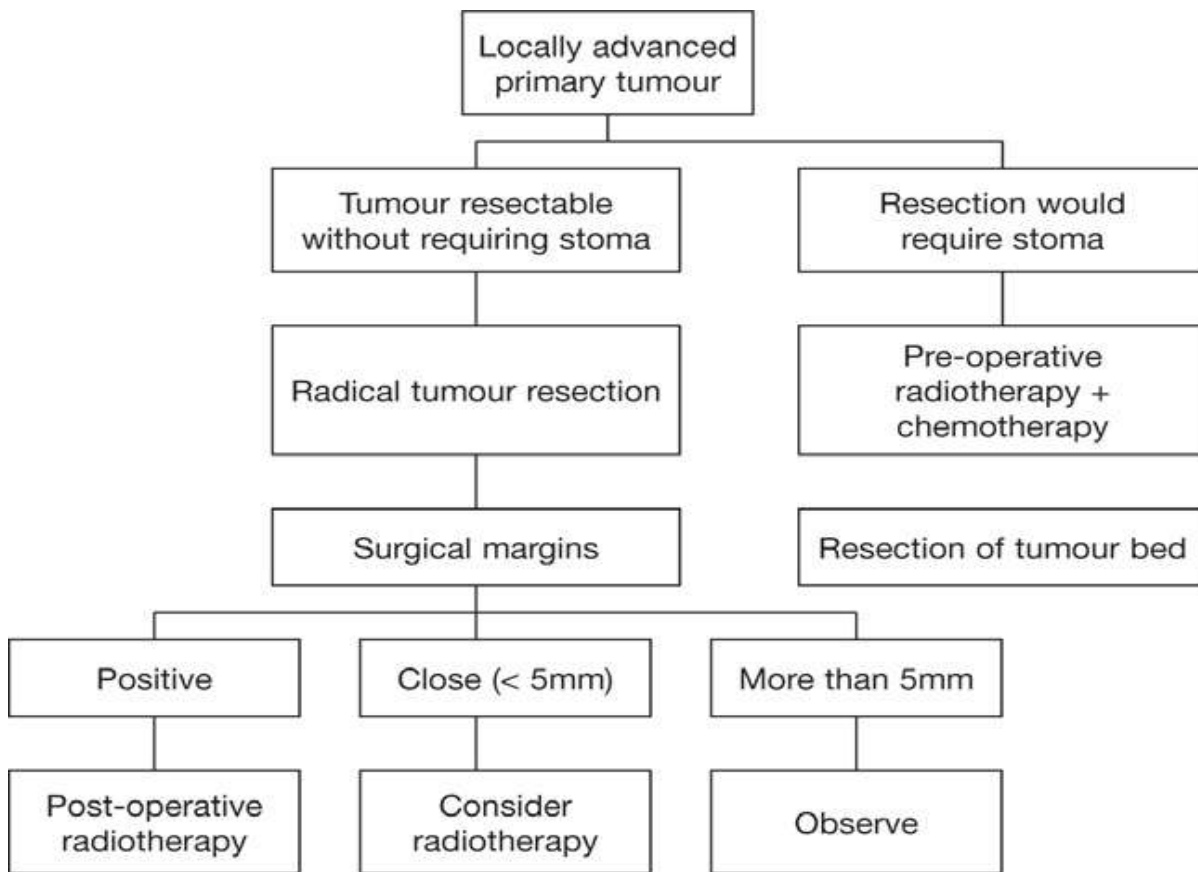
Figure: 2. Management of advanced vulvar cancer

Similarly, observation can be done on the women who present with one positive inguinal node that doesn't have extracapsular infiltration. Pelvic and groin radiation therapy is needed for women who have nodal metastases. The risk of lymphedema increases with an increase in treatment either surgical or radiation therapy, and counseling is needed regarding this issue.

Adjuvant radiotherapy has evolved to include; positive surgical margins, lympho-vascular space invasion (LVSI), nodal tumour thickness ≥5 mm as well as any lymph node macro metastasis ≥5 mm, two or more lymph node micro metastases (5 mm) and any extra capsular spread (8).

2.4. Survival of Cancer of the Vulva Patients

Survival of patients with vulvar cancer (VC) is dependent on an inter-play of both patient level and health system factors. The extent of adjacent organs involved, tumor size, the stage of the disease, and the nodes involvement are key considerations (2).

2.4.1 Health System Factors

A critical factor contributing to survival of patients is the waiting time to definitive management. This can be attributable to patient level factors such as inability to pay for the services and health system factors such as lack of radiotherapy machines and oncology specialties. A study in Ethiopia showed that there is an increased FIGO stage especially between diagnosis and treatment (3.8 months) (24). In a similar study conducted in Ghana, the average was 52.2 days between diagnosis and admittance, largely due to complicated referral systems (8).

Patients who received standard diagnosis and treatment with radiotherapy in time tended to have longer survival (HR 0.36; 95% CI, 0.14–0.90). Chemotherapy has a prolonged survival of (HRs 0.44, 95% CI, 0.19–1.03) and surgery a prolonged survival of a (0.42; 95% CI, 0.15–1.12, respectively) (2).

Cost of care influences the adherence to treatment and subsequent survival of the patients with vulvar cancer (VC). In countries where the health insurance both national and private does not completely cover the cost of cancer treatment, out of pocket payment is required along with long travels for treatment. With this type of payment method, there exist high default rates (8).

The type of treatment and associated complications also influence the survival of the patients with vulvar cancer. The standard care for vulva carcinoma has always been inguinal lymphadenectomy and radical vulvectomy which resulted in a 90% survival rate but was also associated with both emotional and physical sequelae (8). In Ghana, the local recurrence is about 6-7% and disease survival rates are about 98-99% (8). In Ghana, 87% of the patients had radiotherapy interruptions during the treatment, averaging 6-120 days (8).

2.4.2 Disease Recurrence

Disease recurrence is a measure of treatment success and may occur either due to disease progression or new development. In about 26-37% of all the cases, there is a relapse of the vulva squamous cell carcinoma, and in

about two years of treatment, there develops about 40-60% failures and they are mostly local (25). A report by an Italian Cancer Task Force [CTF] study showed that in 37.2% of women in the study (187 out of 502), there was a recurring of tumor (25). In 53.4% of the cases the site of failure was the perineal area, in 18.8% it was the inguinal, in 5.7% it was the pelvic, in 7.9% it was distant, and in 14.2% it was multiple. Most of the isolated recurrences tend to be more common in patients who have negative lymph nodes and Stage I cancer, and multiple failures become often in those patients who have advanced stage disease (26).

In vulvar cancer, the status of the lymph node is the most reliablefactor for assessing the prognosis(27,28). In patients having negative nodes, the five year survival rate is estimated between 70-98% and it reduces to about 12-41% to the patients who have metastatic nodes. A histological grade, size of the tumor, the depth of stromal invasion, and LVSI determine the incidence of positive groin lymph nodes (18,29). A study by the Gynecological Oncology Group [GOG] showed that tumors ≤2 cm diameter had a 18.9% groin node metastasis rate and for larger tumors, the rates increased to 41.6% with independent predictors of nodal involvementbeing; suspicious or fixed/-ulcerated nodes($p < 0.0001$), LVSI ($p < 0.0001$), older age ($p = 0.0002$) andgreater tumor invasion ($p = 0.03$) (28).

2.4.3 FIGO Stage

The stage of the tumor tends to be a prognostic variable that is always independent (30,31). In the FIGO Annual Report (32), stage I cancer had a 5-year survival rate of 78.5%, stage II was 58.8% (HR = 1.9, 95% CI = 1.4–2.7), stage III was 43.3% (HR = 3.3, 95% CI = 2.4–4.7), stage IV was 13% (HR = 12.4, 95% CI = 8.3–18.5) (31), according to the FIGO classification of 1988. A new and revised classification by FIGO was introduced in 2009 (33). Any tumors that have negative lymph nodes and are in the lower regions of the vulva, vagina, and anus are now considered as stage II since their clinical outcome is satisfactory (34).

Surgical evaluation of lymph nodes combined with radical local excisions in the early-stage vulva cancer results in a low morbidity and higher cure rates (5). In advanced disease however, the recommendation is use

of chemoradiation and surgery (2). The diagnosis from 2006 to 2012 in the US, based on the SEER program 18 databases, regarding the 5-year relative rate of VC patients, is 71.9% (10). In England, population-based data of patients diagnosed between 2007 and 2009 showed a 1-year survival rate of 85.2% (11). A study conducted by Homesley et al (33) showed that minimal risk patients had a 98% 5-year survival rate as compared to 29% of high-risk patients (5).

2.4.4 Parameters Relative to the Primary Tumor

In several series, there was no prognostic value of significance of the tumor grade (26) when it is was compared to the outcome of the study of Podratz et al. (30), and there was a significantprognosis in the study of Lavie et al.(35). Some authors (26,36)found that the survival at the univariate analysis was related to LVSI, while other authors (37)indicated it as an independent factors on determining prognosis (38).

In a study conducted by Nola et al. (39)there was a 87.3% 5-year survival rate for the patients who had a stromal invasion of ≤5mm and a 13.3% for the patients who had a more invasive stromal invasion that was significant ($p < 0.001$) while the difference was significant at multivariate analysis ($p < 0.001$). Nicoletto et al. findings showed another independent prognostic factor for relapse-free was stromal invasion of >9mm (40).

Furthermore, majority of the previous studies have not indicated a single relevant prognostic factor for the extent of stromal invasion (29). An unfavorable clinical outcome is associated with an increased angiogenesis and altered characteristic of the vessels(26). A significantly high micro-vessel density [MVD] might not be a good predictivefactor(26). In Obermair et al.study involving 25 patients, a 10-year survival rate for low MVD and high MVD group was 85.7% and 37.5% respectively ($p = 0.01$) (26).

2.4.5 Patient Age

Some of the authors reported that there was worse prognosis with an increased age (37) and others didn't detect any prognostic relevance with the age of the patient (41). A study by Raspagliesi et al. showed a 100%

10-year survival rate in patients< 30 years and it decreased to 53% in patients > 60 years ($p = 0.002$)(37). However, statistical significance was failed to be achieved using this parameter when conducted using a multivariate analysis that included status of the lymph nodes and LVSI in addition to age. According to Burger et al. (35), patients 72 years old had a 80% 5-year survival rate and those older had a 49% survival rate ($p = 0.001$); but it didn't become significant even after a suboptimal tumor therapy correction (38).

2.4.6 Biological Variables

Blood Variables

Thrombocytosis and anaemia have been investigated and found to be possible pointers to metastatic disease(38). Thrombocytosis can be due to biological events cascade that are correlated with tumor aggressiveness (42), whereas an increased proliferation of the tumor cell, a decrease in therapy resistance, apoptosis signal cell response, angiogenesis enhancement, and an increased metastatic potential is due to anemia and hypoxia (43). A higher positive groin lymph nodes incidence is a sign of anemia mostly in vulvar squamous cell carcinoma patients (43). Hefler et al. reported that hemoglobin levels <12 g/dl had a correlation with a low univariate analysis survival ($p = 0.002$) (44).

