A COMPARATIVE STUDY ON PRESENTATION OF VULVAL CANCER IN PATIENTS BELOW 50 YEARS AND AT 50 YEARS AND ABOVE AT KENYATTA NATIONAL HOSPITAL

A proposal for dissertation submitted in partial fulfillment of the requirements for the award of the degree of Master of Medicine (Obstetrics and Gynecology) of the University of Nairobi.

By

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MBCh.B (NRB)

H58/80615/2015

DECLARATION

I declare that this proposal is my original work and has not been presented for the award of any degree at any other institution or university.

Signed…….. Date…….

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This proposal is presented with our approval as university supervisors.

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LIST OF ABBREVIATIONS

KNH – KENYATTA NATIONAL HOSPITAL

PAP SMEAR – PAPANICOLAOU SMEAR

HPV – HUMAN PAPILLOMA VIRUS

VIN – VULVAL INTRAEPITHELIAL NEOPLASIA

HIV – HUMAN IMMUNODEFICIENCY VIRUS

VNED – VULVAR NON NEOPLASTIC EPITHELIAL DISORDERS

LS – LICHEN SCLEROSUS

SCC – SQUAMOUS CELL CARCINOMA

UCLA – UNIVERSITY OF CALIFORNIA LOS ANGELES

FIGO – INTERNATIONAL FEDERATION OF GYNECOLOGISTS AND OBSTETRICIANS

UON- UNIVERSITY OF NAIROBI

ABSTRACT

Introduction

Vulval cancer is uncommon and is known to predominantly affect elderly women. However, the emerging trend of affection of younger women is worrying, therefore, needs to be investigated. Recent years have shown an increase in the trend of vulval cancer in women below the age of 50 years. This phenomenon has not yet been elucidated in our set up. This study, therefore, seeks to compare sociodemographic, clinicopathologic features and management strategies in the two groups with an aim to explain the change in age patterns over time.

Objective: To determine the difference in the sociodemographic, clinicopathologic features and management strategies in the presentation of vulval cancer at diagnosis below 50 and 50 years of age and above over a time period of 10 years in a tertiary care hospital.

Methodology: A comparative cross sectional study design was used. The hospital records of 115 patients with histologically proven vulvar cancer who presented to Kenyatta National Hospital in the last ten years from 2008 to 2018 were reviewed at the records department at Kenyatta National Hospital and the following information was recorded on a prestructured questionnaire. Information based on age, clinicopathologic presentation, staging, management strategy and complications, antecedent lesions and concurrent conditions was studied. The data collected was recorded in a data entry sheet then coded, processed and cleaned off any inconsistencies and outliers and further analysed using SPSS version 21.0. Characteristics of the two groups were compared using appropriate statistical tests. All reported P values was two-tailed with the statistical significance set at $P < 0.05$. Data was compared with published literature.

Results: The mean presenting age of these patients had a downward trend from 64 to 38 years**.** There was a strong history of HIV co- infection in the women below 50 years (P <0.001). They were also found to have a significantly higher level of education (P 0.008) and had more complaints of per vaginal bleeding (P 0.002) than their counterparts.

In terms of duration of symptoms before presentation, smoking history or tumor size there was no statistical difference. Both groups presented with advanced stage disease. Management strategy was largely similar with age and complications arising from treatment were also similar across the two groups.

Conclusion: There seems to be a trend in our patient population where younger women are increasingly presenting with symptoms characteristic of vulval cancer. Human immunodeficiency virus appears to be important as an aetiologic factor and is more common in this age group . Vulval bleeding is a common presenting symptom in patients below 50 years. Education encouraging the early detection and prevention of HIV might alter the rising incidence of this disease in younger women.

