BURDEN, MANAGEMENT AND OUTCOMES OFPATIENTS WITH HISTOLOGICALLY CONFIRMED VULVARCANCER AT THE KENYATTA NATIONAL HOSPITAL

(Retrospective studyof the period January 2014 –December 2018)

Principal Investigator:

Dr. NasraJattaniBoru

H58/88984/2016

Senior Health Officer

Department of Obstetrics and Gynecology

A dissertation submitted in partial fulfillment for the award of degree in Masters of Medicine in Obstetrics and Gynecology at the University of Nairobi.

DECLARATION

I declare that this research is to be undertaken in part fulfillment of the Masters of Medicine in Obstetrics and Gynecology from the University of Nairobi and was my original work and has not been undertaken and presented for a degree in any other university.

Signature:  **Date:** 22/10/2021

Dr. Nasra Jattani Boru, MBChB

CERTIFICATE OF SUPERVISORS

This dissertation was submitted with our approval as supervisors;

Signature:..... Date:21/10/21.....

Dr Margaret Kilonzo,MBChB, M.Med (Obs/Gynae)

Lecturer, Department of Obstetrics and Gynecology,

Faculty of Health Sciences, University of Nairobi.

Signature:..... Date:21/10/2021.....

Dr. Rose J. Kosgei, MBChB, MMed (Obs/Gynae).

Senior Lecturer, Department of Obstetrics and Gynaecology,

Faculty of Health Sciences, University of Nairobi.

CERTIFICATE OF AUTHENTICITY

This is to certify that this thesis is the original work of Dr Nasra Jattani Boru, an MMed student in the Department of Obstetrics and Gynecology, College of Health Sciences, University of Nairobi, under the guidance and supervision of Dr Margaret Kilonzo and Dr Rose Kosgei.

This thesis has not been presented in any other university for award of a degree.

Signature:..... **Date:** 26/10/2021

Professor, Eunice J. Cheserem, MBChB, MMed (Obs/Gynae), PGDRM

Associate Professor Faculty of Health Sciences,

Chairperson, Department of Obstetrics and Gynecology

University of Nairobi.

LIST OF ABBREVIATIONS

CRT:	Chemo Radiotherapy
HIV:	Human Immunodeficiency Virus
HPV:	Human Papillomavirus
HSIL:	High Grade Squamous Intraepithelial Lesion
LSIL:	Low-grade Squamous Intraepithelial Lesions
SCC:	Squamous Cell Carcinoma
VIN:	Vulvar Intraepithelial Neoplasia
VC:	Vulvar Cancer

OPERATIONAL DEFINITIONS

Vulvar LSIL lesions: Are benign manifestations of the skin's reaction to an HPV infection; they are often self-limited and should not be considered as potentially neoplastic lesions.

Vulvar HSIL: High grade squamous intraepithelial lesions comprising of vulvar intraepithelial neoplasia (VIN) 2 and 3 characterized by neoplastic cells still confined to the epithelium and have not crossed the basement membrane.

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 sclerosus, but not with HPV infection.

Simple Vulvectomy: Simple 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.

Wide local excision: Excision of an individual lesion with a 1 cm margin followed by approximation 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.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

TABLES

FIGURES

ABSTRACT

Background: Each year, around 27,000 women are diagnosed with vulvar cancer (VC) globally,accountingfor approximately2-6% of malignancies of the female genital tract. While the causes of VC are unknown, a link with Human Papilloma Virus (HPV) and Human Immunodeficiency Virus (HIV) have been documented. However, there is limited information on vulva cancer in sub-Sahara Africa wherethere is a high prevalence of HPV and HIV infections. Most published reports are of small and heterogeneous groups of patients.In Kenya, data on vulvar cancer is limited.

Objective: To determine the burden, presentation, and management andoutcomes of women with vulvar cancer at Kenyatta National Hospital between 2014 and 2018.

Methodology: Data was collected using a data extraction tool, entered into an Excel sheet and analyzed using SPSS version 23 software. The incidence of cancer of the vulva was calculated, the descriptive statistics of patients presented as mean or proportions, and univariate analyses used to determine the association betweenindependent and dependent variables. Kaplan Meier statistics were used to determine the survival rate of patients by staging, treatment modality, and HIV status.

Results:vulvar cancer constitute 3.5% of gynecological cancer during the study period with the mean age of 50.9 years. Majority of patients were married (40.3%), unemployed (62.3%) and had primary education (68.9%). Eighty four were HIV positive (60.4%) and were statistically significantly younger (41 years) than HIV negative vulvar cancer patients (60 years). Squamous cell carcinoma (SCC) was the commonest histology type (98.1%), while 57 patients had metastatic tumors (47.5%), seven to lymph nodes (12.2%) and five to the anus (8.8%). A vulvar mass (76.1%) and ulcers (25.2%) were the commonest clinical presentation. A majority of patients were in stage III vulvar cancer (57.8%) and received combination therapy (37.8%), mainly radiotherapy and combination therapy (48.9%). Deaths were 15/159 (9.4%) in a median time of 1.7 months with the 5-year survival rate found to be 64.8%. Stage IV and III vulvar cancer patients had a 5-year survival rate of 69.1% and 32.5%. HIV positive patients had a lower 5-year survival rate (55.2%) than HIV negative patients (88.5%), while the survival rate after single and combination therapy were 71.6% and 75.7%.

Conclusion: Vulvar cancer was found to occur in younger patients who are HIV positive and most seek treatment late with advanced disease. Advocacy and sensitization programs that can improve the health seeking by at-risk of vulvar cancer needed.

1.0 CHAPTER ONE: INTRODUCTION

Each year, approximately 27,000 women are diagnosed with vulvar cancer globally. Incidence rates range from<0.3/100,000 females in Asia and1.6/100,000 females in North America and Europe.(1,2)While VC represents 3 to 5% of gynecological cancers, it remains an important disease affecting sexuality in women(2). Data from sub Saharan Africa is scarce, studies in Ghana and Nigeria reported rates of 2% of gynecological cancer.(3–6) while an Ethiopian study found incidence of 1.4/100,000 females.(7) There were no readily available studies on vulvar cancer in Kenya.Vulvar cancer has a bimodal age distribution with mean age at diagnosis in high income countries being 65yrs but may present in younger patients which is attributed to the presence of HPV infection. The limited studies available in Africa have shown that the disease tends to occur in much younger women and in some cases 10-15 years younger than women indeveloped countries.(5,7,8). The reason for age discrepancy may be due to the high prevalence of HPV and HIV infections in Sub Sahara Africa.

HPV and HIV infections are strongly associated with development of vulvar cancer. A systematic review and meta-analysis of 33 studies on Caucasian and Asian women with vulvar cancer reported that the prevalence of HPV varied from 3% to as high as 76%.(9)A study in Botswana reported at least one HPV strain among HIV positive vulvar cancer patients. Similar cohort study in Ethiopia found higher proportion of HIV positive patient with vulvar cancer were younger than 4oyears(7,10,11). In a large meta-analysis of women from five continents with normal cytology,Africa had the highest prevalence of HPV (24%) (12) . The*Kenya HPV related diseases summary report of 2017*recordeda 9% prevalence of HPV among women with normal cytology.(13)These factors are likely to affect the characteristics of vulvar cancer diagnosed and managed at KNH.

The prognosis of patients with vulvar cancer is quite good with early diagnosis and treatment. The stage of disease, tumor size, and status of surgical margins are sensitive predictors of survival(14)withoverall 5-year survival decreasing drastically with increase in FIGO staging and lymph node (LN) metastasis:pooled estimates showed overall 5-year survival was 84% for patients without LN involvement and 30% for those withmore than 3 LN metastasis(15). However, in low income countries like Kenya, most women presented withadvance disease and received sub optimal treatment leading to much poorer outcomes than for women in high income countries.(4,5,7,16).

2.0 CHAPTER TWO: LITERATURE REVIEW

2.1 Anatomy of the Vulva

The vulva is part of the female external genitalia, which includes the labia majora, labia minora, clitoris, vestibule, vaginal introitus, and urethral meatus. The Bartholin complexes (vestibular glands and ducts) are also considered components of the vulva, and malignancies arising in these structures are grouped with vulvar cancers.

Functionally, the vulva directs urine flow, prevents foreign bodies from entering the urogenital tract, and is a sensory organ for sexual arousal. The blood supply to the vulva is predominantly from the internal pudendal artery with a smaller contribution from the external pudendal artery. The anterior aspect of the vulva is innervated by the ilioinguinal and genitofemoral nerve. The posterior aspect of the vulva is innervated by the perineal branch of the posterior cutaneous nerve of the thigh laterally and the pudendal nerve centrally. The majority of the vulva is drained by lymphatics that pass laterally to the superficial inguinal lymph nodes. The clitoris and anterior labia minora may also drain directly to the deep inguinal or external iliac lymph nodes.