The VEGF (vascular endothelial growth factor) levels that are elevated (>445 pg/ml) are linked with a shortened survival that is disease-free ($p = 0.03$). There still exists a controversy between the SCC (squamous cell carcinoma antigen) levels and clinico-pathological parameters correlation (45). Hefler et al. showed that in 61 patients suffering from pT1 and pT2 disease who surgery was done, showed that the levels of SCC were not in tandem with the status of the lymph nodes (44).

Tissue Variables

The vulvar cancer rate of aneuploidy ranges from 13-83%, but it has failed to be detected in most of the studies especially between the clinical outcome and DNA content relationship (44).According to Lerma et al. only 28

patients suffering from stages I and II of the cancer correlated significantly with univariate analysis survived (46).

In 26–80% of vulvar cancer patients, there has been reported a P53 over-expression and/or mutation (47). The main difference between basaloid or warty carcinomas and differentiated kertinizing neoplasm is that that p16 positive and p53 negative and converse respectively. In some studies, p53 expression was reported as a poor predictive biomarker (46). According to Hoffmann et al. in patients with a p53 expression that was less than 122 pg/mg, the median survival rate was shorter than those who had a lower expression, and the Ki-67 had no impact on the patient's survival(48).

According to Fons et al. there was a 86% 5-year survival rate on the assessed 50 vulvectomy specimens, with caspase-3 positive tumors against a survival rate of 64% for patients having a caspase 3-negative tumors (49). Good caspase-3 immunostaining was establishto be an independent positive prognostic factor for survival (HR = 0.2, 95% CI = 0.04–0.97) (49).

2.5Conceptual Framework

2.5.1 Narrative

Cancer of the vulvar is more common among elderly women who present with history of vulvar itchiness and growth. The diagnosis entails performing general clinical examination, biopsy for histological diagnosis and staging. Investigations that are routinely done to complement the diagnosis include kidney and liver function tests, hemogram, pelvic and chest imaging as may be indicated. Surgery is the mainstay of management and based on the disease stage, radiotherapy and or chemotherapy in addition to other supportive treatment such as blood transfusion whenever indicated. Post treatment follow up is on a longer-term basis with spacing of the clinical appointments based on the clinical and imaging response of the patient.

2.4.2 Figurative Presentation of the Conceptual Framework
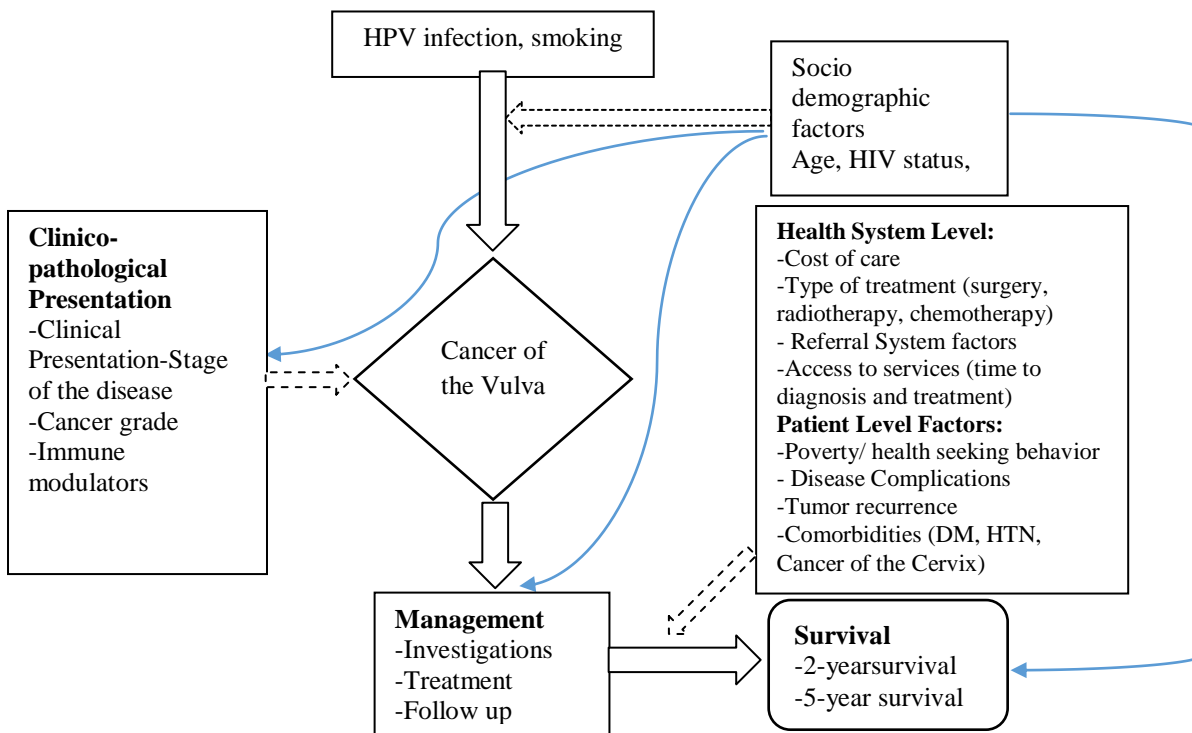
Figure 3: Conceptual Framework

2.6 Study Justification

Despite being a relatively rare cancer, patients in Africa and other developing regions in the world continue presenting with late diagnosis and delayed management of vulva cancer. The presence of weak health systems, poverty and high cost of health care in these set ups pose a challenge to the early diagnosis and effective management.

Despite there being a lack of randomized controlled trials to assess the disease presentation, diagnosis, management and prognosis, observational studies have shown that there is a correlation between the clinico-pathological presentation of patients with vulvar cancer and the survival after treatment. Never the less, there is paucity of data and literature about vulvar cancer from developing countries including Kenya. This study therefore aimed to determine the clinico-pathological presentation, management and survival rates of patients managed for cancer of the vulva at theKenyatta National Hospital (KNH) between 2012- 2017.

The findings from the study will guide early identification of the clinico-pathological factors that may lead to the improvement of patients' survival. These will be incorporated into the clinical management guidelines for patients with cancer of the vulva at the KNH and other hospitals managing patients with cancer of the vulva.

2.7Research Question

What is the clinico-pathological characteristics, management, and survival of patients treated for cancer of the vulva at Kenyatta National Hospital (KNH) between 2012 and 2017?

2.8 Study Objectives

2.8.1 Broad Objective

To evaluate the clinico-pathological characteristics, management and survival of patients treated for cancer of the vulva at Kenyatta National Hospital between 2012 and 2017?

2.8.2 Specific Objectives

Among women with cancer of the vulva managed in KNH between 2012 to 2017 to:

1) Determine the clinico-pathological characteristics

2) Describe the management of cancer of the vulva

3) Determine twoand five-year survival of patients managed for cancer of the vulva

CHAPTER THREE: METHODOLOGY

3.1 Study Design

The study was a retrospective descriptive cohortstudy; the cohort wasmade up of women with cancer of the vulva managed in Kenyatta National Hospital (KNH) between 2012 and 2017. This being a study that entailed assessment of survival of patients who were treated for cancer of the vulva, a cohort study design was best suited; it was retrospective in nature since vulvar cancer is rare and therefore to allow for data collection within a short period of time and within the period of the fellowship program.

3.2 Study Site and Setting

The site of the study was in KNH in Nairobi Kenya. The KNH is the largest referral hospital in Kenya. It also doubles as the teaching hospital of the University of Nairobi (UoN) and the Kenya Medical Training College (KMTC). Its catchment area is drawn from all over the country. The hospital has a bed capacity of 2,500 patients, though its bed occupancy is mostly double this. The Gynecological Oncology unit manages an average of 200 reproductive cancer patients a year, out of which 30 are cancer of the vulva patients.

Patients diagnosed with cancer of the vulva are managed in the Gynecologic Oncology outpatient clinic 18, Gynecologic oncology wards 1B and 1D and in the Radiotherapy Department. The staff members comprise of one Gynecologist Oncologist, eight Gynecology Oncology Fellows, Obstetrics and Gynecology Residents, Medical & Clinical Officers Interns, and Nursing staff among other support staffmembers.

In the outpatient clinic, management plans for new patients are made and reviews for patients is carried out. Patients with acute conditions, those requiring chemotherapy or salvage radiotherapy are admitted and managed in the wards. Acute conditions that require admission include anemia, deep venous thrombosis, acute infections, renal failure and per vaginal or vulval bleeding.

Chemoradiation is offered in the radiotherapy unit. Salvage radiotherapy is given when there is bleeding. Palliative care is part of the management plan for the patients. A multidisciplinary team approach in employed in care. Auxiliary services that form part of the Gyn Oncology unit include Departments of General Surgery, Plastic Surgery, Urology, Urogynecology, Pathology, Interventional Radiology, Nutrition and Psychosocial support.

The KNH Department of Research & Programs keeps Research Electronic Data Capture (REDCap) software for reproductive cancers since 2009. There are about 6,000 individual case records of gynecologicalcancer patients, out of which 5% belong to those patients with cancer of the vulva. The cancer of the vulva database has variables on the following captured: demographic characteristics, clinical characteristics, staging, pathology, surgical management, radiotherapy management, chemotherapy, follow up and treatment outcomes.

3.3 Study Population

Patients with cancer of the vulva that were managed at the KNH between 2012 to 2017 formed the study population.

3.3.1 Inclusion Criteria

1. All patients with a documented histological diagnosis of cancer of the vulva

3.3.2 Exclusion Criteria

1. Patients with metastatic cancer to the vulva (secondary tumours)

2. Patients with cancer of the vulva with incomplete data/ missing files

3.4 Sample Size Calculation

The sample size was calculated using the log rank test statistic for survival analysis. The assumptions for the calculation were derived from a similar study conducted by Linn et al where 103 patients who had vulvar cancer were treated at the University Medical Center Hamburg-Eppendorf between 1996 and 2003. They were analyzed in regards to the relevance of the prognosis in respect to the different clinico-pathological variables and the 2 and 5-year survival.In this study, the 5-year overall survival for 53 patients with unilateral lymph

node metastasis was 52%, while patients without groin involvement (17)after five years had a survival rate of 91.4%(2). Applying this in the stat calc software for logrank test statistic gave a total sample size of 92 with the following definitions:

n = Desired sample size

d= value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

p1= survival rate among patients with unilateral lymph node involvement at 5 years (52%)

p2= survival rate among patients without lymph node involvement at 5 years (91.4%)

Type I error = 0.05   Type II error = 0.20

Ratio of group 1 to group 2 = 3:1

Substituting this in the medcalc   software as follows:

Sample size: survival analysis (logrank test)

Options

Type I error (Alpha, Significance)	0.05
Type II error (Beta, 1-Power)	0.20

Data

Survival rate Group 1	0.52
Survival rate Group 2	0.914
Ratio of sample sizes in Group 1 / Group 2	3

Result

Number of cases required in Group 1:	69
Number of cases required in Group 2:	23
Total sample size (both groups together)	**92**

Add 10% for incomplete/missing data,   (92+9.2= 101)