CHAPTER ONE:INTRODUCTION

The vulva is a highly specialized external female sex organ. It consists of the mons pubis, the labia, clitoris, vestibular structures, urethral and vaginal openings. (1) All these structures can harbor a diverse group of both benign and malignant lesions. Carcinoma of the vulva is an uncommon disease that affects the vulva and accounts for 5% of the malignancies of the female reproductive tract. (2)(3)

All women are at risk of gynecological cancers. This risk is increased as women grow older. (4) Cancer of the vulva specifically has been known as a disease of elderly women particularly between the ages of 70 and 80 years. (5) However, in recent years, the incidence has increased among younger women. It is for this reason that a possible cause has been looked into to compare both populations for differences and similarities in presentation. This was illustrated in a comparative study of 78 women above and below 45 years of age diagnosed with vulval cancer between 1979 and 1993 in the United States in which the mean age st diagnosis went down from 69 to 55 years. (6)(7) This study found that there is a trend where younger women present with vulval cancer with an association with HPV and other sexually transmitted diseases. In the last 30 years, there has been an upward surge of vulval cancer in women aged 40-49 years. (8) Zongo et al from Burkina Faso found that the average age of presentation of patients with vulvar cancer was 55 years.(9)

The etiology of vulval cancer is not known with certainty. It is however thought to be associated with human papilloma virus depending on the age population affected. (10) HPV was shown to be responsible for 60% of vulval cancers. (6) The younger population seems to be predisposed to HPV dependent cancer of the vulva whereas the older population is not HPV dependent and is seen mostly in elderly patients. (10). Other predisposing factors include cigarette use, cervical or vulval intraepithelial neoplasia, education level, nutrition, vulval dystrophy, genital tract infections, poor health seeking behaviour, socioeconomic status and immunosuppressive disease however the epidemiologic evidence is inconclusive. (11)(6)

Traditionally, management of vulval cancer has been primarily surgical through radical vulvectomy and bilateral inguinofemoral lymph node dissection. (12) This has led to several complications with increased morbidity and mortality. Currently, the management is stage dependent and includes neoadjuvant therapy with sentinel node mapping in an aim to improve quality of life and prognosis of the patients. Treatment of cancer of the vulvar does

not differ significantly with age(7) although women above the age of 45 years have been noted to have advanced stage disease.

The outcome of vulvar carcinoma is depends on the stage of the disease, nodal status, clinical tumour diameter and presence of spread to nearby organs. In patients with negative node status, the 5 year survival rate is 91%. (13)

CHAPTER TWO: LITERATURE REVIEW

Epidemiology

Vulval cancer is classified as the fourth reproductive tract cancer after uterine, cervix and ovarian in the United States. (5) About 60% of vulvar cancer cases occur in developed countries. (14) The incidence rates vary depending on which country is considered, the lowest rates being reported from Asian and African populations. (15) In the United States, some data suggest that black women present at a younger age and have an increased probability of distant spread which is a consistent finding across the different tumor models. (6) Annually in the USA, there are 4700 new cases and 990 deaths from vulval cancer. (16)

A study done at Yalgado Ouedraogo University Hospital of Ouagadougou in Burkina Faso between January 2013 and June 2015 also ranked it as the fourth most common cancer with a mean age of affected women at 55 years. (9) They only had 20 confirmed cases in 30 months which further emphasizes that it is uncommon.

The cancer registry data from Uganda and Zimbabwe between 1998 and 2002 show an incidence rate of 7 and 16 cases of vulval cancer respectively. (17)According to the cancer registry in Kenya, there is currently no data available on the incidence and prevalence rate of vulvar cancer. (18). However, a ten- year review of carcinoma of the vulva done at Kenyatta National Hospital between 1974 and 1983 gave a prevalence rate of 3.3% of all gynecological malignant tumors. It was also ranked as the fourth commonest, superseded by cervix, ovarian and uterine cancers. Kenyatta National Hospital is a public level 6 teaching and research hospital in Nairobi, Kenya. It is the largest referral hospital in East and Central Africa. As at the end of 2016 there were 31 confirmed cases of vulvar cancer at the hospital that year. This is a rise from 7 admitted and confirmed cases in 2004. Of these rising incidences of vulvar cancer, there has been an increase in the number of younger women diagnosed. The increasing incidence of HPV related VIN among younger women may account for the drop in mean age of diagnosis of vulval cancer.