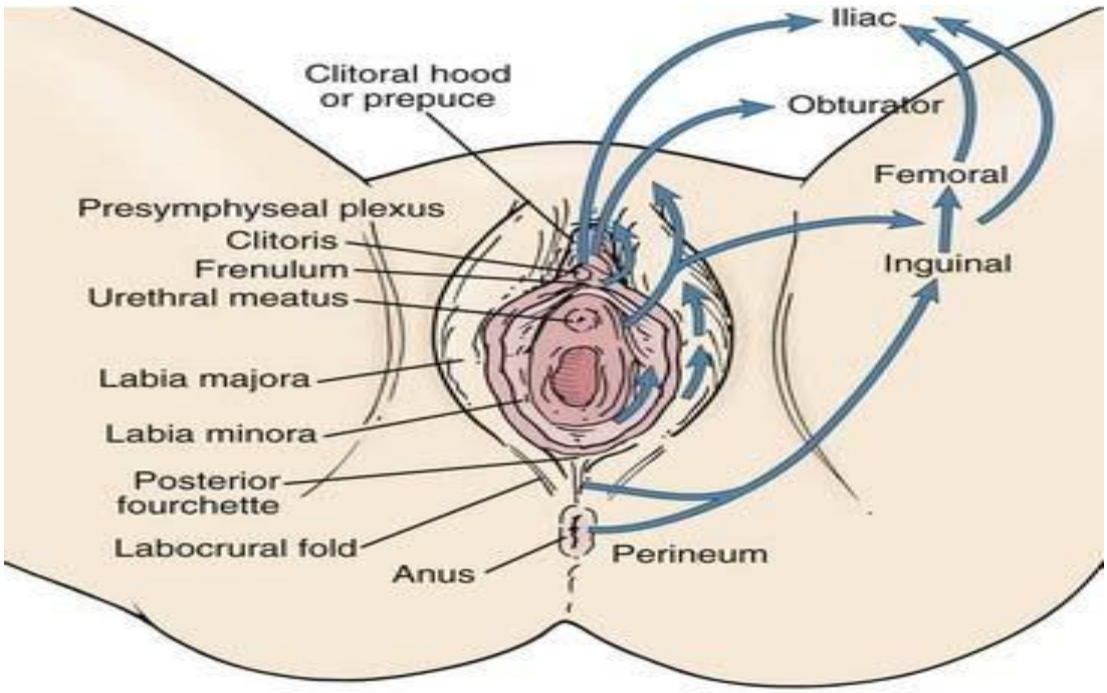

Figure 1: Surface anatomy of the vulvar and its lymphatic flow(17)

2.2 Pathophysiology of Cancer of the Vulvar

The development of both vulvar low-grade squamous intraepithelial lesions (LSIL) and vulvar high-grade squamous intraepithelial lesions is associated with human papillomavirus (HPV) infection, as is the corresponding vulvar cancer of the warty and basaloid subtypes. Multifocal vulvar HSIL and multicentric vulvar HSIL are most often associated with high-oncogenic-risk HPV subtypes 16, 18, and 31 and should be considered premalignant lesions. In contrast, vulvar condylomaacuminata are usually, but not exclusively, associated with low-oncogenic-risk HPV subtypes 6 and 11.

The anogenital epithelium is derived from the embryonic cloaca and includes the cervix, vagina, vulva, anus, and lower three centimeters of rectal mucosa up to the dentate line. Since the entire region shares the same embryological origin and is susceptible to similar exogenous agents such as HPV infection, squamous intraepithelial lesions in this area are often both multifocal and multicentric. Thus, women with VIN may have synchronous or metachronous neoplasia of other lower genital tract sites. There is evidence that some cases of high-grade VIN and vaginal intraepithelial neoplasia represent a monoclonal lesion derived from high-grade or malignant cervical neoplasia.

The pathogenesis of differentiated VIN is less well understood than vulvar LSIL or HSIL. It is typically associated with lichen sclerosus. The risk of vulvar squamous cell carcinoma in women with lichen sclerosus is approximately 5%. Differentiated VIN is found adjacent to 80 percent of vulvar squamous cell carcinomas. The diagnosis of solitary differentiated VIN is very challenging and appears to be associated with a rapid progression tosquamouscell carcinoma. Patients with lichen sclerosus with dyskeratosis and parakeratosis, hyperplasia, and/or basal cellular atypia tend to have the highest risk of progression to squamous cell carcinoma. There are no known biomarkers to reliably identify the patients at highest risk.

Carcinogenic infections are an important cause of cancer, particularly in less developed countries. HIV has been shown to increase cancer risk only in combination with other carcinogenic infectious agents(2). Among vulvar cancers, HPV–18, HPV–31, HPV–33, and HPV–45 were identified to play a smaller role than in cervical cancer .A study done in Botswana to describe the prevalence of select oncogenic viruses within vulvar squamous cell carcinoma

(VSCC) and their association with Human Immunodeficiency Virus (HIV) status found HPV16 was the most prevalent HPV strain (82.9% by PCR, 94.7% by either PCR or Immunohistochemistry.(10) HIV infection has also been shown to influence the development of a number of cancers associated with oncogenic viruses other than HPV, such as Kaposi's sarcoma Herpes virus(10).HPV type 16 was the predominant HPV type in high-grade vulvar pre-cancer and vulvar cancer, particularly basaloid and warty cancer (18,19).

Other risk factors of VC include; genital warts, cervical neoplasm, low education level, lower household income and low social economic status. High number of sexual partners, early age at first sexual intercourse and cigarette smoking was reported among patients with VC. Condyloma and non-invasive VC was detected during routine/frequent Pap smear. This was noted among younger women but presence of condyloma and VC was reported in all age groups (20,21).

2.3 Classification of Vulvar Cancer

Vulvar cancer can be classified into two groups according to predisposing factors: the first type correlates with a Human Papilloma Virus infection that causes vulvar intraepithelial neoplasia and occurs mostly in younger patients. The second group is not HPV associated and occurs often in elderly women without neoplastic epithelial disorders. Vulvar non-neoplastic epithelial disorders (VNED) and advanced age are believed to cause cellular atypia, a precursor to cancer.

There are multiple histologic subtypes of vulvar cancer, and these subtypes differ by HPV status, age group and mortality. Knowing the epidemiology of these different types is important because HPV-associated vulvar Cancer could potentially be prevented by HPV vaccines(18). The most common histologic type of vulvar malignancy is squamous cell carcinoma (SCC) 94.7%(22). Other histologies include melanoma, basal cell, Bartholin gland adenocarcinoma, sarcoma, Paget disease and rare verrucous carcinoma of the vulva affecting postmenopausal women.

2.4 Clinical Presentation of Cancer of the Vulva

The most commonly described symptom of vulvar cancer is a long history of pruritus. Less frequently reported symptoms include vulvar bleeding, dysuria, discharge, and pain. The most obvious manifestation of vulvar cancer is a vulvar lump or mass, which may present as ulcerated, leukoplakia, fleshy, or warty lesions. Less frequently reported symptoms include vulvar

bleeding, dysuria, discharge, and pain(14,23). In another study the symptomatology was dominated by vulvar pruritus (48.7%) and the average size of the tumor was 3.96cm(22). Mean age at diagnosis was 67.1 years and delay in seeking medical attention was 48.2 months.

Squamous cell carcinoma (SCC) accounts for approximately 95% of malignant tumors of the vulva and can be grouped into three main histological subtypes of vulvar SCC: warty, basaloid, and keratinizing. The predominant type, keratinizing, accounts for 65%–80% of vulvar SCCs while the basaloid and warty types of SCC account for the remaining 20%–35%. The keratinizing type usually occurs in postmenopausal women. The warty/basaloid types tend to occur more often in premenopausal or perimenopausal women. The keratinizing type is usually formed by well or moderately differentiated cells with an absence of koilocytosis(23,24).

2.5 Diagnostic Criteria of Cancer of the Vulva

A complete pelvic examination is performed. Assessment for tumor diameter, local extension to vagina, urethra, anus, bladder, rectum, and enlarged inguino-femoral lymph nodes. Bimanual pelvic examination and recto-vaginal examination are performed to assess local extension to the vagina, anus, rectum, or bladder. Colposcopyof the vulva, vagina, and cervix is performed. Biopsies are performed as needed to confirm invasive disease and assess depth of invasion. The inguinal and supraclavicular lymph nodes are palpated. If the inguino-femoral nodes are enlarged, a biopsy is performed to confirm nodal metastases. For patients with locally advanced primary lesions, an examination under anesthesia may be necessary to allow for a thorough evaluation to determine the extent of disease. Cystoscopy and proctoscopy may be performed if clinically indicated.

Diagnostic imaging of the pelvis, abdomen, or chest may complement physical examination. There are few data comparing imaging modalities in vulvar malignancies, and the choice of imaging modality to evaluate local, regional and distal spread is often based on institutional or personal preference.Magnetic resonance imaging (MRI) of the pelvis may assist in defining the local extent of disease if surgery is planned, especially for patients with locally advanced cancers. It is also helpful in radiation planning in patients who are not surgical candidates. A chest radiograph is obtained if lung metastases are suspected based on a symptom of shortness of breath and if no other chest imaging has been performed.

2.6 Staging of Cancer of the Vulva

Vulvar cancer is staged using the American Joint Committee on Cancer TNM staging system and the International Federation of Gynecology and Obstetrics (FIGO) staging systems. These two systems are very similar; both classify vulvar cancer on the basis of three factors: the size of the tumor (T), whether the cancer has spread to lymph nodes (N), and whether it has spread to distant sites (M). The final diagnosis is dependent upon thorough histopathologic evaluation of the operative specimen (vulva and lymph nodes).

Table 1. Staging vulvar cancer (TNM and International Federation of Gynecology and Obstetrics, FIGO(23)

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.