Therefore, the calculated minimum sample size will be **101**

3.5 Data Variables

Table 2: Independent and dependent variables for the study

Specific Objectives	Independent variables	Dependent variables	Sources of data
Determine the clinico-pathological characteristics	Socio-demographic characteristics	Age, Marital status, Religion, Education level, Smoking	Patient files
	Clinical characteristics	HIV status, Parity, BMI, Contraceptive use, Comorbidities (DM, HTN, DVT, Anemia), Date of cancer diagnosis, presenting symptoms, FIGO staging	

	Pathological characteristics	Histologic type, stage, Grade,LVSI, Lymph node status	
Determine the treatment Options	Modes of treatment	**Surgery:**Radical vulvectomy, Radical vulvectomy + Lymphadenectomy, Simple vulvectomy **Radiotherapy:**External beam RT alone, Brachytherapy alone, External beam + Brachytherapy **Chemotherapy:**Chemo alone, (Dose, Sessions, Type of chemo used) **Combination Therapy:**External beam +brachytherapy +chemo, External beam RT + Surgery, Chemo-radiation	
Describe the management of cancer of the vulva	Types of management	**Diagnosis of cancer of the vulva** Histological diagnosis, Clinical diagnosis alone, Computerized tomography (CT) alone, Ultrasound scan alone, MRI alone, Both CT and ultrasound scan, Unilateral or bilateral	
Determine treatment outcomes	Treatment outcomes	Alive, died in hospital, lost to follow up, Remission, Resistance / residual, Distant metastasis, Recurrence, Palliative care, if recurrence: site of recurrence and treatment given, Treatment outcomes will be compared	
Determine the two- and five-year survival	Follow up and mortality	Time to death survival analysis, Date of death, Mean/median follow up time	
	Disease free survival	2- and 5-year survival	

3.6 Data Collection and Management

Data was collected using a data abstraction form (Appendix 1).Two research assistants, clinical officers were trained by the Principal Investigator on data abstraction. Data was abstracted from the case files into an excel database for cleaning and analysis.

3.7 Data Reliability and Validity

The data capture tools for patients at KNH are globally accepted standardised instruments that capture accurate data. Because the collected data was retrospective in nature, our data collection tool was not pretested to ascertain its reliability. However, the face validity technique was used to ascertain the validity of our data capture tool. The data abstraction toolwasshared with colleagues and lecturers in the department of obstetrics and gynaecology to gauge its suitability for data collection. Their suggestions werefactored into the final copy of the tool.

3.8 Data Quality Assurance Procedures

We put in place two measures to make sure the data we collected was of high integrity and acceptable scientifically. First, only research assistants with a medical background (clinical officers or nurses with background training in basic research) were used during the data collection process. They also underwent a rigorous training on data collection practices such as confidentiality and the techniques for extracting retrospective data accurately. Secondly, data capture tools were checked for accuracy by the data manager and data cleaned before analysis.

3.9 Data Management and Analysis

The collecteddata was uploaded in a spreadsheet for cleaning before analysis using the Statistical Package for Social Scientists Software (STATA version 12).Endpoints for this research included mortality or previous check-up. A search in the literature, ten clinico-pathological variables considered for evaluation in regards to the patients' survival: age, type of the tumor, invasion depth, status of the lymph nodes, stage, grade, resection margin involvement, lymphvascular space involvement, registration in NHIF andHIV status.

Univariate analysis was performed for each factor, management and treatment and presented as table of proportions. Continuous parameters such as age were analyzed with univariate Cox regression and log-rank test was used for all categorical variables.

3.11 Ethical Considerations

This study proposal was submitted and approved by the Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee. Permission to carry out the study wasalso granted by the KNH Research Department and the Department of Obstetrics and Gynecology. This study was considered of minimum risk due to its retrospective nature. For those lost to follow up or with incomplete data, efforts were made to contact the patient/ kin through the phone calls as recorded in the patient files. Phone call consent (Appendix 2) was requested before seeking further information on the patient. This was important especially on getting information on patient overall survival.

CHAPTER FOUR: RESULTS

Following ethical approval by the KNH-UoN ERC, the KNH Research & Programs Department and the Obstetrics & Gynaecology Department, data for the study was collected in October and November 2020. All the 128 patients with a diagnosis of cancer of the vulva (CV) and who were managed at the KNH Gynaecologic Oncology and Radiotherapy unitsduring the period of the study were included.Between 2012 to 2017, vulvar cancer accounted for 12.1% (128/1057) of all patients with reproductive tract cancers managed at KNH.As shown in figure 3, a total of 24 records were excluded; 11due to mis-classification/coding of the diagnosis and 13 due to incomplete data across most critical variables.
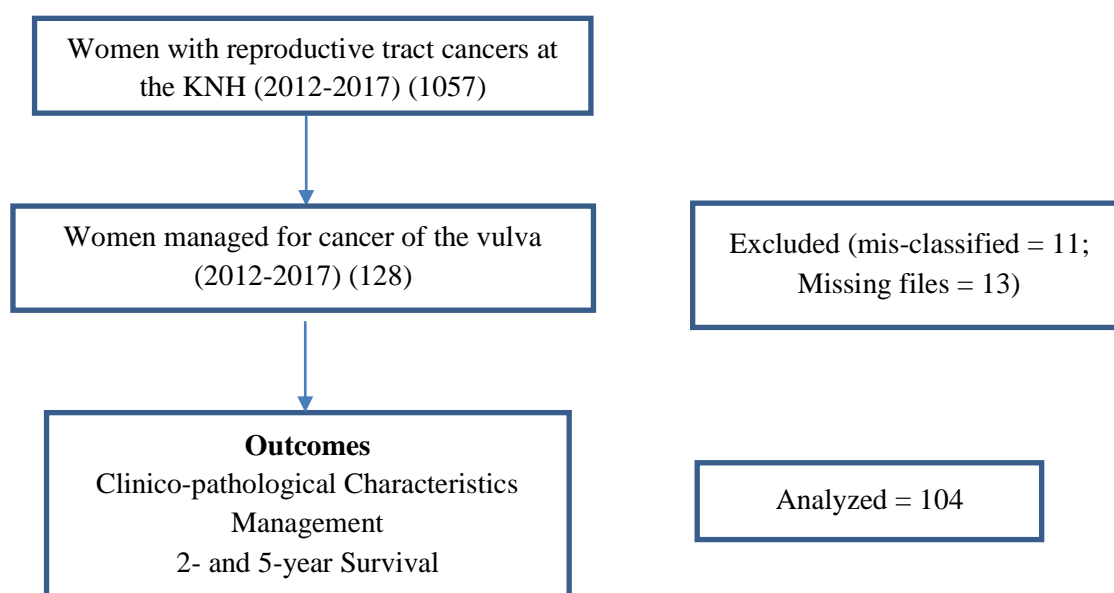
Figure 4: Study flow diagram

Secondary data were collected regarding their clinico-pathological characteristics, the management of their condition and the outcome of treatment. It is worth noting that since the data were retrieved from secondary sources, missing data were inevitable. In the subsequent tables, the category of "*Not stated*" is included to show the frequency of the missing data. However, this category was excluded in the denominator while calculating percentages of the available data.

Socio-demographic information

As shown in table 3, about 85% of the patients were aged above 35 years with a median age of 47 years (IQR 38.0 – 58.5). More than half (55.2%) had normal weight while only 4 (3.9%) had a history of smoking. Regarding parity, a majority (40.2%) had 2 or 3 children.

Table 3: Socio-demographic characteristics of patients managed for cancer of the vulva at the Kenyatta National Hospital between 2012 and 2017 (n=104)

Variable	Category	Frequency	Percent
Age group	<35 years	16	15.4
	35-50 years	47	45.2
	>50 years	41	39.4
BMI*	Underweight	6	9.0
	Normal weight	37	55.2
	Overweight	19	28.4
	Obese	5	7.4
	Not stated	*37(35.6%)*	-
Parity	0 to 1	9	9.8
	2 to 3	37	40.2
	4 to 6	26	28.3
	>6	20	21.7
	Not stated	*12(11.5%)*	-
Smoking history	No	100	96.2
	Yes	4	3.9

Clinical Characteristics of the patients

The clinical characteristics of the patients are presented in Table 4. The results reveal that more than three quarters (78.5%) were diagnosed with stage III or Stage IV cancer. It is also notable that the data on FIGO staging of half of the patients (53/104; 51%) were not available. More than half (60.5%) were HIV positive and 96.2% of them (HIV+) were on ART. A third (33.7%) were using contraceptives at the time they were diagnosed and about one-tenth (9.6%) had history of other cancer.

Table 4: Clinical Characteristics of the patients managed for cancer of the vulva at the Kenyatta National Hospital Kenya between 2012 to 2017

Variable	Category	Frequency	Percent
Year of diagnosis	2012	24	24.1
	2013	19	18.3
	2014	22	21.2
	2015	19	18.3
	2016	12	11.5
	2017	7	6.7
HIV status	Negative	34	39.5
	Positive	52	60.5
	Not stated	*18(17.3%)*	-
ART use (If HIV +)	No	2	3.9
	Yes	50	96.2
Contraceptive use	No	68	67.3
	Yes	33	33.7
	Not stated	*3(2.9%)*	-
FIGO stage	Stage IA	1	2.0
	Stage IB	4	7.8
	Stage IIA	3	5.9
	Stage IIB	3	5.9
	Stage IIIA	11	21.6
	Stage IIIB	13	25.5
	Stage IVA	16	31.4
	Not stated	*53(51%)*	-
History of other cancer	No	92	88.5
	Yes	10	9.6
History of genital warts	No	93	90.3
	Yes	10	9.7
	Not stated	*1(1.0%)*	-

Symptoms presenting at diagnosis are illustrated in Figure 5. Since one patient could have multiple symptoms, the percentages were calculated for each symptom out of all the patients. Nearly all (93.3%) patients had vulva lesions/swelling while approximately a quarter (23.1%) had vulvar itch.

Figure 5: Presenting diagnosis symptoms among patients managed for cancer of the vulva at the Kenyatta National Hospital Kenya between 2012 to 2017(multiple response; n=104)

Pathological Characteristics

As shown in table 5, half of the patients (49.5%) had cancer of the vulva with vaginal involvement. Three-quarters (75.3%) had one lesion and a majority (62.8%) had a tumor size of 5cm and above. A quarter (25.0%) had inguinal lymph node on the left side and a similar percentage had on the right side. Regarding histology, 89.2% had squamous cell carcinoma. A minority of the patients had LVSI (17.3%) and nodal invasion (17.2%).