A review by ACOG in 1997 revealed that about 15% of vulval cancer cases occur in female patients below 40 years of age. (19) Other predisposing factors are: age at coitarche, multiple sexual partners, history of cigarette use, immunosuppression, history of sexually transmitted infections and low socioeconomic status. (20)(6) According to literature from Jamaica, there is a strong correlation between carcinoma of the vulva and history of chronic granulomatous

venereal diseases. (21,22). These younger women are mostly seen in stage I/II disease however cases of stage III /IV disease in immunosupressed patients have been documented.

A study done by de Melo Maia et al in Brazil found that the median age of onset of vulvar cancer was 70 years. These patients were mostly white and had little or no schooling.(23) A study on vulvar cancer in China on epidemiology and risk analysis done in 2017, also showed that patients aged ≥ 50 years had a lower level of education than their younger counterparts. (24). However Lanneau et al (USA) found that younger patients aged < 45 years had a lower socioeconomic status than their older counterparts. The data on the sociodemographic status of patients with vulvar cancer in our setup has not been described thus far.

Squamous cell cancer is the commonest histological type, and accounts for 95% of neoplasms affecting the vulva. This is followed by melanoma, sarcoma, basal cell and Paget's disease of the vulva. (5)(25)(2)

Despite the scarcity of cancer registries and lack of mortality data in sub-Saharan Africa, it is clear that HPV associated diseases are a major cause of morbidity and mortality with the highest incidence of HPV infection found in eastern and western Africa. (17)

Cutaneous vulval lesions are commonly encountered at gynecological clinics with 2% of women with benign melanocytic nevus. VIN 2 or 3 which are high grade intraepithelial lesions are seen in 5 per 100000 women with an upward trend over the past 3 decades. (26)

Pathophysiology

Vulval cancer has several histologic types. Squamous cell affects mostly older women however the clinical, pathology and immunohistochemical characteristics are poorly characterized in younger women. (27) It is presumed that the illness presents in two ways. The first type is HPV dependent and has a classic, warty or Bowenoid type appearance. (6) It leads to vulval intraepithelial neoplasia - usual type (uVIN), a predisposing factor to vulval cancer. The high risk HPV subtypes i.e. 16, 18 and 33 account for 55.5% of HPV related vulval cancers. (6)Approximately 80% of women with VIN III go on to develop invasive disease. (28) This type of vulval cancer often affects younger women. The second type is HPV independent and is the keratinizing, differentiated or simplex type and involves vulvar non- neoplastic epithelial disorders (VNED), which result in cellular atypia and eventually

cancer. (6) (29) This is seen in elderly patients and is associated with differentiated VIN (dVIN).

The most common histologic type in women aged below 50 years is not known in our set up.

A study was done in the department of pathology, at The British Columbia University to examine clinical and pathological features of invasive squamous cell carcinoma in young women below 40 years. Results showed that there has been an upsurge of invasive squamous cell carcinoma in young women which is associated with HPV. In some cases, Lichen sclerosus and VIN was identified. (27) . Vulval lichen sclerosus is a precursor lesion whose hallmark is fibrosis and clinical and pathologic persistence. (30)The histologic changes that are characteristic of lichen sclerosus are more often than not noted in tandem with squamous cell carcinoma. Chronic inflammation and scarring are a well recognized hallmark of oncogenesis. (30) An investigational study done in the department of pathology, Albany medical college in 1998 revealed that, vulvar LS both promotes and initiates oncogenesis further explaining the simultaneous coexistence of the two diseases. (30) Of symptomatic vulvar LS patients, 9% went on to develop VIN lesions and another 21% developed SCC. The LS lesions came before the cancer by an average period of 4 years. Of note, the keratinocytes of LS express the tumor suppressor gene - p53 which may be implicated in the pathway of oncogenesis. (30)