2.7 Background of the Study

Depending on the results of surgical staging, women are categorized as having early or advanced stage disease (25):

a) Early stage disease is defined as FIGO stage I or II. These patients should undergo a surgical excision including adjuvant treatment based on the findings at the time of surgery.

b) Locally advanced stage disease is defined as stage III or IVA. Operative treatment is preferred whenever feasible. Patients who are not surgical candidates should receive primary chemo radiation.

c) Stage IVB disease includes women with distant metastases – a primary chemotherapy is recommended, provided patients are candidates for systemic treatment. If not, palliative care is appropriate.

2.8 Management of Vulvar Cancer

Decisions regarding which patients are managed with surgery and adjuvant therapy versus those who are treated non-surgicallyis dependent on the stage of the disease and the patient's baseline health. The patient should be individually evaluated for the ability to tolerate surgery and adjuvant therapy.For most medically fit patients without evidence of distant disease, the standard approach to treatment is surgery and adjuvant therapy (6). In unresectable, locally advanced disease, chemoradiation is preferred to radiation therapy (RT) alone. Weekly Cisplatin 50 mg/m^2concurrently with radiation to the vulvar, groin and lymph nodes in the radiation fields(26).

However, in most large centers, the traditional en bloc resection has been replaced by the so-called triple incision. Besides the vulvectomy dissection-shape incision, two separate incisions in the groin area are made for inguinal lyphadenectomy. This procedure shows a markedly lower rate of wound-healing disorders(23). In recent years sentinel node evaluation has been advocated in early stage cancers to reduce complicationsofinguino-femorallymphadenectomy. In addition, groin node debulking followed by radiotherapy have been proved to be effective(27).

Complications such as wound breakdown, infection, lymphedema, and sexual dysfunction have consistently been associated with surgical treatment leading to disabling treatment-related morbidity. In recent years, chemo radiation therapy (CRT) is increasingly preferred as primary or adjuvant treatment in vulvar cancer with the comparative advantage of reducing treatment-related morbidity and improving recurrence and survival rates(28). Intensity modulated RT (IMRT) may be advantageous in the treatment of vulvar cancer because it may reduce dose to small bowel, rectum, and bladder thereby decreasing treatment-related toxicity.(29)

2.9 Clinical Outcomes

The prognosis of patients with vulvar cancer is quite good when convenient treatment is provided in a timely manner. Inguinal and/or femoral node involvement is the most significant prognostic factor for survival in patients with vulvar cancer. Extra capsular growth of lymph node metastases, two or more affected lymph nodes, and more than 50% replacement of lymph nodes by tumor are predictors of poor survival.

The overall 5-year survival rate ranges from 70% to 93% for patients with negative nodes and from 25% to 41% for those with positive nodes. Other prognostic factors include stage, capillary lymphatic space invasion, and older age. Recurrent lesions in the lymph nodes, as well as in distant sites, are not amenable to surgery or radiotherapy. They are difficult to treat, and the 5-year survival rate is generally less than 5%.

The stage of disease, tumor size, and status of surgical margins are sensitive predictors of survival(14).Vulvar cancer patient’s characteristics and survival in part of sub Saharan Africa were chronic HPV and HIV infections. Study in Ethiopia of 86 patients with VC showed the median age of the patients was 39 (range: 20–85) years, 83% with known HIV status were positive and 81% presented with FIGO stages 2 or 3. The 1- and 2-year survival rates were 80% and 51%, respectively. Mode of therapy received was surgery, radiotherapy and chemotherapy. Patients who received therapy had better survival than those who did not. Due to the high HIV positivity rate, suggestion that all VC patients should be tested and HIV patients should have an inspection of the vulva during cervical cancer screening was made(7).

2.10 Conceptual Framework

2.10.1 Narrative

Although Vulvar cancer is an uncommon neoplasm that makes up less than 5% of all gynecological cancers, over last two decades, there is a significant increase in the burden of the disease especially in women lessthan 60 years of age consistent with changing sexual behaviors and increasing exposure to HPV. Some of the social demographic risk factors of vulvar cancer are; Age- with the diseases mostly seen in women older than 65 years of age, low economic status and low levels of education.The most commonly described symptom of vulvar cancer is pruritus. Less frequently reported symptoms include vulvar bleeding, dysuria, discharge, and pain. These non-specific symptoms contribute to late presentation and diagnosis. The most obvious manifestation of vulvar cancer is a vulvar lump or mass.HPV and HIV infections are strongly associated with development of vulvar cancer, studies have reported that the prevalence of HPV varied from 3% to as high as 76%(9). The most common histological type of vulvar cancer is squamous cell carcinoma. The standard management of vulvar cancer is surgical vulvectomy and adjuvant therapy outcome and 5-year survival rates are high for early stage disease while advanced FIGO stage and the number of lymph node metastasis are the main negative predictors of outcome.(15).

2.10.2 Diagrammatic

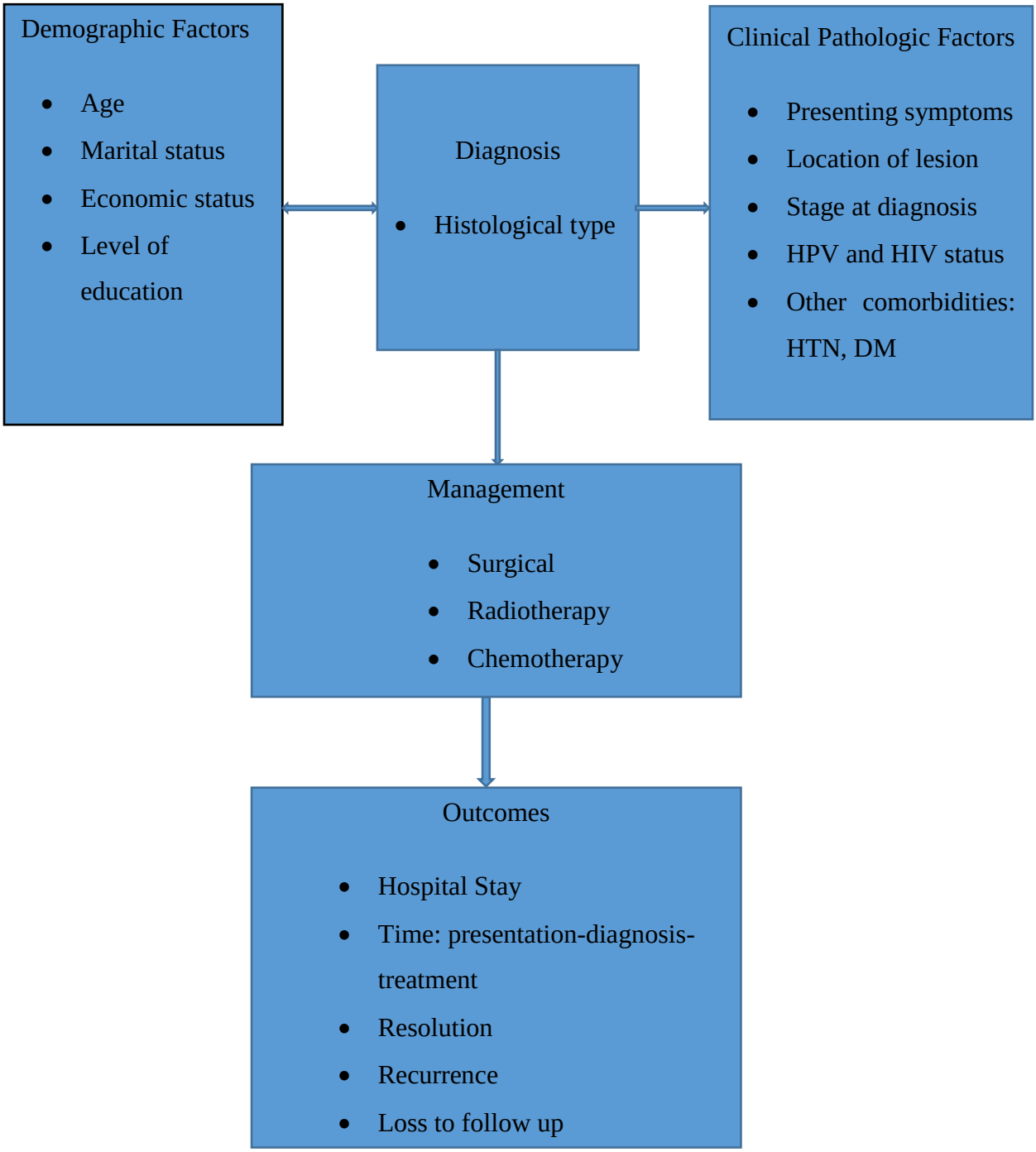

Figure 2. Conceptual framework

2.11 Study Justification

The prevalence of vulval cancer is between 3%-7.6% and is associated with significant morbidity and mortality, if confounded with diseases such as diabetes mellitus and hypertension. A recent study in South Africa found a significant association between the HIV status of patients and the age at diagnosis of vulvar cancer. In the study, Butt demonstrated that HIV positive patients were more likely to develop vulvar cancer at a young age, but called for follow-up studies to corroborate the finding. Such data is missing in Kenya. Moreover, the profile of vulvar cancer, which includes its burden and the clinical outcomes of patients on different treatment modalities has not been studied sufficiently, while the level to which comorbidities such as HIV influence the clinical outcomes of patients is not well-explored. The study filled these gaps. The burden, treatment modalities, and clinical outcomes of vulval cancer was demonstrated in a cohort of Kenyan women who received medical care at Kenyatta National Hospital.between 2014-2018.