Table 5: Pathological characteristics for patients managed for cancer of the vulva at the Kenyatta National Hospital Kenya between 2012 to 2017

Variable	Category	Frequency	Percent
Vaginal involvement	No	51	50.5
	Yes	50	49.5
	Not stated	*3(2.9%)*	-
Inguinal lymph node involvement	Left side	13	25.0
	Right side	13	25.0
	Both	26	50.0
	Not stated	*52(50.0%)*	-
Number of lesions	1	70	75.3
	2	18	19.4
	3	5	5.4
	Not stated	*11(10.6%)*	-
Tumor size	<1cm	1	2.3
	1-2cm	7	16.3
	3-4cm	8	18.6
	5-7cm	19	44.2
	>7cm	8	18.6
	Not stated	*61(58.7%)*	-
Done EUA/EWA	Yes	100	97.1
	No	3	2.9
	Not stated	*1(1.0%)*	-
Pathology report filed	Yes	98	96.1
	No	4	3.9
	Not stated	*2(1.9%)*	-
Histology	Squamous cell	91	89.2
	Adenocarcinoma	3	2.9
	Basal cell carcinoma	3	2.9
	Botryoidal rhabdomyosarcoma	1	1.0
	Neoplasia III(Bowen's disease)	1	1.0
	Neuroendocrine carcinoma	1	1.0
	Other	2	2.0
	Not stated	*2(1.9%)*	-

Grade	I	7	46.7
	II	6	40.0
	III	2	13.3
	Not stated	*89(85.6%)*	-
LVSI	No	81	82.7
	Yes	17	17.3
	Not stated	*6(5.8%)*	-
Nodal invasion	No	82	82.8
	Yes	17	17.2
	Not stated	*5(4.8%)*	-

85.6% (89/104) of pathologist reports had no grading done. Figure 6 is an illustration of the site of local spread among patients with vulvar cancer. More than two-thirds (68.0%) hadinvolvement in the vagina, 38% in the anus and 18% in the clitoris.

Figure 6: Site of local spread among patients managed for cancer of the vulva at the Kenyatta National Hospital Kenya between 2012 to 2017 (n=50; multiple response)

The most common type of tumor was the ulcerative type (71.2%), followed by fungating type (23.1%) and infiltrative type (8.7%) as shown in figure 7 below;
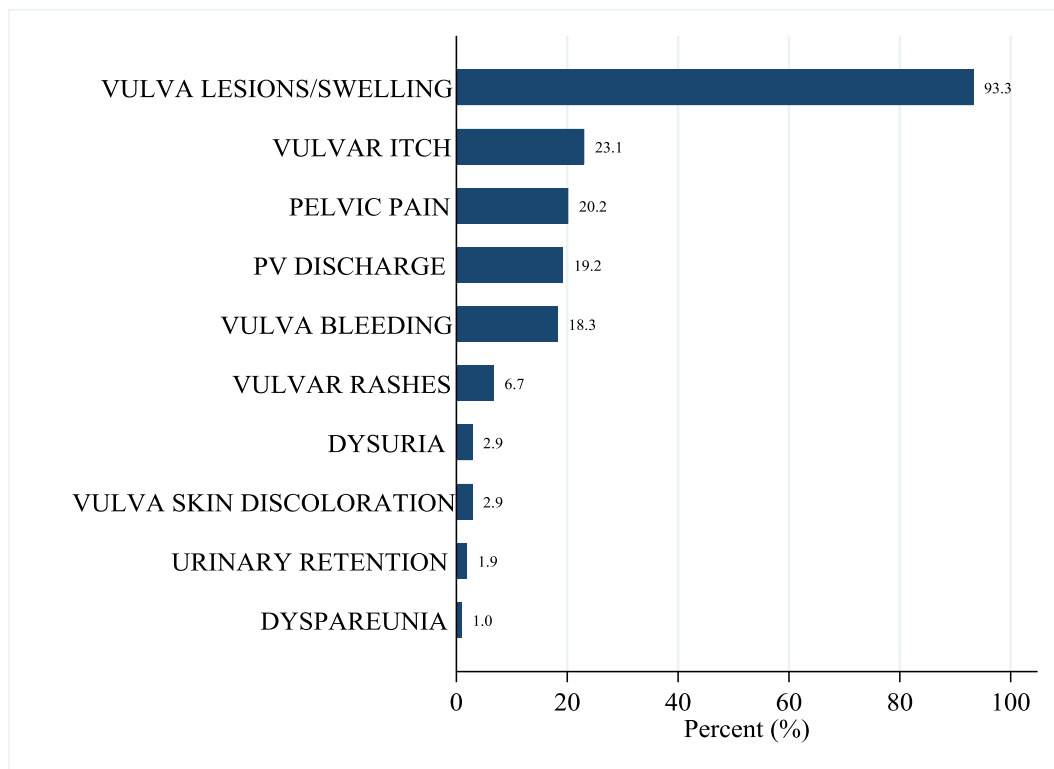
Figure7: Tumor type among patients managed for cancer of the vulva at the Kenyatta National Hospital Kenya between 2012 to 2017 (multiple response; n=104)

Management of cancer of the vulva

Almost all patients (98.0%) were examined under anesthesia and over half (52.0%) were determined to be at stage III (i.e. stages 3, 3A and 3B). The primary treatment was radiotherapy for three-quarters (75.5%). Approximately a quarter (27.0%) received chemotherapy. By the end of the study period, 29.8% of the patients had died, 26.0% were still alive while the rest (44.2%) were lost to follow-up.

Table 6: Management of cancer of the vulva who were seen at the Kenyatta National Hospital Kenya between 2012 to 2017

Variable	Category	Frequency	Percent
Examination	Under anesthesia (EUA)	99	98.0
	Without anesthesia (EWA)	2	2.0

	Not stated	*3(2.9%)*	-
Clinical stages during EUA	Stage 1A	2	8.0
	Stage 1B	2	8.0
	Stage 2	5	20.0
	Stage 2B	1	4.0
	Stage 3	8	32.0
	Stage 3A	2	8.0
	Stage 3B	3	12.0
	Stage 4	1	4.0
	Stage 4A	1	4.0
	Not stated	*74(71.2%)*	-
Primary treatment	Radiotherapy	71	75.5
	Surgery	23	24.5
	Not stated	*10(9.6%)*	-
Reason for radiotherapy	Curative intent	73	88.0
	Palliative	10	12.1
Type of radiation therapy	Brachytherapy	14	17.1
	External beam	68	82.9
Chemoradiation given	No	65	73.0
	Yes	24	27.0
	Not stated	*8(7.7%)*	-
Chemotherapy used (if Chemoradiation was given)	Cisplatin	24	100.0
Chemo+ Radiotherapy	Yes	18	17.3
	No	86	82.7
Final treatment outcome	Alive	27	26.0
	Died	31	29.8
	Lost to follow-up	46	44.2

The findings during tumor examination of the patients are presented in Figure 8 below. More than half of the tumors involved right labia majore (56.3%) and left labia majore (53.1%).
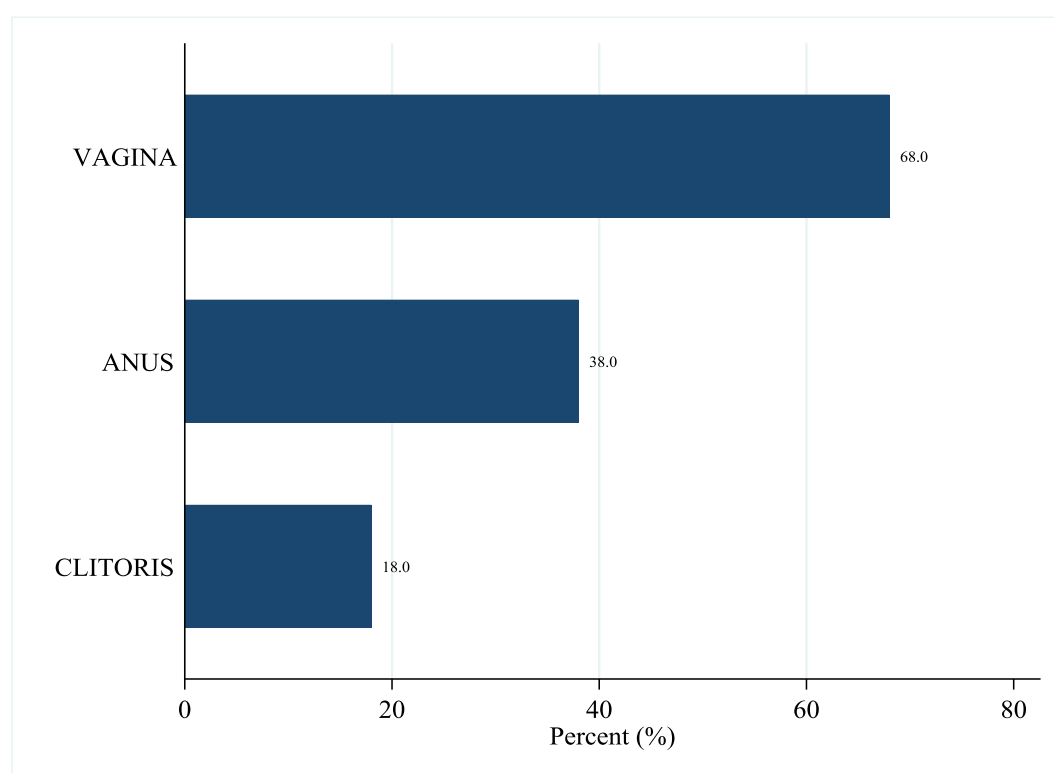
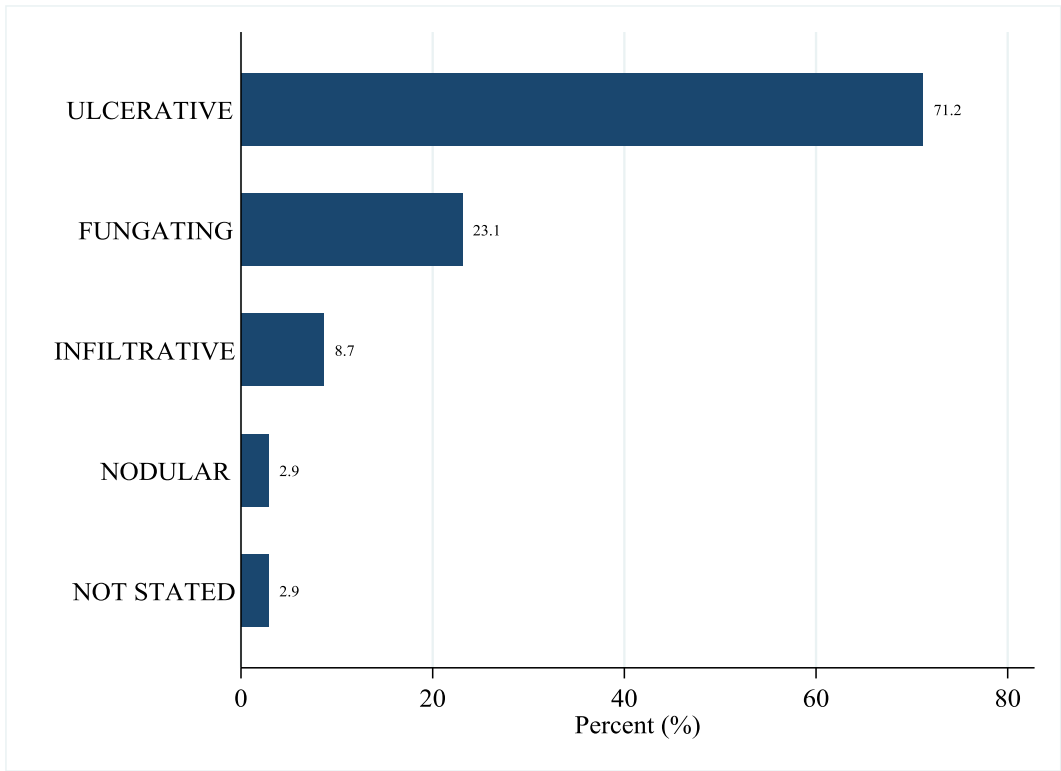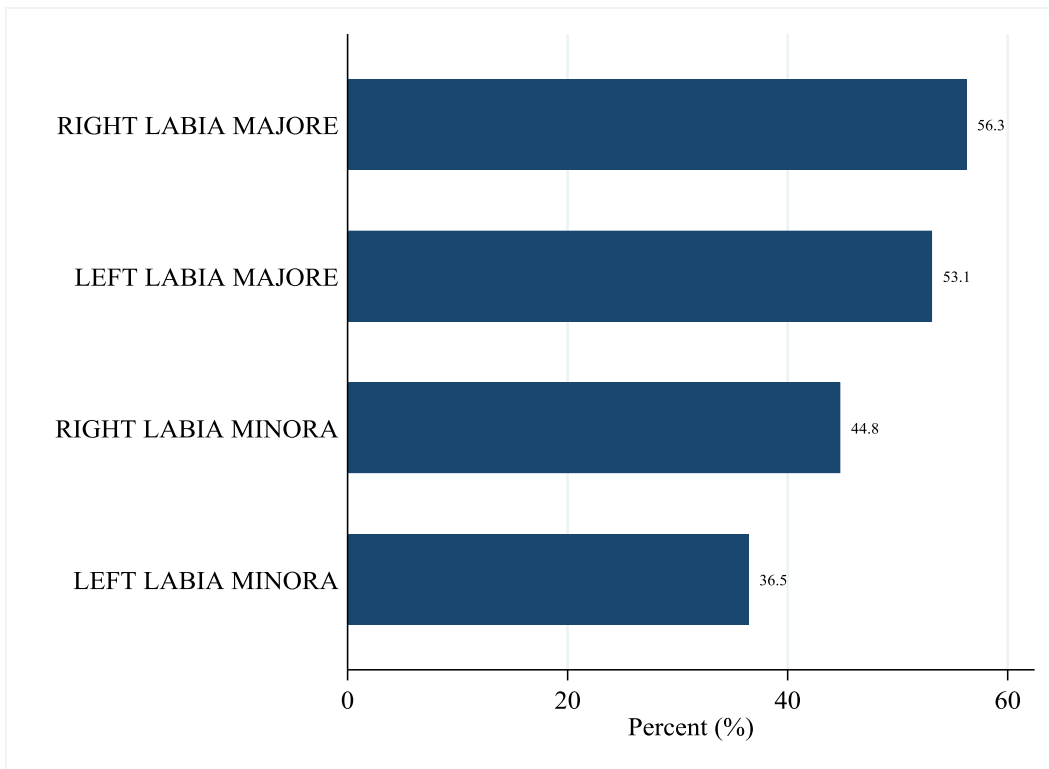*Figure 8: Findings during EUA or EWA tumor examination among patients managed for cancer of the vulva at the Kenyatta National Hospital Kenya between 2012 to 2017 (multiple response; n=196; 8 patients had missing records)[EUA- Examination Under Anaesthesia; EWA- Examination Without Anaesthesia]*