Melanoma entails 2-9% of tumors of the vulva and is common in white non- Hispanic older women between 65 to 75 years. (20) It affects mostly the areas around the clitoris and the labia. (31) It is mostly pigmented lesion, but non pigmented lesions can also occur. The histologic subtypes include: superficial spreading, nodular (worst prognosis), lentigo maligna , acral lentiginous and desmoplastic. (29) It is often diagnosed at late stages because of it's non specific symptoms and has a poor prognosis. Multifocality is also more common. Therefore, it is important, to evaluate the whole genital system in vulvar melanomas. (29)

Vulvar sarcomas comprise 5% of vulval tumors. (32) Leiomyosarcoma being the most common. (32)(33) Others include: malignant fibrous histiocytoma, malignant rhabdoid tumor, angiosarcoma and epithelioid sarcoma which occur less often. They are often misdiagnosed as benign tumors resulting in delayed or wrong treatment. Vulval leiomyosarcoma arises commonly from the labia majora, bartholin gland area, clitoris and labia minora in descending order. The average presenting age is reported to be between 33 and 50 years. (33) It can recur either locally or distally and is slow growing. It also has a poor

prognosis. Initially it can be painless, with discomfort as the predominant symptom in the vulval area with enlarged nodes. (33)

Basal cell carcinoma accounts for 2-4%. It occurs in post-menopausal Caucasian women who are usually 74 years old. (34)(35) Etiology remains unknown however syphilis, chronic irritation, chronic infection, e.g., vulvovaginitis, trauma such as a burn or scar, radiotherapy and arsenics have been pointed out as risk factors. (34) It usually presents as a nodule or a ulcer with rolled edges and ulceration at the center. It sometimes has a non-specific presentation and may mimic other dermatological lesions like eczema, psoriasis or seborrheic keratosis. (6) (34)As a result, the recommendation is that all suspicious vulval lesions should be examined and biopsied to make an early diagnosis.

Paget's disease of the vulvar comprises less than 1% of vulvar cancers. It is seen in patients of 60 to 70 years of age. Pruritus is the symptom that is most commonly seen in 70% of the patients. (6) The lesions have an eczema like appearance with slightly raised edges and a red background and can appear on several areas like the vulva, mons pubis, the perineum and perianal areas. Patients with Paget's disease should be evaluated for incidental tumors as about 20 to 30% have a non- contiguous carcinoma.

The commonest histological type of vulvar cancer in younger women has not been studied in our set up.

The clinical presentation of all the histological types of vulval cancer is largely the same although varies according to the stage of the disease. Most patients complain of a unifocal ulcer, mass or plaque which can be fleshy, warty or nodular. The mass can be on the labia, perineum, clitoris ,and mons pubis. (6) Lesions can be in several locations in 5% of cases thus a comprehensive physical exam of surrounding structures must be done. Asynchronous malignancies, commonly cancer of the cervix is found in about 22% of patients with a vulval malignancy. (36) Pruritus is also a common complaint associated with vulvar disorders especially with underlying lesions like lichen sclerosus.

Vulval bleeding or lesions with a discharge, painful urination or enlarged lymph node in the inguinal area are not seen as much and point to late stage disease. (6) In some circumstances, some women have no symptoms at time of diagnosis.

Vulvar cancer in older patients seems to have an association with co-morbidities. Illnesses such as diabetes, hypertension, and obesity have an associatio with vulvar cancer, yet do not

seem to be causative. Stroup et al (USA) found that older women diagnosed with cancer of the vulvar had two or more co-morbidities. (37)

Diagnosis of vulvar cancer is based on histology and vulvar biopsy. (6) Visual inspection of the vulva is first done during a pelvic exam or for any vulvar complaints from a patient. Any suspicious lesion that is raised, fungating or has altered pigmentation should be biopsied. If there is clinical suspicion but a lesion is not obviously noted then a 5% acetic acid solution is applied copiously and the vulva examined using a colposcope. Areas that turn acetowhite and have abberhant vascular patterns are then biopsied. (6)

Vulval cancer metastasizes in three ways: by direct spread to nearby organs like the urethra, vagina, anus and clitoris. It can also spread through the lymphatic system to the inguinal-femoral lymph nodes in early disease. Hematogenous spread, has also been identified and occurs in late stage illness and in patients with extensive lymph node involvement. (6)

Management of vulvar carcinoma

Management varies and can be simple or complex. Each patient is managed differently based on tumor size, it's location, medical fitness of the patient and patient's desire. Presence of nodes also influences mode of treatment.