2.12 Study Question

What is the burden, management and outcomes of patients with histologically confirmed vulva cancer at the KNH between 2014-2018?

2.13 Study Objectives

2.13.1 Broad Objective

To determinetheburden,management and outcomes of patients with histologically confirmed vulvar cancer at the KNHbetween 2014- 2018

2.13.2 Specific Objectives

Among patients with histologically confirmed vulvar cancer at KNH to determine

- **a)** The socio-demographic and clinical characteristics
- **b)** The burden, stage at presentation and treatment modalities.
- **c)** The managementoutcomes

3.0 CHAPTER THREE: METHODOLOGY

3.1 Study Design

This is a retrospective study of histologically diagnosed vulva cancers seen at Kenyatta National Hospital between January2014 and December 2018. Patients' records was extracted from the hospital registry. A data extraction tool is used to extract the following information from the patients' file: socio-demographic status, presenting symptoms, location of the lesion, stage of the disease using revised FIGO 2009 staging system, histological type,HPV and HIV status, Diabetes mellitus and Hypertension comorbidities, date of first attendance, date of commencement of treatment, treatment received and outcome.

3.2 Study Area

The study was undertaken at the Kenyatta National Hospital (KNH)which is the largest public, teaching and referral hospital in the country serving patients from a broad socio – cultural divide not only from Kenya but also from East and Central Africa. The hospitals' oncology unit is managed by a multi-disciplinary team of professionals from different departments including gynecological oncologists, oncology nurses, nutritionists, social workers, pathologists, pharmacists, radiologists and hematologists. On average, 1200 patients are reviewed at the oncology clinic annually with approximately 50 women diagnosed with and receiving treatment for vulvar cancer.

3.3 Study Population

The study population was generated from records of women who were diagnosed with vulvar cancer at the KNH or referred to the hospital with a diagnosis of vulvar cancerfrom January 2014to December2018. The period of 5 years was settled on as it provided the study team with an appropriate sample size for analysis. In addition, the records for this period are more likely to be easily accessible. Records of approximately 187patients was isolated for randomization.

3.4 Sample Size Determination and Formula

The sample size was calculated using the formula for finite population (less than 10,000) as follows.

$$n = \frac{Z^2_{1-\alpha/2} \times p(1-p)}{d^2}$$

Assumptions for calculating the sample size

n = Desired sample size

Z = value from standard normal distribution for 95% confidence level (1.96)

p = expected true proportion (estimated at 10.9%, from Butt et al (2017))

d = estimated error (0.05)

Substituting this in the formula gives a sample size of 150 as follows:

$$n = 1.96^2 \times 0.109 (1-0.109)$$

$$0.05 \times 0.05$$

To factor in for missing data, the formula of 1/1-f*the calculated sample size of 150 was used. Prof.E.Cheserem in her study on establishing the characteristics and management of ovarian cancer at the Kenyatta National Hospital in 2013, established that missing data accounted for 10%.

Therefore, the recalculated sample size = 1/1-0.10*150 = **165**

3.5 Sampling Procedure

Patient informationwas retrieved from the Records department at the KNH after seeking a written authorization from the hospital Records officer. Data extraction was done by the principal investigator and two research assistants and entered into a structured data extraction tool.Once the patient records have been identified and separated per year, simple random

sampling using random tables was used to arrive at the appropriate files for data extraction. Files that did not have data as per the data extraction tool was replaced by the next randomly selected file from the same year. Data was then be extracted on to the specially designed data collection tools.

For the 187 participants, proportionate sampling was applied to arrive at the number to be sampled from each of the years based on the patient numbers as shown in the table below:

Table 2. Proportions of patients from the KNH gynecology ward and oncology department

Hospital	Number of VC patients	Proportionate sample
2014	29	770
2015	32	700
2016	38	835
2017	23	1094
2018	37	1243

3.6 Recruitment of Study Participants

3.6.1 InclusionCriteria

Patients with a histological diagnosis of cancer of the vulva

3.6.2 Exclusion Criteria

Patients with other reproductive tract cancers (cancer of cervix, endometrium, vagina, ovaries, and any patients with metastasis of this tumors to vulvar).

3.7 Data Variables

Table 3. Data variables

Exposure variables	Outcome variables	Sources of data
Clinical presentation Stage at diagnosis HPV status HIV status Treatment type: radiotherapy, chemotherapy, surgery	Hospital stay Loss to follow up Death 1-5-year survival rate	Patients file

3.8 Study Materials

Materials used for this study included stationery, data retrieval forms, storage files, flash drives, hard drives and password protected computers.

3.9 Training Procedures

The two research assistants, both registered clinical officers with experience in data collection received the appropriate training and a piloting of the data collection tool was done.

3.10 Quality Assurance Procedures

The following measures was taken for quality assurance through all the stages of the study.

- Data obtained from the records and files was counterchecked by the data manager to ensure it was correctly filled. This was done on a daily basis
- Data was stored in password protected computers, hard drives and flash drives that was accessible to only the principal investigator, supervisors and statistician to ensure confidentiality is maintained.

3.11 Ethical Considerations

The study proposal was submitted to the KNH/UON ERC for approval before the commencement of the study. In addition, permission was sought from the Department of Obstetrics and Gynecology UON and the KNH administration to carry out the study. Since the study was retrospective the patient's consent was not required but requested a waiver for consent for the study from the ethics committee. Patients' data was also be de-identified to maintain confidentiality.

3.12 Data Management and Analysis

Data was collected using a specially designed data extraction tool, entered into an excel sheet and analyzed using SPSS software. The burden of cancer of the vulva was calculated. Descriptive statistics for the socio demographic characteristics was presented using means, variance and standard deviation; bivariate analysis was conducted to establish association between treatment regimen and outcomes. Kaplan Myer curve was used to present time to diagnosis, treatment, discharges and where applicable, to demise.

3.13 Study Results Dissemination Plan

The final results was published into a thesis that was presented at the Department of Obstetrics and Gynecology both KNH and UON. It was also presented in other fora like conferences or seminars and to health care workers involved in the management of patients with Vulvar cancer. A report of the study findings was shared with the KNH-UoN ERC team and with the KNH. Following the presentation to the department, a manuscript was submitted to the GynecologicalOncology journal for publication.

4.0 CHAPTER FOUR: RESULTS

4.1 Study Flow Chart

One hundred and ninety patient files were screened for eligibility, 31 were excluded due to primary cancer was not vulvar. In total, 159 files met the criteria for inclusion for data extraction and analysis. A sample survey was done for all the159 files that fell within the 10% acceptable expected sample size of 165.

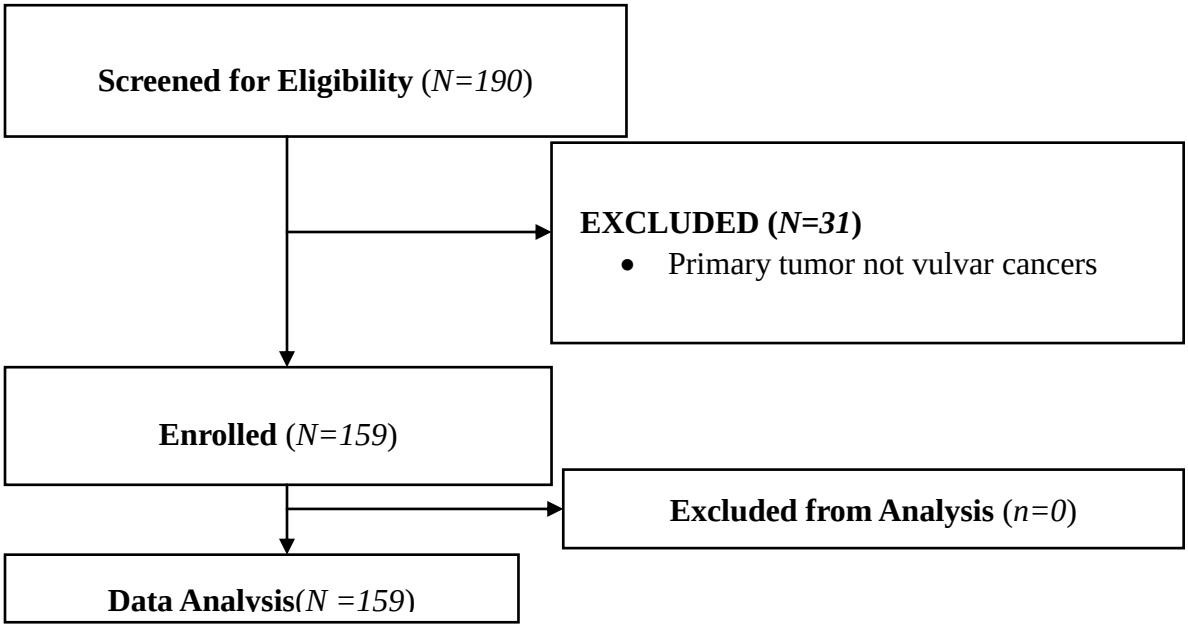

Figure 3. Study flow chart

4.2 Socio Demographic and Clinical Characteristics of Patients

During this study period, 159 patients with vulvar cancer were identified.The mean age was 50.97 years (range 17 to 95 years). At the time of diagnosis, majority of the patients were married (40.3%), unemployed (62.2%) and had attained primary education(42.8%).The commonest clinical presentation was a vulvar mass (76.1%), ulcers (25.2%) and itchiness (15.7%). 10 presented with vulvar pain (7.5%) and six (3.8%) had pruritic discharge. The labia majora was the commonest vulva cancer location (37.7%), followed by the labia minora (30.2%).125 patients (78.6%) did not have comorbidities, while 18 (11.4%) and 8 (5.0%) had hypertension and diabetes mellitus (DM).