Survival Analysis

The median follow-up time was 11 months (IQR: 5-26 months). Starting with 102 vulva cancer patients at risk of death, the probability of death was 50% given that one had survived up to 42 months. The failure rate increased steadily from diagnosis (time=0) up to about 40 months, after which it became relatively steady. The confidence interval widens with time since the number of patients at risk reduces over time, leading to more unstable estimates.As shown in figure 9, the two- year survival rate was 71% while the five-year survival rate was 45% as shown in figure 9 below.
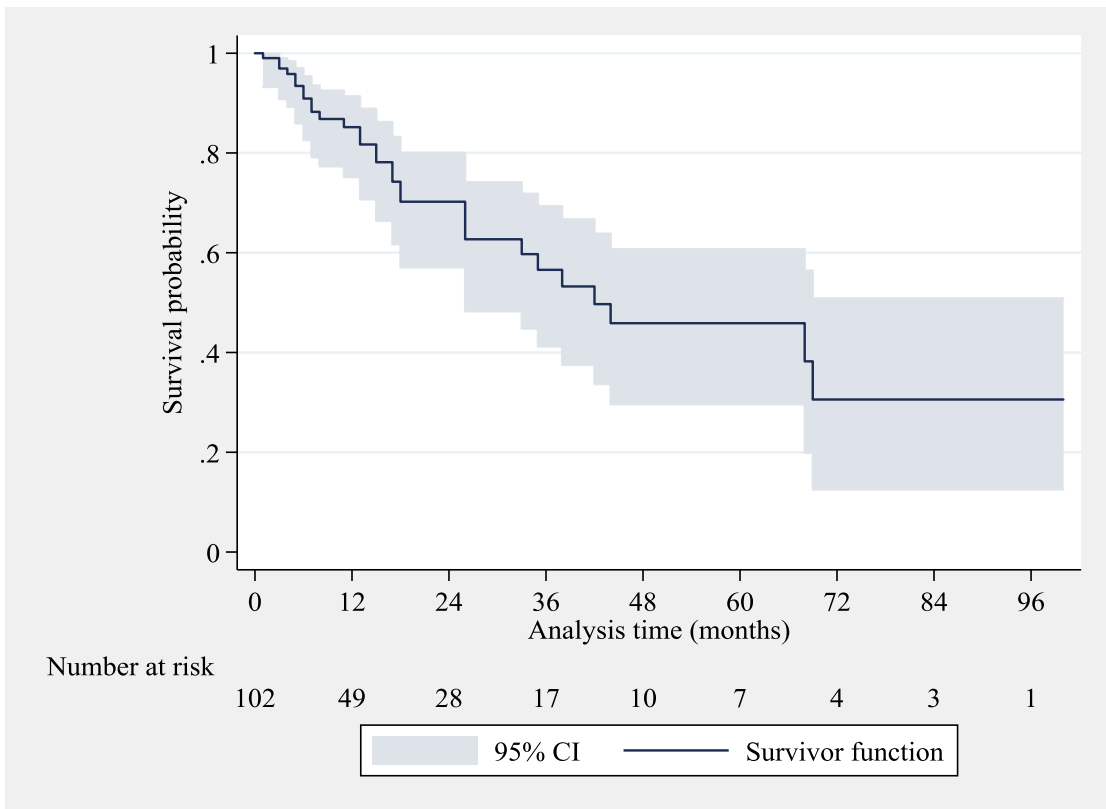
Figure 9: Kaplan-Meier survivalestimates of all patients managed for cancer of the vulva at the Kenyatta National Hospital Kenya between 2012 - 2017. 2yr survival rate was 71%, while 5yr survival was 45%

Survival Analysis by FIGO Staging

From figure 10 below, the survival experience of the patients by FIGO stage seemed to differ from about 18 months onwards. Patients with FIGO stage 4 appear to have the worst survival experience (i.e. highest failure rate with 5 year survival being zero). The findings reported after log-rank test showed insignificant variability regarding overall survival of the patients by FIGO stage (P-value=0.912).
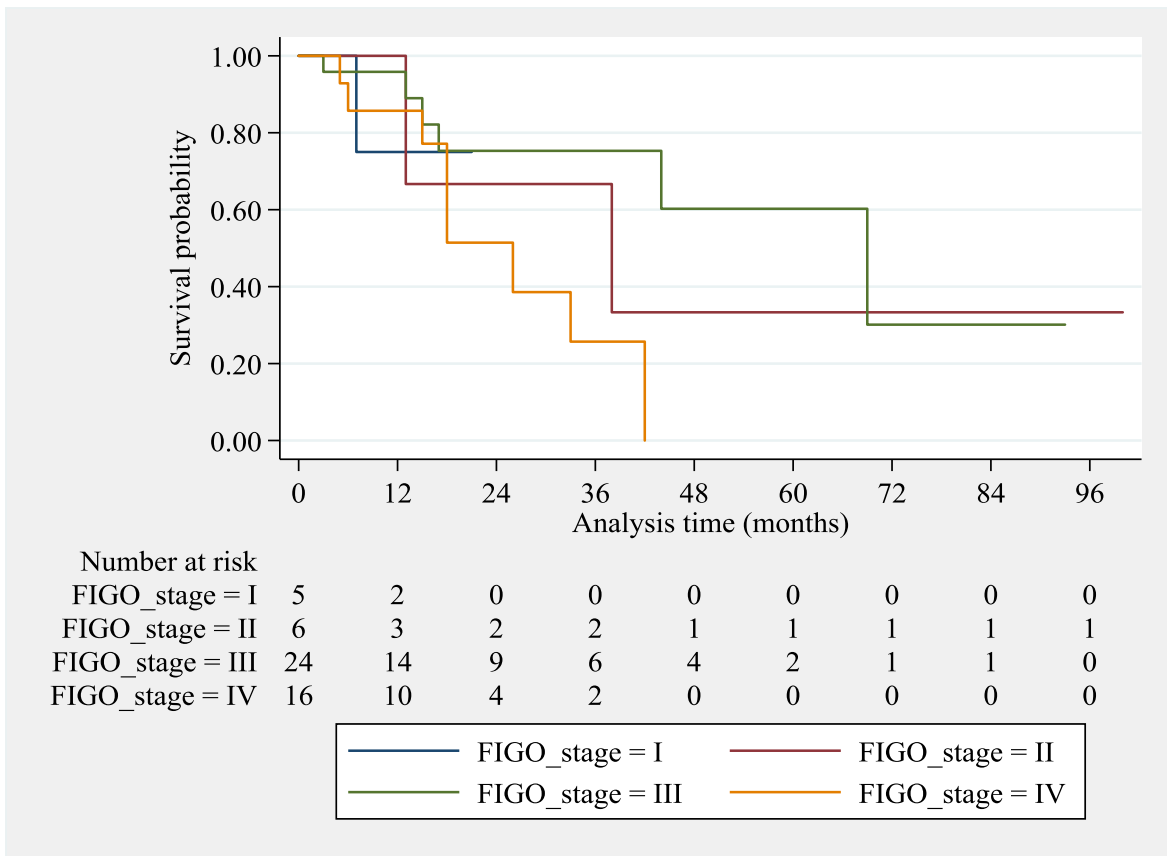
Figure 10: Kaplan-Meier survival estimates of patients by FIGO stage at diagnosis among patients managed for cancer of the vulva at the Kenyatta National Hospital Kenya between 2012 to 2017 (p=0.912)