The HIV status of 139 patients (87.4%) was available in files. Eighty-four were HIV positive (52.8%), 55 (34.6%) were HIV negative while 20(12.6%) HIV status were unknown. The youngest patient in the HIV positive group was 21 years and 17 years in the HIV negative group. The oldest patients were 79 in the HIV positive group and 95 years in the HIV negative groups. HIV positive patients were statistically significantly younger than HIV negative ones [Z=-6.18, p<0.01]. The median age of HIV positive and negative women was 41 years and 60 years respectively (Table 5)

Table 4. Demographic and clinical presentation of patients with histologically confirmed vulvar cancer at KNH between Jan 2014 and Dec 2018

		N (159)	%
Age	Mean (median)		50.97±15.9 (48)
Education Level	Primary	68	42.8
	Secondary	49	30.8
	Tertiary	42	26.4
Marital Status	Married	83	52.2
	Single	27	17.0
	Widowed	38	23.9
	Divorced/Separated	11	6.9
Occupation	Self Employed	55	34.6
	Formal Employment	5	3.2
	Unemployed	99	62.2
HPV status		0	0
HIV status	Positive	84	52.8
	On ARV	84	100
	Negative	55	34.6
	Unknown	20	12.6
Clinical presentation	mass	121	76.1
	Pruritus	25	15.7
	Others *	13	8.2
Location	Labia majora	60	37.7
	Labia minora	48	30.2
	Mons pubis	32	18.9
	Fouchette	7	4.4
	Clitoris	12	7.5
Histology	SCC	156	98.1
	Verruca	3	1.9
Comorbidities			
	HTN	18	11.4
	DM	8	5.0
	Others**	8	5.0
	None	125	78.6
Others* Warts, inguinal swelling, bleeding, discharge, Others**: Dementia, TB, asthma, kidney disease.			

Table 5. The HIV serostatus of vulvar cancer patients stratified by age (N=139)

	HIV Serostatus			
Age	Positive	Negative	Z	P
Mean	42.7±8.99	59.62±17.75	-6.18	<0.01
Median	41	60		
Minimum	21	17		
Maximum	79	95		

4.3 TheBurden, Stage at Presentation and Treatment Modalities

During the study period 4541cases of gynecological cancer were reviewed. Vulvar cancer was 4thcommonest constituting 159(3.5%) cases.Mortality was an outcome for 27.7% (44/159).By the International Federation of Gynecology and Obstetrics (FIGO) staging, stage III vulva cancer was the commonest (46.5%), followed by stage IV (35.8%). Twenty-one patients (15.1%) were in stage II at the time of diagnosis. Seven patients (12.3%) had a palpable lymph node.The commonest histology type was Squamous cell carcinoma (SCC) (98.1%). There were three patients with verruca (1.9%).

Of 159 patients with vulvar cancer 125(78.6%) patients received treatment and 34 (21.4%) had palliative care. Forty-six patients (36.8%) had radiotherapy as primary treatment, 30 (24.0%) had surgery and twenty three (18.4%) had chemo-radiotherapy. Out of the 159 patients, 30 of these patients had radical vulvectomy. Ten patients (6.3%) had side effects following treatment, with wound sepsis reported in four of those who had surgery.

Table 6. Burden, stage at presentation, and treatment modalities of patients with a histologically confirmed vulvar cancer at KNH between Jan 2014 and Dec 2018

		N	%
Outcome	Dead	44	27.7
	Alive/unknown	115	72.3
Stage	I	11	6.9
	II	32	20.2
	III	60	37.7
	IV	56	35.2
Cancer treatment		125	78.6
Combination		47	37.6
	Radiotherapy and chemotherapy	23	48.9
	Surgery and radiotherapy	14	29.8
	Surgery and radiotherapy and chemotherapy	8	17.0
	Surgery and chemotherapy	1	2.1
	Radiotherapy and adjuvant	1	2.1
Monotherapy		78	62.3
	Radiotherapy	46	36.8
	Surgery	30	24.0
	Chemotherapy	2	1.60
Palliative care		34	21.4

4.4 Managements Outcomes

Of the 159 patients, 69 (43.4%) are still on regular follow-up in a median duration of 3.35 months [range of 1 to 18 months]; 18 (11.3%) had a resolution while 4 (2.5%) patients had vulvar cancer recurrence in a median duration of 10.69 months [range of 2 to 35 months].46 (28.9%) were lost to follow-up in a median time of 3.16 months [range of 0-43 months]. Forty four patients died during follow up (27.7%) in a median time of 1.7 months [range 0 to 27 months].

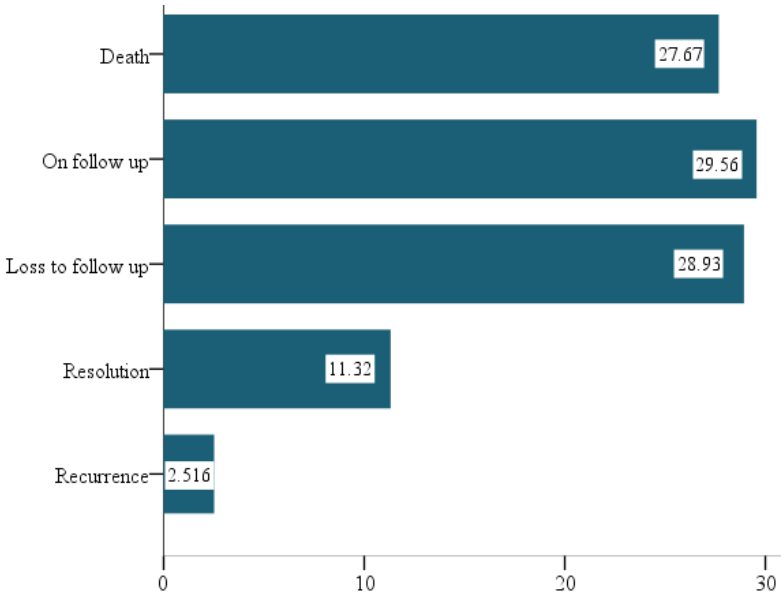

Figure 4. Outcomes of vulvar cancer patients

The cumulative five-year survival rate was 64.6%. The median survival was not reached.

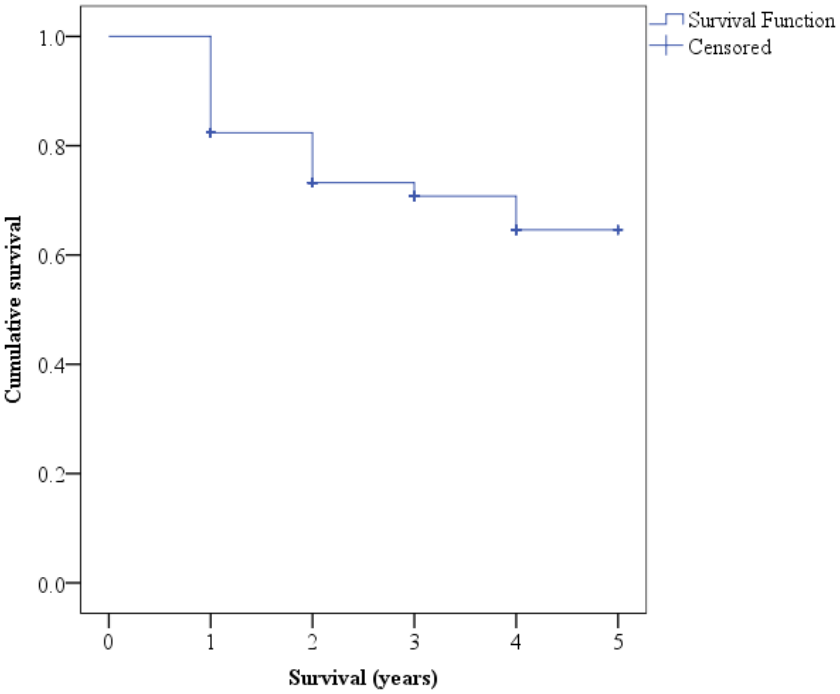

Figure 5. Cumulative survival rate of vulvar cancer patients at the KNH

4.5 Survival Rate by HIV Status of Vulvar Cancer Patients

Twenty nine(18.2%) of 84 HIV positive and 15 (9.4%) of 55 HIV negative patients died with the mean duration to death found to be 29.8 months (range 22.4-37.3) in HIV positive group and 40.4 months (range 34.3-46.1) in HIV negative group. The one year cumulative survival rate was 73.6% in the HIV positive group and 88.5% in the HIV group, while the two-year and three year cumulative survival rates were 73.6% and 88.5% for HIV positive patients and 55.2% and 88.5% respectively HIV negative (Figure 8). Cumulative survival rates were comparable statistically (X^2=2.49, p=0.11)

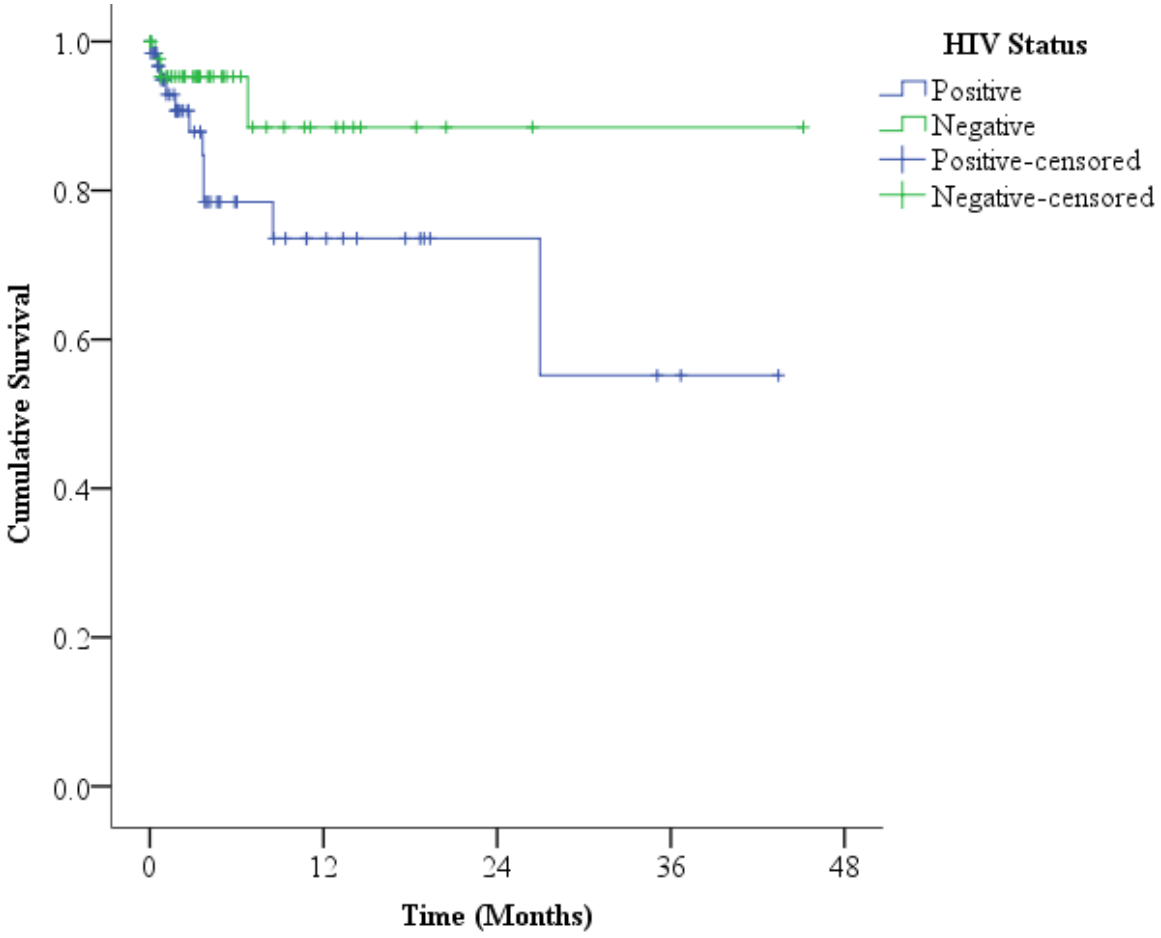

Figure 6. Cumulative survival rate by HIV status of vulvar cancer patients

4.6 Cumulative Survival Rate by Modality of Management of Vulvar Cancer Patients

Three of the patients on combination therapy and seven on monotherapy died during the study period. The mean duration to death was 38.7 months (range 30.9-46.5) among patients on combination therapy and 33.8 months (range 26.9-40.7) on monotherapy. The one and two year cumulative survival rate was 95.4% among patients who received combination and 75.7% for those on monotherapy. By the fourth year, the survival rate was comparable at 71.6% on combination and 75.7% on monotherapy (X^2=2.25, p=0.133).

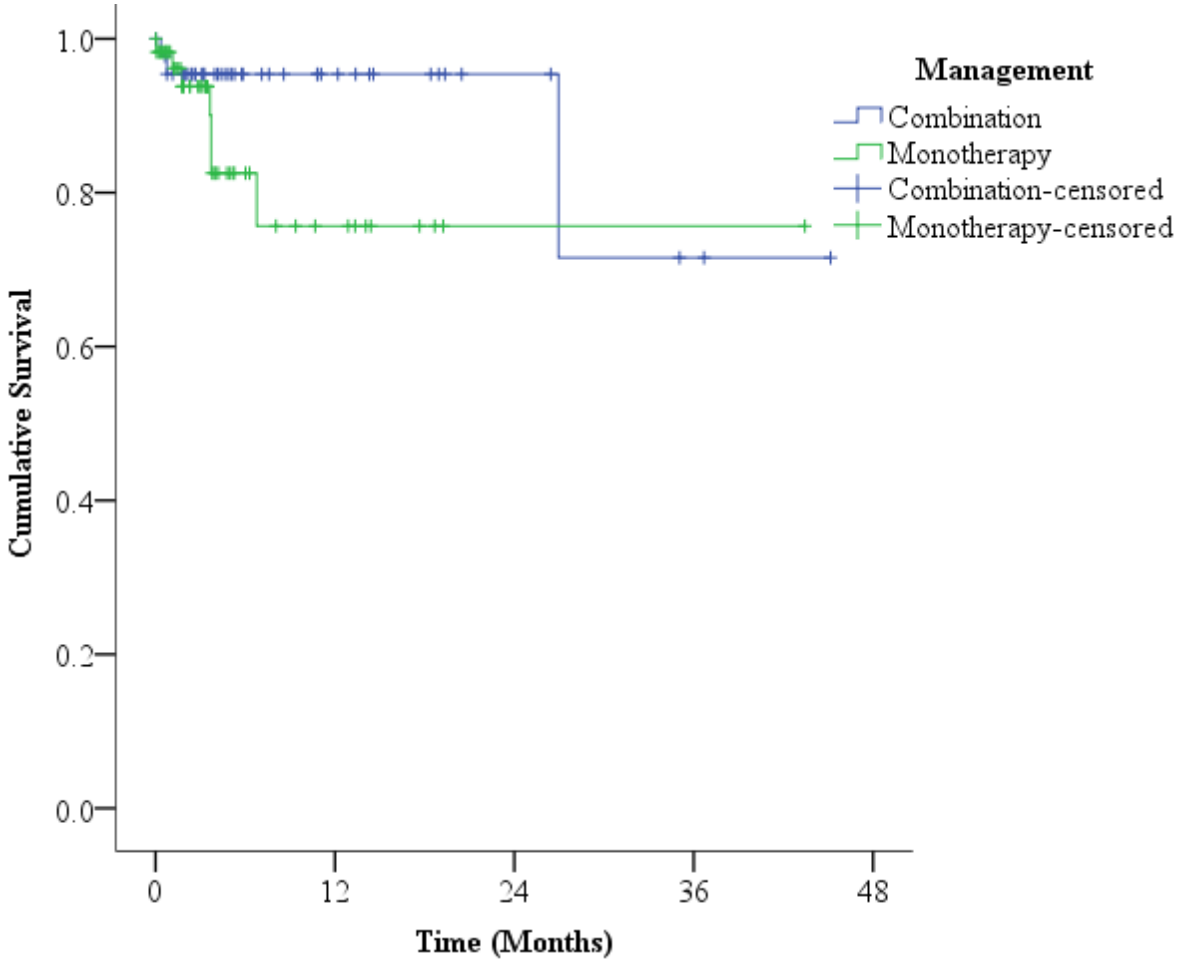

Figure 7. Cumulative survival rate by modality of management of vulvar cancer patients

4.7 Cumulative Survival by Stage of Cancer

The cumulative five-year survival rate for stage I, II, III, and IV vulvar cancer patients varied statistically significantly (X^2=32.8, P<0.01). Overall, stage I, II, III, and IV cancer patients had a five-year survival rate of 90.9%, 82.0%, 66.9%, and 36.2% respectively.