Survival Analysis by HIV Status

Graphically, the patients grouped by HIV status seemed to have similar failure functions since the 95% confidence intervals overlap throughout the follow-up period. This observation was supported by the results of log-rank test which revealed no significant difference in the overall survival of the two groups (P-value=0.565)
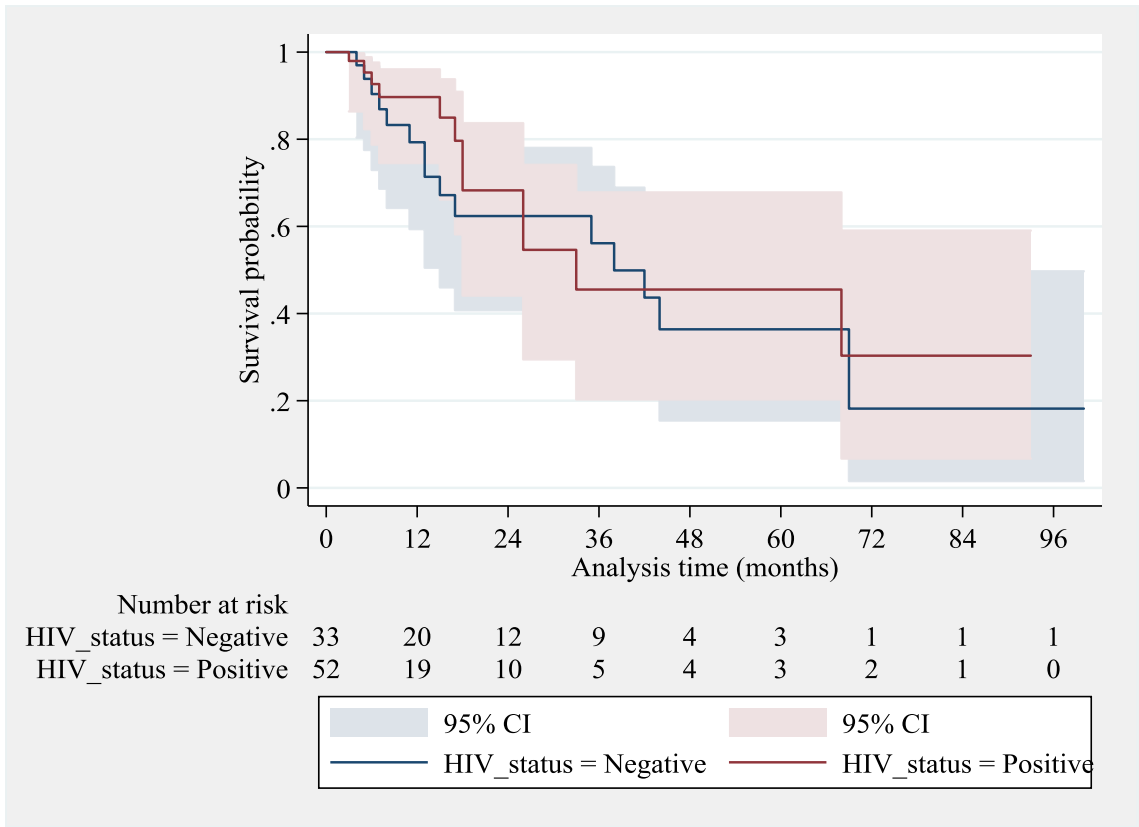
Figure 11: Kaplan-Meier survival estimates of patients by HIV status among patients managed for cancer of the vulva at the Kenyatta National Hospital Kenya between 2012 to 2017

Survival Analysis by Vaginal Involvement

From the visual inspection of Figure 12, patients with central structure involvement (ie, vagina, urethra and anus) had worse survival experience (i.e. higher failure rates) than those without. Despite this observation, their confidence intervals overlap, implying that the difference is not significant. Statistical test for the difference in the failure curves showed no significant difference between the two groups of patients (P-value=0.154).
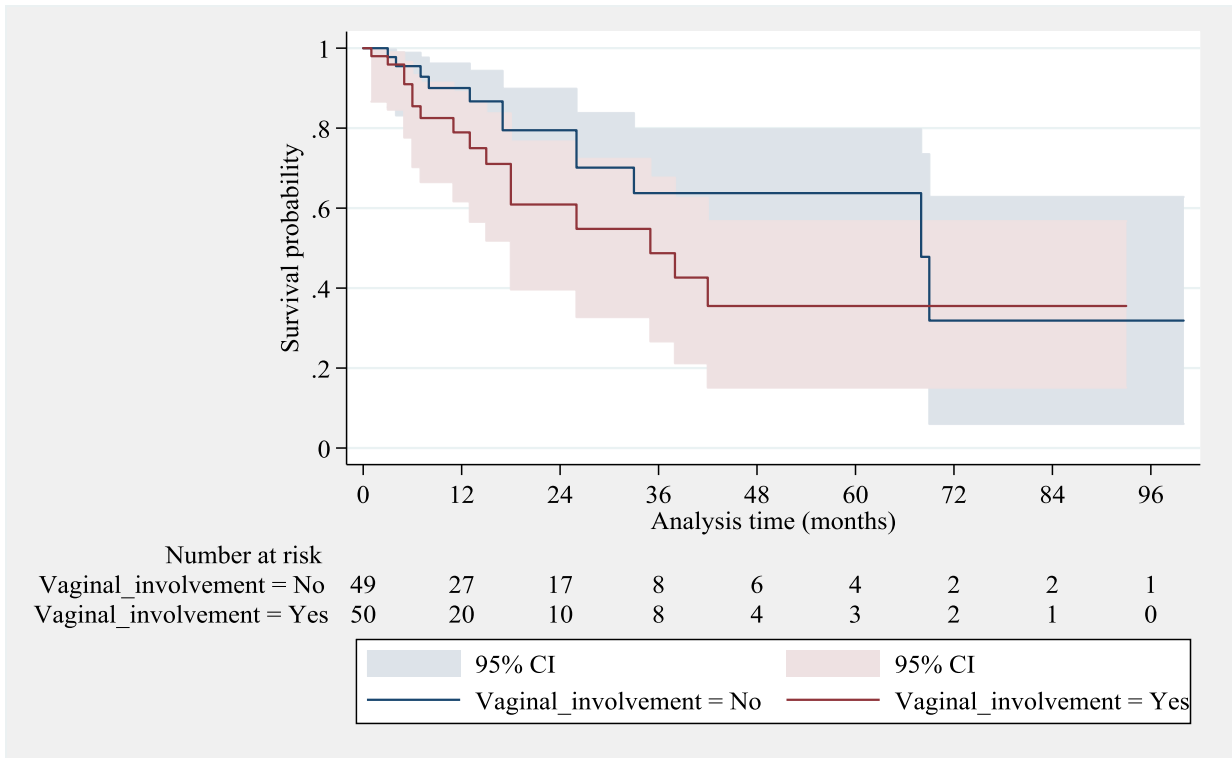
Figure 12: Kaplan-Meier survival estimates of patients by central structure involvement (vaginal/clitoral/anal)among patients managed for cancer of the vulva at the Kenyatta National Hospital Kenya between 2012 to 2017

Survival Analysis by Inguinal Lymph Node Involvement

Patients grouped by inguinal lymph node involvement seemed to have similar survival experience. There was no statistically significant difference in the failure functions of patients by lymph node involvement at 5% level of significance (P-value=0.322)
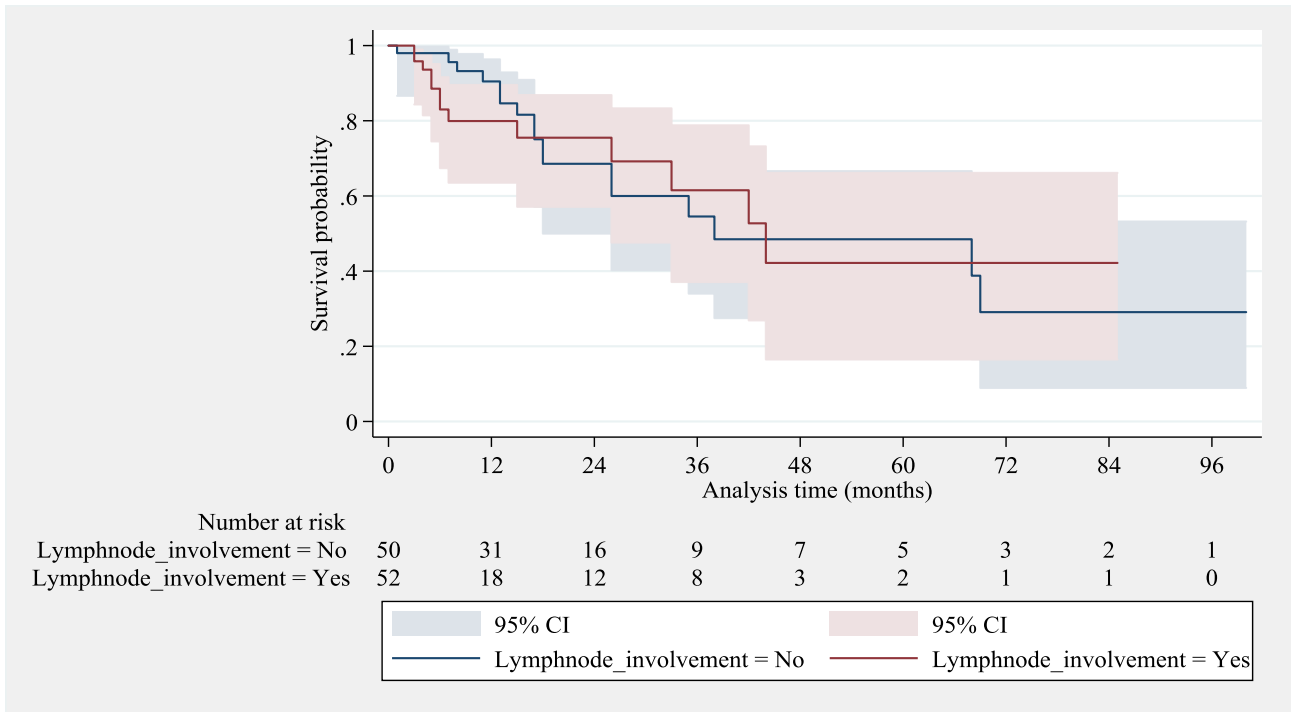
Figure 13: Kaplan-Meier survival estimates of patients by inguinal lymph node involvement among patients managed for cancer of the vulva at the Kenyatta National Hospital Kenya between 2012 to 2017. (p-value is 0.748)

Comparison of Survival by Possible Risk Factors

To compare the failure functions by potential predictors, log-rank test was used. There was no significant difference in the failure functions of patients across all the predictors considered, at 5% level of significance as shown in table 7.