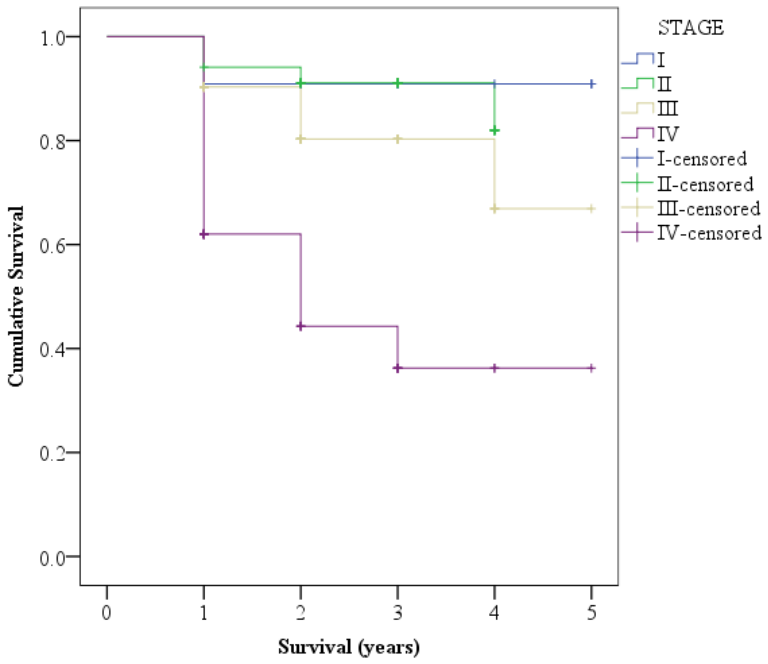

Figure 8. Cumulative survival by stage of cancer

5.0 CHAPTER FIVE: DISCUSSION, CONCLUSIONS, AND RECOMMENDATIONS

5.1 Discussion

Epidemiological characteristics of vulvar cancer patients managed at KNH matched published data. As in studies in Nigeria and South Africa, vulvar cancer was common in the fourth decade of life accounting for 3.5% 0f all gynecological cancers(16,30) The mean age was 50.9 years, with age range of 17 and 95years. Thiswas comparable to studies from Africa with an average of 10-15 years younger than women with vulvar cancer in high income countries. Patients were mostly married (40.3%) and the commonest type of VC was squamous cell carcinoma (SCC) histology (98%). According to the cancer registry of Kenya, 90% of vulvar cancers are SCC, which was in line with our findings. Our results were also in line with global data: from Italy (100% SCC) (31), Tunisia (94.7%) (22) and New Zealand (95% SCC) (32), but higher than the US (75% SCC) (33) where other histologies may include melanoma, basal cell carcinoma, adenocarcinoma and Paget disease.

Of the 159 vulvar cancer patients managed at KNH between 2015 and 2018, 37.7% presented for treatment at an advanced FIGO stage III, while 35.2% were in stage IV. This contradicts findings from the developed world where stage I and II constitute 58% of vulvar cancer diagnoses (31). This may be explained as being due to lack of adequate health services and poor health seeking behaviors in Kenya being barriers to accessing vulvar cancer treatment services.

Indications from literature are that vulvar cancer patients from low and middle income countries are more likely to present to hospital late, which complicates treatment and the prognosis of the disease. In a multicenter epidemiological and clinicopathological study in Tunisia, 53.8% of patients present for treatment in stage III vulvar cancer(22). The study evaluated 75 vulvar cancer cases with a median age of about 65 years and stressed the need for designing programs that can facilitate early diagnosis of vulvar cancer and its management. Studies in Ethiopia and South Africa corroborated the results of Tunisia and others, with 81.0%of vulvar cancer patients in Ethiopia (7) and 50% in South Africa (7) presenting for treatment at advanced stage (III and IV)(7,16,22).

In Kenya, the lack of adequate health insurance and poor health seeking behavior are some barriers for accessing vulvar cancer services, which should be targeted in controls (34). Advocacy programs that inspire patients to seek treatment early has been found to be effective. Sensitization on the symptoms of vulvar cancer and routine physical and histological examinations for vulvar cancer have also been proposed in Morocco (35).

Pruritus is a commonly reported clinical presentation for vulvar cancer in literature. The presence of vulvar masses, ulcers, discharge, and pain have also been reported in different cohorts of patients. We found similar results at KNH. Over 76% of patients had a vulvar mass, mostly on the labia majora, labia minora, Mons pubis, andclitoris. Such lesions can be leukoplakic, ulcerated, warty, or fleshy and often present with pain (23). Pruritus (15.7%) and less commonly described vulvar cancer symptoms such incontinence, bleeding, and discharge were also reported. A study in German, vulvar cancer patients presented with similar symptoms (23). In Chinese women, pruritus and vulvar masses were common clinical symptoms of vulvar cancer (36).

Radiotherapy was the primary treatment modality for vulvar cancer patients at KNH (36.8%). Radical vulvectomy was the main surgical intervention offered. Similar findings have been reported internationally and locally. In Thailand, combination therapy was required for 50.0% of women with SCC of the vulvar. Of those who required a surgery, radical local excision with dissection of groin nodes (bilateral) was the commonest surgical modality.

In Nigeria, the majority of vulvar cancerpatients were managed with radicalvulvectomy(30). However, because of late presentation, such patients were prone to having adverse reactions to the surgery. Sepsis, vomiting, diarrhea, rashes, and lower abdominal pain were the commonest adverse treatment outcomes at KNH.

The one, two, and three-year survival of cancer patients managed at KNH was high at 81.0%, 81.0%, and 64.8% respectively. Even though our results conformed to the data from the American cancer society (71%) and Butt and Botha in South Africa (58.8%)(16), contrary findings have been reported in literature. In the USA, lower survival rate of 43-48% were reported in patients with stage IVB vulvar cancer. Moreover, these participants had a grossly positive persistent lymphadenopathy, which might have been a confounder (37).

Thailandreported a survival rate of 50.8%(38)andEthiopia 52.8%,(7,38)even though the patients evaluates in both study had many comorbidities(7,38). Thus, if managed well, vulvar cancer patients live long and productive lives.

5.2 Conclusions

This is the first study to describe the burden, management and outcome of histologically confirmed vulvar cancer at KNH between 2014 and 2015. Vulvar cancer accounted for 3.5% of all gynecological cancers with a median age of 48yrs. The most common tumor location was labia majora with majority presenting at an advanced FIGO Stage III and IV; all cases were of squamous cell carcinoma histologic subtype. These patients were more likely to be treated with radiotherapy, surgery chemotherapy alone or a combination of two or all modalities. Majority of the patients were HIV-positive (87.4%) with an overall five year survival rate of 64.6%. Loss to follow up 46(29.56%)

5.3 Recommendations

Advocacy or sensitization programs that can improve health seeking behavior of at-risk women are needed.

Indication of HPV strain found in histological result of biopsy taken. Help in creating awareness of the benefits of the HPV vaccine.

Due to high HIV positivity amongst patients with vulvar cancer, we suggest HIV patients on follow-up to undergo routine vulvar inspection during routine cervical cancer screening.

Proactive follow-up of patients needed to ensure compliance to treatment

5.4 Study Limitations

The study was retrospective in nature therefore selection bias, misclassification of information were limitations. To minimize this,files were capturedusing the ICD 9/10 to minimize bias. In addition, a markup of 10% had been applied while calculating the sample size to cater for missing data. Sampled files with missing relevant data were replaced by picking the next ones randomly.

REFERENCES

1. Sankaranarayanan R. Worldwide burden of gynaecological cancer : The size of the problem. 2006;20(2):207–25.

2. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Heal [Internet]. 2016;4(9):e609–16. Available from: http://dx.doi.org/10.1016/S2214-109X(16)30143-7

3. Dittmer C, Katalinic A, Mundhenke C, Thill M, Fischer D. Epidemiology of vulvar and vaginal cancer in Germany. Arch Gynecol Obstet. 2011;284(1):169–74.

4. Nkyekyer K. Pattern of gynaecological cancers in Ghana. East Afr Med J. 2000;77(10):534–8.

5. Okolo CA, Odubanjo MO, Awolude OA, Akang EEU. A Review of Vulvar and Vaginal Cancers in Ibadan , Nigeria. North Am J Med Sci [Internet]. 2013;6(2):76–81. Available from: http://www.najms.net/a-review-of-vulvar-and-vaginal-cancers-in-ibadan-nigeria/

6. Eke AC, Alabi-isama LI, Akabuike JC. Management options for vulvar carcinoma in a low resource setting. World J Surg Oncol [Internet]. 2010;8(1):94. Available from: http://www.wjso.com/content/8/1/94

7. Kroeber ES, Mathewos A, Wondemagegnehu T, Aynalem A, Gemechu T, Piszczan S, et al. Vulvar cancer in Ethiopia. Med (United States). 2018;97(9).

8. Dadzie MA, Aidoo CA, Vanderpuye V. Vulva cancer in Ghana – Review of a hospital based data. Gynecol Oncol Reports [Internet]. 2017;20:108–11. Available from: http://dx.doi.org/10.1016/j.gore.2017.03.015

9. Zhang J, Zhang Y, Id ZZ. Prevalence of human papillomavirus and its prognostic value in vulvar cancer : A systematic review and meta-analysis. 2018;1–15.

10. Tesfalul M, Simbiri K, Wheat CM, Motsepe D, Goldbach H, Armstrong K, et al. NIH Public Access. 2015;24(4):758–65.

11. Rantshabeng PS, Moyo S, Moraka NO, Ndlovu A, Macleod IJ. Prevalence of oncogenic human papillomavirus genotypes in patients diagnosed with anogenital malignancies in Botswana. 2017;1–8.

12. Bruni L, Diaz M, Castellsague X, Ferrer E, Bosch FX, Sanjose S De. Cervical Human Papillomavirus Prevalence in 5 Continents : Meta-Analysis of 1 Million Women with Normal Cytological Findings. 2010;202.

13. Human Papillomavirus and Related Diseases Report. 2017;(July).

14. Piura B, Rabinovich A, Cohen Y, Friger M GM. Squamous cell carcinoma of the vulva in the south of Israel. J Surg Oncol. 1998;3(67):174–81.