Table 7: Comparison of survival across possible risk factors among patients managed for cancer of the vulva at the Kenyatta National Hospital Kenya between 2012 to 2017

Variables	Observed events (deaths)	Log-rank test Chi^2	P-value
FIGO clinical stage			
Stage I	1	4.64	0.200
Stage II	2		
Stage III	6		
Stage IV	8		
Age group			
<35 years	4	0.78	0.677
35-50 years	12		
>50 years	14		
Parity			
0 to 1	1	1.78	0.620
2 to 3	9		
4 to 6	6		
>6	11		
HIV status			
Negative	15	0.33	0.565
Positive	12		
Contraceptive use			
No	18	0.16	0.689
Yes	10		
History of other cancer			
No	26	0.02	0.885
Yes	3		
Primary treatment			
Radiotherapy	19	1.07	0.301
Surgery	7		
Vaginal involvement			
No	12	2.03	0.154
Yes	16		
Inguinal LN involvement			
Right side	6	2.27	0.322
Left side	3		
Both	4		
Inguinal LN involvement			
No	17	0.10	0.748
Yes	13		

Note: LN-lymph node

Factors Associated with Survival of the Cancer of the Vulva Patients

Cox proportional hazards model was fit to determine the factors associated with time to death among the patients. Only parity was found the have a significant effect on the risk of death (see table 8 below). Controlling for the other variables in the model, for every additional child a patient had, there was a 66% increase in the hazard (HR=1.66, 95% CI:1.24-2.22). In other words, the more children a patient had, the higher the risk of death.

Table 8: Factors associated with time to death - Cox proportional regression model among patients managed for cancer of the vulva at the Kenyatta National Hospital Kenya between 2012 to 2017

Predictors	Hazard Ratio	P-value	95% C.I
FIGO stage			
Stage I	1.00		
Stage II	0.35	0.423	0.03 - 4.56
Stage III	0.28	0.194	0.04 - 1.92
Stage IV	0.18	0.113	0.02 - 1.50
Age in years	0.95	0.066	0.90 - 1.00
Parity	1.66	**0.001**	1.24 - 2.22
HIV status			
Negative	1.00		
Positive	2.27	0.446	0.28 - 18.81
Contraceptive use			
No	1.00		
Yes	1.35	0.67	0.34 - 5.38
History of other cancer			
No	1.00		
Yes	1.11	0.91	0.18 - 6.89
Primary treatment			
Radiotherapy	1.00		
Surgery	0.51	0.463	0.08 - 3.11
Vaginal involvement			
No	1.00		
Yes	2.94	0.061	0.95 - 9.08

CHAPTER FIVE: DISCUSSION AND RECOMMENDATIONS

A total of 104 patients diagnosed with primary vulvar carcinoma were evaluated for prognostic factors. The median age for the patients was 47 years (IQR 38 - 58.5) with 39.4% being in the post-menopausal age. The median age for the participants was higher compared to the study done in Ethiopia by Kroeber et al, where the median age was 39 years (range 20-85years) (50). This group was significantly younger those patients from the United States (SEER, 68 years)(10) and Germany where the mean age of diagnosis of vulva cancer was around 57.0 years(12). The younger age in developing countries could be attributable to the concurrent high rates of HIV infection.

Out of the 86 patients with a documented HIV status, a majority (60%) were HIV infected and on anti-retroviral therapy. The data was consistent with what was reported in South Africa indicating roughly half of the VC patient were HIV positive in 2014 but the figure dropped to 41% in 2015 while (51) and in Ethiopia where the prevalence was 85%(5).

Vulvar carcinomas histologic types include squamous cell carcinoma (keratinizing/nonkeratinizing), basaloid, verrucoid, melanoma, basal cell carcinoma, Bartholin gland adenocarcinoma, sarcoma, and Paget disease(46). In our study, keratinizing/non-keratinizing squamous cell carcinomas accounted for 89% of all the vulvar cancers. Our findings are comparable to a study by Cao et al, who in a meta-analysis of vulvar cancer, found that Keratinizing/nonkeratinizing squamous cell carcinomas accounted for 91.2% of the tumors(46).

Of the 52 patients who had staging of the cancer indicated, a majority (77%) presented in late stage (stage III and above) while out of the 98 reports with lympho vascular space reporting, only 17% were reported to have lympho-vascular space invasion; 17% had nodal invasion.Compared to the study in Ethiopia by Kroeber, out of the 48 patients with vulva cancer, 83% had FIGO stages 3 to 4 cancer(5) and in Ghana where 75%(8) of the women presented in late stage. Late presentation of women with vulvar cancer is common in developing

countries. Most of the patients tend to seekdifferent types of treatment delaying seeking medical attention not unless the symptoms deteriorate. Those seeking medical attention early enough are met with a challenge of inability to detect vulva cancer. There may also be challenges with the referral system with resultant disease progression.

From our study, half of the patients (49.5%) had cancer of the vulva with vaginal involvement. Three-quarters (75.3%) had one lesion and a majority (62.8%) had a tumor size of 5cm and above; 79% of the tumors were ulcerative. A quarter (25.0%) had inguinal lymph node on the left side and a similar percentage had on the right side. More than two-thirds (68.0%) was involved in the vagina, 38% in the anus and 18% in the clitoris. More than half of the tumors involved right labia majore (56.3%) and left labia majore (53.1%). These findings are comparable to those in study by Deka et al, in India, where there was a slight predominance of the tumor to affect the right side, with 56% of the patients presenting with involvement of the right labia and 68% involving the vagina; most of the tumors were ulcerative (71.2%)(52).

Tumor grading was only available in 15% of the cases; with 46% being well differentiated. Similarly, in a study by Kroeber in Ethiopia, there was very poor reporting of the tumor grading (21%) but with higher proportion of patients (73%) reported as well differentiated(5).

Almost all patients (98.0%) were examined under anesthesia and over half (52.0%) were determined to be at stage III (i.e. stages 3, 3A and 3B). The primary treatment was radiotherapy for three-quarters (75.5%). Approximately a quarter (27.0%) received chemotherapy, with cisplatin being the drug of choice. By the end of the study period, 29.8% of the patients had died, 26.0% were still alive while the rest (44.2%) were lost to follow-up.

Compared to a similar study in Ethiopia, the management proportion was surgery (37%) and radiotherapy (38%) and 33% received chemotherapy(5). In this study, the main stay of primary treatment was radiotherapy

at 85% followed by surgery at 23%, with most patients (82.9%) undergoing external beam radiation. The mode of treatment may be due to the late presentation of the patients.

The literature indicates adjuvant radiotherapy as an evolving practice that includes positive surgical margins >8 mm, lympho-vascular space invasion (LVSI), and thickness >5 mm as well as any lymph node macro metastasis ≥5 mm, (53). In our study, adjuvant radiotherapy was indicated for 10 patients.

The median follow-up time was 11 months (IQR: 5-26 months). Starting with 104 vulva cancer patients at risk of death, the probability of death was 50% given that one had survived up to 42 months. The overall 2-year survival rate was 71% while the 5-year survival rate was calculated at 45%. It should be noted though that 41% of study participants were lost to followup and therefore censored out of these survival analysis. It's plausible that these could affect the actual survival rates.

In a study by Kroeber, the 1- and 2-year survival rates for all VC patients were 80% and 51%, respectively(5), while in a study byDadzie in Ghana, the two and five year survival was 56.7% nd 36.7% respectively among thirty patients managed with radiotherapy although majority (70%) have stage IVA(8).

Age as a variable was contentious with some studies reporting no prognostic relevance Some (41)while in others, increase in age was directly related to worsening prognosis(49). For instance, in Raspagliesi et al. (37) study, the those aged below 30 years had a 100% 10-year survival rate but worsened to 53% for those aged above 60% (p = 0.002). Another study by Burger et al.(49), showed a decline of 5-year survival rate from 80% to 49% on varying the age from below 72 years and those aged over 72 years (p = 0.001). Woelber et al., reported that age, classification of the tumor, severity of invasion, nodal statusand margin involvement had a positive influence on vulvar cancer and survival rates when univariate analysis was conducted (53). In our study however, these did not attain statistical significance.

Tumor stage is an independent prognostic variable (54). From our study, patients with FIGO stage 4 appeared to have the worst survival experience. The results from log-rank test however revealed that there was no significant difference in the failure functions of the patients by FIGO stage (P-value=0.200).

In the FIGO Annual Report(26), the 5-year overall survival according to the old 1988 FIGO classification (Table 3) was 78.5% for stage I, 58.8% for stage II (HR = 1.9, 95% CI = 1.4–2.7), 43.3% for stage III (HR = 3.3, 95% CI = 2.4–4.7), and 13.0% for stage IV (HR = 12.4, 95%CI = 8.3–18.5)(31).

A retrospective study by Raspagliesi et al. showed nodal status from the 398 vulvar cancer cases to be the leading prognostic factor(37). The finding was made after comparing nodal status with other tumor-related variables. The study also proposed that variables linked to positive nodes for instance the extracapsular spread would be essential when evaluating additional risks (37). The 5-year survival rates was reported to be 70 - 98% and 12 – 14% among those women with negative nodes and those with metastatic nodesrespectively.(38).In our study however, there was no statistically significant difference in survival among patients who had inguinal lymph node involvement compared to those without lymph node involvement.

In contrast, a study conducted by Rhodes et al. showed deteriorating survival for patients reported to have positive inguinal lymph nodes only in univariate analysis(55). However, a multivariate tests showed no statistical significance(55). The inconsistent in the results was best explained by heterogeneous treatment strategies given the extensive variation on vulvar cancer with most centers treating a handful of patients in a year.

The patients grouped by HIV status seemed to have similar failure functions since the 95% confidence intervals overlap throughout the follow-up period. This observation was supported by the results of log-rank test which revealed no significant difference in the failure functions of the two groups (P-value=0.565). The findings are comparable to a study by Kroeber where it was concluded that morbidity due to HIV did not have

a large effect on the vulvar cancer (VC) patients' overall survival time(5). Most patients had long been on anti-retroviral therapy (ART) at the point of diagnosis for a mean time of more than 3 years.

Patients with vaginal involvement had worse survival experience (i.e. higher failure rates) than those without. Statistical test for the difference in the failure curves showed no significant difference between the two groups of patients (P-value=0.154).Only parity was found to have a significant effect on the risk of death. Controlling for the other variables in the model, for every additional child a patient has, there was 37% increase in the hazard (HR=1.37, 95% CI:1.06-1.79). In other words, the more children a patient had, the higher the risk of death.

Conclusion

In conclusion, patients present in late stage with a diagnosis of cancer of the vulva, a majority of the patients are HIV positive and are treated using radiotherapy and though not significant statistically, tumor stage and size influenced survival with a 2- and 5-year survival rate of 61% and 45% respectively. Increased parity is also a significant determinant of overall survival for vulvar cancer.

To our knowledge, this is the very first such study in Kenya focusing on clinico-pathological characteristics, management and survival of vulvar cancer patients. It forms a baseline for similar future studies in the country. It's hoped therefore that this study findings will inform policy on the management of patients with vulvar cancer and indeed other gynaecological malignancies.

Recommendations

1. Efforts be put in place to enhance early diagnosis of vulva cancer, early initiation on effective treatment and follow up.

2. There's need to emphasize the importance of routine examination of HIV infected patients for possible vulval lesions and to have a high index of suspicion when such lesions are present.

3. Gynaecologic oncologists and pathologists to work more closely to improve specimen reporting in terms of critical aspects of the pathology which have a bearing on the management and outcomes of vulvar cancer patients. The gynaecologists also to improve on the reporting of EUA/ staging findings.

4. A checklist should be formulated to ensure all vital information is captured during clerkship. This can be incorporated into a software database ie REDCAP housed within the institution.

5. MOH/ KNH to develop guidelines and protocols on management of patients with vulvar cancer, including structures to ensure long-term follow-up and reduced loss to follow-up.

6. Further studies to be done to determine barriers to early diagnosis and treatment of vulvar cancer patients and how these can be mitigated. A qualitative study may be best suited for this.

Study Limitations

One of the identified limitations was based on the research type being retrospective and monocentric nature. However, given the low prevalence of vulvar cancer, completing a prospective study is near to impossible. Even though there was missing information on critical variables such as grading of the tumor, the findings from this study had valuable insight into vulvar cancer patients in a Sub-Saharan African setting. Secondly, the information sourced from the family members in the follow-up calls proved to be somehow vague leading to lack of precise survival rates.Strength for this study was the high volume of patients with vulvar cancer treated at KNH and the uniformity in treatment by surgical and radio-oncological specialists due to low inter-patient variability.

Study Timeframe

Activity	Jun 20'	Aug 20'	Aug 20'	Sep 20'	Dec 20'	Feb 21'	Mar 21'
Proposal Development	■						
Proposal Presentation		■					

Ethics Committee Review			▓▓				
Data Collection				▓▓			
Data Analysis					▓▓		
Results Presentation						▓▓	
Publication							▓▓

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APPENDICES

Appendix 1: Data Abstraction Form

KENYATTA NATIONAL HOSPITAL

CANCER OF THE VULVA

DATA ABSTRACTION FORM

QUESTIONNAIRE

Hospital number:

Date of 1st Out Patient/ Clinic contact at KNH   Not recorded ( )

Date of 1st diagnosis of Vulvar Cancer (VC)   Not recorded ( )

Date of first admission to hospital   Not recorded ( )

Date of Surgery   Not recorded ( )

Date of Radiotherapy commencement   Not recorded ( )

Date of Radiotherapy completion   Not recorded ( )

Date of chemotherapy commencement   Not recorded ( )

Date of final discharge from hospital   Not recorded ( )

Date of last review if still in care   Not recorded ( )

Date of death   Not recorded ( )

1) DEMOGRAPHIC CHARACTERISTIC

Date of birth: Not recorded ( )

Age   Not recorded ( )

Weight(Kg)   Not recorded ( )

Height (cm)   Not recorded ( )

2) CLINICAL CHARACTERISTICS

Para: 0;   1-3;   4-6: 7-8:   >9

Family planning: NO ( )   YES ( )

     If yes: Hormonal ( )   Non Hormonal ( ) Specify …………………….

HB at diagnosis: <6:   6-8: 8-10: 10-12:>12

HIV status: Positive ( )   Negative ( )   Unknown ( )

If HIV positive: **1stCD4 Viral load:**
Countat VC diagnosis:

ART Use: No ( )   YES( )   Not recorded ( )

Smoking: Yes ( )   No ( )   Not recorded ( )

History of Prior other cancer (Y)   (N)   Not recorded ( )

History of prior Genital warts (Y)   (N)Not recorded ( )

Symptoms: Vulvar Itch ( ) Vulvar Rashes ( ) Vulvar skin discolouration ( ) Vulvar Bleeding ( )
Vulvar Lesions/ Swellings ( )   PV Discharge ( )   Pelvic Pain (   )   Dysuria ( ) Urinary
retention ( )Dyspariunia ( )   Other ( ) state………………

3) Clinical staging during EUA:
a) Was the examination done?
Examination Under Anesthesia [EUA]   ( )
Examination Without Anesthesia [EWA]   ( )
b) Findings during EUA or Examination without anesthesia (EWA)
Tumor location: Labia majora ( ) (R) (L) ; Labia Minora ( ) (R) (L)

Vaginal involvement: NO ( )   YES ( )   specify:

Clitoris ( ) Anus ( ) Rectum ( ) Vagina ( )

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 tumour: (<1): (1-2): (2-4): (4-6): (>7cm)
f) FIGO clinical staging: staged (Y) (N)

Stage 0 ( )

Stage IA ( )

Stage IB ( )

Stage II   ( )

Stage III A ( )

Stage IIIB ( )

Stage III C   ( )

Stage IV A ( )

Stage IVB ( )

a) MRI: ( ) CT SCAN ( )
b) MRI findings   : CT Scan findings
Cervical Tumor size:

Tumor location:

Vaginal involvement: NO ( )   YES ( )   specify:

Parametrial involvement: ( )

Inguinal LN ( ) Right side ( )   Left Side ( )   Both ( )

Pelvic LN ( ) Right side ( )   Left Side ( )   Both ( )

Distant mets (Y) ; (N)…. SPECIFY

Ultrasound scan done (Y)   (N); NORMAL : ABNORMAL

CXR Done (Y) ;   (N)

4) Pathology of EUA/EWA biopsy
a) Pathology report NO ( )   YES ( )

Histology

Squamous cell ( )   : Basal cell carcinoma ( ) : Sarcoma   ( )

Adenocarcinoma ( )   : Melanoma   ( )   : Pagets disease ( )

Adeno-squamous   : Bartholins   ( )

Basaloid ( )   : Warty carcinoma   ( )   Other**specify…………….**

b) **Grade**

Not stated ( )

1 ( )

2 ( )

3 ( )

c) **Depth of stromal invasion:** <1 mm: 1-2 mm: 3-4mm: >4mm
d) **LVSI**: (Y); (N)
e) **Nodal invasion** : (Y) (N)
f) **POST-OP COMPLICATION: (Y); (N)**
   Wound breakdown ( ): infection ( ): Lymphoedema ( ): Contractures ( )
   DVT ( ):   OTHER ….. Specify……

5) RADIOTHERAPY AS PRIMARY TREATMENT
6) Date when VC was suspected
a) **Date when Histological Diagnosis was made:**
b) **Surgery given as primary treatment:** NO ( ) YES ( )
c) Radical vulvectomy ( ); Simple vulvectomy ( ); Inguinal Lymphadenectomy ( )
d) **Date when surgery was done**
e) **Radiotherapy given as primary treatment:** NO   YES
f) **Radiotherapy given as Adjuvant radiotherapy:** (Y); (N)
g) **Start date of Radiotherapy treatment**
h) **Reason for radiotherapy:**
   Neoadjuvant ( ) Treatment ( ) Salvage/emergency ( ) Palliative ( )
   If salvage/emergency specify reason

i) **Type of radiation therapy:** External beam ( ) Brachytherapy ( )

j) **If external beam:** Dose…….. Sessions …… Not indicated ( )

k) **If brachytherapy:** Dose…… Sessions……. Not indicated ( )

l) **Chemoradiation given:** NO ( ) YES ( ) Not indicated ( )

m) **If chemoradiation, which chemotherapy was used:**
Cisplatin ( ) 5FU ( ) Others ( ) specify Not indicated ( )

n) **Treatment** interruption (Y) (N) : IF YES SPECIFY TOTAL DAYS INTERRUPTED…….

o) **Date of discharge from radiotherapy/ date of death**
Date ………… Not indicated ( )

7) FINAL TREATMENT OUTCOME

a) **When was the last date of review**

b) **What is the final treatment outcome?:**
Alive ( )
Died in hospital ( )
Lost to-follow-up ( )
Remission ( )
Resistance/ Residual ( )
Recurrence( )
Palliative care ( )

c) **If recurrence:** (Y) (N): LOCAL ( )/ DISTANT MET ( )

Date of recurrence diagnosis ….

How long in months did it take from last treatment date to recurrence

What was the site of recurrence:
Vulvar ( ); Clitoral ( ); Anal ( ); Urethral ( ); Labia Majora ® (L); Labia Minora (R) (L)
Vaginal ( ) Pelvis ( )
Distant metastasis ( )
Other ( )

What was the treatment given:
Surgery ( )
Radiation alone ( )
Chemoradiation ( )
Palliative ( ); colostomy, catheterization; urinary diversion
Other ( )

Table 4: Treatment outcomes among patients with cancer of the vulva managed in KNH, 2012 to 2017

Variable	N(%)
Alive	

Died in hospital

Lost to follow up

Remission

Resistance/ residual disease

Distant metastasis

Palliative care

Recurrence

    Site of recurrence

        Perineum

        Pelvis

        Distant metastasis

        Other**… specify**

    Treatment given for recurrence

        Surgery

        Radiotherapy alone

        Chemoradiotherapy

        Other

    OUTCOME OF RECURRENCE TREATMENT   ALIVE ( )

        DEAD ( )

Table 5: Treatment outcomes by HIV infection status among patients with cancer of the vulva managed in KNH, 2012 to 2017

Variable	HIV Positive	HIV Negative	
	N	N	p-value
	n(%)	n(%)	

Alive

Died in hospital

Lost to follow up

Remission (cured)

Resistance/ RESIDUAL DISEASE

Distant metastasis

Palliative care

Recurrence

Site of recurrence

Perineal

Pelvis

Distant metastasis

Other

Treatment given for recurrence

Surgery

Radiotherapy alone

Chemoradiotherapy

Other

Appendix 2:

PHONE CALL VERBAL CONSENT

MANAGEMENT AND SURVIVAL OF CANCER OF THE VULVA FOR PATIENTS TREATED AT KENYATTA NATIONAL HOSPITAL, 2012-2017

I am Dr Innocent Maranga, the lead researcher in a study looking at management and follow-up of patients with cancer of the vulva treated at the Kenyatta National Hospital. This study will

evaluate 160 patients who have been in care since 2012-2017, 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 vulva.

This study has been approved by Kenyatta National Hospital/University of Nairobi Ethics & Research Committee. The Ethics Committee has granted access to your file. 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

USIMAMIZI NA KIWANGO CHA KUISHI KWA WAGONJWA WALIOTIBIWA SARATANI YA VULVA/ SEHEMU NYETIKATIKA HOSIPITALI KUU YA KITAIFA YA KENYATTA, MIAKA YA 2012-2017

Mimi ni Daktari Innocent Maranga, 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 160 ambao wamekuwa katika huduma tangu 2012-2017, 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.

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2725380 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/345

7th October 2020

Dr. Innocent Orora Maranga
Fellow in Gynaecological Oncology
Dept. of Obstetrics and Gynaecology
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Maranga

RESEARCH PROPOSAL – CLINICO-PATHOLOGICAL CHARACTERISTICS, MANAGEMENT, AND SURVIVAL OF PATIENTS TREATED FOR CANCER OF THE VULVA AT KENYATTA NATIONAL HOSPITAL, KENYA: 2012-2017   (P468/09/2020)

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 7th October 2020 – 6th October 2021.

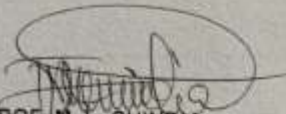This approval is subject to compliance with the following requirements:

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. 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.

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13 OCT 2020

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, KNH
The Dean, School of Medicine, UoN
The Chair, Dept.of Obstetrics and Gynaecology, UoN
Supervisors: Prof. S.B.O. Ojwang, Dept.of Obstetrics and Gynaecology, UoN
               Dr. George Gwako, Dept.of Obstetrics and Gynaecology, UoN

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