15. Zhou, Jinhong GS. The prognostic role of FIGO stage in patients with vulvar cancer: a systematic review and meta-analysis Jinhong Zhou, Guoping Shan 10.1185/03007995.2016.1162147. 2016;

16. Butt JL, Botha MH. Vulvar cancer is not a disease of the elderly: Treatment and outcome at a tertiary referral centre in South Africa. South African Med J. 2018;107(11):1000.

17. Anthony H. Russell LRD. Cancer of the Vulva. In: Leibel and Phillips Textbook of Radiation Oncology. 3rd ed. 2010. p. 1085–110.

18. Saraiya M, Watson M, Wu X, King JB, Chen VW, Smith JS, et al. Incidence of in situ and invasive vulvar cancer in the US, 1998-2003. Cancer. 2008;113(10 SUPPL.):2865–72.

19. Larsson GL, Helenius G, Andersson S, Elgh F, Sorbe B, Karlsson MG. Human papillomavirus (HPV) and HPV 16-variant distribution in vulvar squamous cell carcinoma in Sweden. Int J Gynecol Cancer. 2012;22(8):1413–9.

20. Madsen BS, Jensen HL, Van Den Brule AJC, Wohlfahrt J, Frisch M. Risk factors for invasive squamous cell carcinoma of the vulva and vagina - Population-based case-control study in Denmark. Int J Cancer. 2008;122(12):2827–34.

21. Sherman KJ, Daling JR, Chu J, Weiss NS, Ashley RL, Epidemiology S, et al. Lippincott Williams & Wilkins All use subject to JSTOR Terms and Conditions Genital Other Sexually Transmitted and Vulvar Cancer Diseases , cancer. 2015;2(4):257–62.

22. Chanoufi MB, Touhami O, Boujelbane N, Mhiri R, Kehila M, Khlifi A, et al. Vulvar cancer in Tunisia: Epidemiological and clinicopathological features multicentric study. J Egypt Natl Canc Inst [Internet]. 2017;29(2):95–8. Available from: http://dx.doi.org/10.1016/j.jnci.2017.02.001

23. Alkatout I, Schubert M, Garbrecht N, Weigel MT, Jonat W, Mundhenke C, et al. Vulvar cancer: Epidemiology, clinical presentation, and management options. Int J Womens Health. 2015;7:305–13.

24. Maclean AB. Vulvar cancer: Prevention and screening. Best Pract Res Clin Obstet Gynaecol. 2006;20(2):379–95.

25. Rauh-Hain JA, Clemmer J, Clark RM, Bradford LS, Growdon WB, Goodman A, Boruta DM 2nd, Dizon DS, Schorge JO del CM. Management and outcomes for elderly women with vulvar cancer over time. BJOG. 2014;121(6):719–27.

26. Weinberg D, Gomez-Martinez RA. Vulvar Cancer. Vol. 46, Obstetrics and Gynecology Clinics of North America. 2019. p. 125–35.

27. Bidzinski M, Petersen C, Regauer S, Mahner S, Ulrikh E, van der Velden J, et al. European Society of Gynaecological Oncology Guidelines for the Management of Patients With Vulvar Cancer. Int J Gynecol Cancer. 2017;27(4):832–7.

28. Mulayim N, Silver DF, Schwartz PE, Higgins S. Chemoradiation with 5-fluorouracil and mitomycin C in the treatment of vulvar squamous cell carcinoma. Gynecol Oncol. 2004;93(3):659–66.

29. Hassanzadeh C, Mutch DG, Powell MA, Chundury A, Grigsby PW, Schwarz JK, et al. Intensity modulated radiation therapy for squamous cell carcinoma of the vulva: Treatment technique and outcomes. Adv Radiat Oncol [Internet]. 2017;2(2):148–58. Available from: http://dx.doi.org/10.1016/j.adro.2017.02.006

30. Adekunle O, Marliyya Z, Sunday A, Abimbola K, Richard T, Habiba I, et al. The pattern of carcinoma of the vulva in Zaria, Northern Nigeria. Niger J Basic Clin Sci. 2016;13(1):46.

31. Nicoletto MO, Parenti A, Del Bianco P, Lombardi G, Pedrini L, Pizzi S, et al. Vulvar cancer: prognostic factors. Anticancer Res. 2010 Jun;30(6):2311–7.

32. Dass PH, Kuper-Hommel MJ. A review of squamous cell vulvar cancers in Waikato region, New Zealand. N Z Med J. 2017 Nov;130(1465):19–28.

33. Rogers LJ, Cuello MA. Cancer of the vulva. Int J Gynecol Obstet. 2018 Oct;143:4–13.

34. Muigai J, Jacob L, Dinas K, Kostev K, Kalder M. Potential delay in the diagnosis of vulvar cancer and associated risk factors in women treated in German gynecological practices. Oncotarget. 2018 Feb;9(9).

35. Ouasmani F, Hanchi Z, Haddou Rahou B, Bekkali R, Ahid S, Mesfioui A. Determinants of Patient Delay in Seeking Diagnosis and Treatment among Moroccan Women with Cervical Cancer. Obstet Gynecol Int. 2016;2016:1–9.

36. Xiao X, Meng Y-B, Bai P, Zou J, Zhang Y, Nguyen TMB, et al. Vulvar Cancer in China: Epidemiological Features and Risk Analysis. J Cancer. 2017;8(15):2950–8.

37. Thaker NG, Klopp AH, Jhingran A, Frumovitz M, Iyer RB, Eifel PJ. Survival outcomes for patients with stage IVB vulvar cancer with grossly positive pelvic lymph nodes: Time to reconsider the FIGO staging system? Gynecol Oncol. 2015 Feb;136(2):269–73.

38. Meelapkij P, Suprasert P, Baisai O. Treatment Outcomes of Patients with Squamous Cell Carcinoma of the Vulva: The Largest Series from a Tertiary Care Hospital. Obstet Gynecol Int. 2018 Sep;2018:1–7.

APPENDICES

Appendix I: Data Abstraction Tool

BURDEN OUTCOMES AND MANAGEMENT OF PATIENTS WITH HISTOLOGICALLY CONFIRMED VULVAR CANCER AT THE KENYATTA NATIONAL HOSPITAL

1. Demographic data
    - Age
    - Date of admission …… Date of discharge/ death…….
    - Education level
    - Serostatus
2. Where is the cancer located and the clinical presentation?

3. Has the cancer spread beyond the vulvar?

4. What's the histological diagnosis and the HPV type?

5. What's the stage at diagnosis?

6. What is the mode and duration of the treatment?
    - Surgery
    - Radiotherapy
    - Adjuvant therapy
    - Chemotherapy
7. What is the side-effects of the treatment reported?

8. What the outcome?Resolution, Recurrence, loss to follow up or death

Appendix II: KNH/UON-ERC Letter of Approval

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 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/364

30th September, 2019

Dr. Nasra Jattani Boru
Reg. No. H58/88984/2016
Dept. of Obstetrics and Gynaecology
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Nasra

RESEARCH PROPOSAL: BURDEN MANAGEMENT AND OUTCOMES OF CANCER OF VULVAR AT THE KENYATTA NATIONAL HOSPITAL (P458/06/2019)

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 30th September 2019 – 29th September 2020.

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.

Protect to discover

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 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: Dr. Margaret Kilonzo Dept. of Obstetrics and Gynaecology, UON
Dr. Rose Kosgei, Dept.of Obstetrics and Gynaecology, UON

Resub P458/06/2019

KENYATTA NATIONAL HOSPITAL RECEIVED 25 SEP 2019 KNH/UoN-ERC P.O. Box 20723-00202 NBI

The Chairman,

KNH-UoN Ethics and Research Committee

College of Health Sciences

P.O.Box 19676-00202

Nairobi.

Dr Nasra Jattani Boru

Reg No.H58/88984/2016

Dept of Obstetrics and Gynecology

College of Health Sciences

University of Nairobi

20th September, 2019

Dear Sir,

RE: Revision of research proposal

Research Topic: Burden, Management and outcome of Women with cancer of the vulvar at the Kenyatta National Hospital Gynecology and Oncology department (P458/06/2019)

This is to acknowledge the receipt of your letter Ref no KNH-ERC/RR/692 dated 12th September 2019 on the review of my research proposal submitted to the Ethics and Research Committee.

Thank you for the valuable feedback.

Herein please find a summary of revisions to the proposal that incorporates your valuable observations, comments, suggestions and recommendations together with Two (2) copies of the revised proposal.

	Observation/suggestion	Corrections done	Page
1. Abstract	Please be more precise and present this information in a manner that flows for easy comprehension	The abstract categorized further with data collection, analysis and outcomes presented separately.	
2. Introduction	It should end with by saying what the research gap is that your study intends to fill	The research gap and the aim of the study included in the introduction.	
5. Specific objectives	You have left out outcomes of treatment in the specific objectives.	The objectives have been revised include the outcomes of treatment Second objective removed because we will look at files of patients with histologically diagnosed vulva cancer (mode of diagnosis already determined)	
8. Study timeframe	Update the timelines to reflect the current status of the proposed study.	Gant Chart timeliness adjusted accordingly	

Thank you and hoping for a favorable response.

Yours sincerely,

25/9/19

Dr. Nasra Jattani Boru

H58/88984/2016

KENYATTA NATIONAL HOSPITAL APPROVED 30 SEP 2019 KNH/UoN-ERC P. O. BOX 20723 - 00202 NAIROBI