Management of vulval cancer is primarily surgical and differs according to the stage of the illness. (8) Staging is surgical-pathological and not clinical. The FIGO classification for vulval cancer is as follows:

Staging

- Stage I: Tumour confined to the vulva
- Stage Ia: Lesions less than or equal to 2 cm in size, confined to the vulva or perineum with stromal invasion less than or equal to1 mm. Negative nodes
- Stage Ib: Lesions greater than 2 cm in size or with stromal invasion greater than 1 mm confined to the vulva or
  perineum. Negative nodes
- Stage II: Tumour of any size with extension to adjacent structures (lower 1/3 urethra; lower 1/3 vagina; anus) with negative nodes

- Stage III: Tumour of any size with or without extension to adjacent structures (lower 1/3 urethra; lower 1/3 vagina; anus) with positive inguinofemoral nodes
- Stage IIIa: (i) With 1 lymph node metastasis (≥ 5 mm), or (ii) 1–2 lymph node metastasis(es) (< 5 mm)
- Stage IIIb: (i) With 2 or more lymph node metastases (≥ 5 mm), or (ii) 3 or more lymph node metastases (< 5 mm)
- Stage IIIc: With positive nodes with extracapsular spread
- Stage IV: Tumour invades other regional (upper 2/3 urethra; 2/3 vagina) or distant structures
- Stage Iva: Tumour invades any of the following
  (i) Upper urethral and/or vaginal mucosa; bladder mucosa; rectal mucosa or fixed to the pelvic bone, or

  (ii) Fixed or ulcerated inguinofemoral lymph nodes.
- Stage Ivb: Any distant metastasis including pelvic lymph nodes (8)

The prescribed treatment for early disease entails wide radical excision of the primary tumor with free margins of at least 15mm and inguinofemoral lymphadenectomy or sentinel node mapping. (38) Inguinal node dissection is howevernot done in stage 1a squamous cancer, melanoma and basal cell carcinoma.

In previous decades, there has been an evolution to the surgical approach to management of vulvar carcinoma. Previously the approach was a radical vulvectomy with bilateral inguino-femoral lymphadenopathy which was associated with severe morbidity and poor quality of life. A study done in 1994 in the Department of Obstetrics and Gynecology at UCLA school of medicine revealed that there is a similar outcome and survival for patients who underwent modified, conservative vulvectomy versus those who underwent radical vulvectomy. The most important prognostic factor is the lymph node status. (39) In stage 1b disease, diseection of the groin nodes is warranted and the technique is recommended is the triple incision technique to reduce morbidity.

Management of malignant melanoma of the vulva involves wide local excision. There has been no benefit shown for block dissection of the inguinal region. (8) Recurrence in these patients is high and is in line with with the depth of invasion. For basal cell carcinoma,

the same applies because it is rarely associated with lymph node metastasis. They are therefore managed by wide local excision or radiation therapy.

Management of advanced vulvar cancer requires a multidisciplinary approach with plastic surgery involvement for purposes of reconstructive surgery if need be. The surgical approach depends on size and location of the tumor. Some tumors will require a radical vulvectomy, and in cases where there is the risk of sphincter damage, preoperative radiotherapy and or chemotherapy is an option to reduce tumor volume or to have curative intent. This also applies to recurrent disease.

Complications

Despite technical advancements, complications following surgical treatment for vulva cancer remains high. (40) They are divided into short and long term and entail:

Short-term

Breakdown of the wound
Local Infection
Thrombosis

Long-term

Pressure sores and necrosis due to prolonged immobilization
Introital stenosis after surgery
Urine and fecal incontinence
Rectocele
Inguinal lymphocyst
Lymphedema
Hernias
Psychosexual challenges

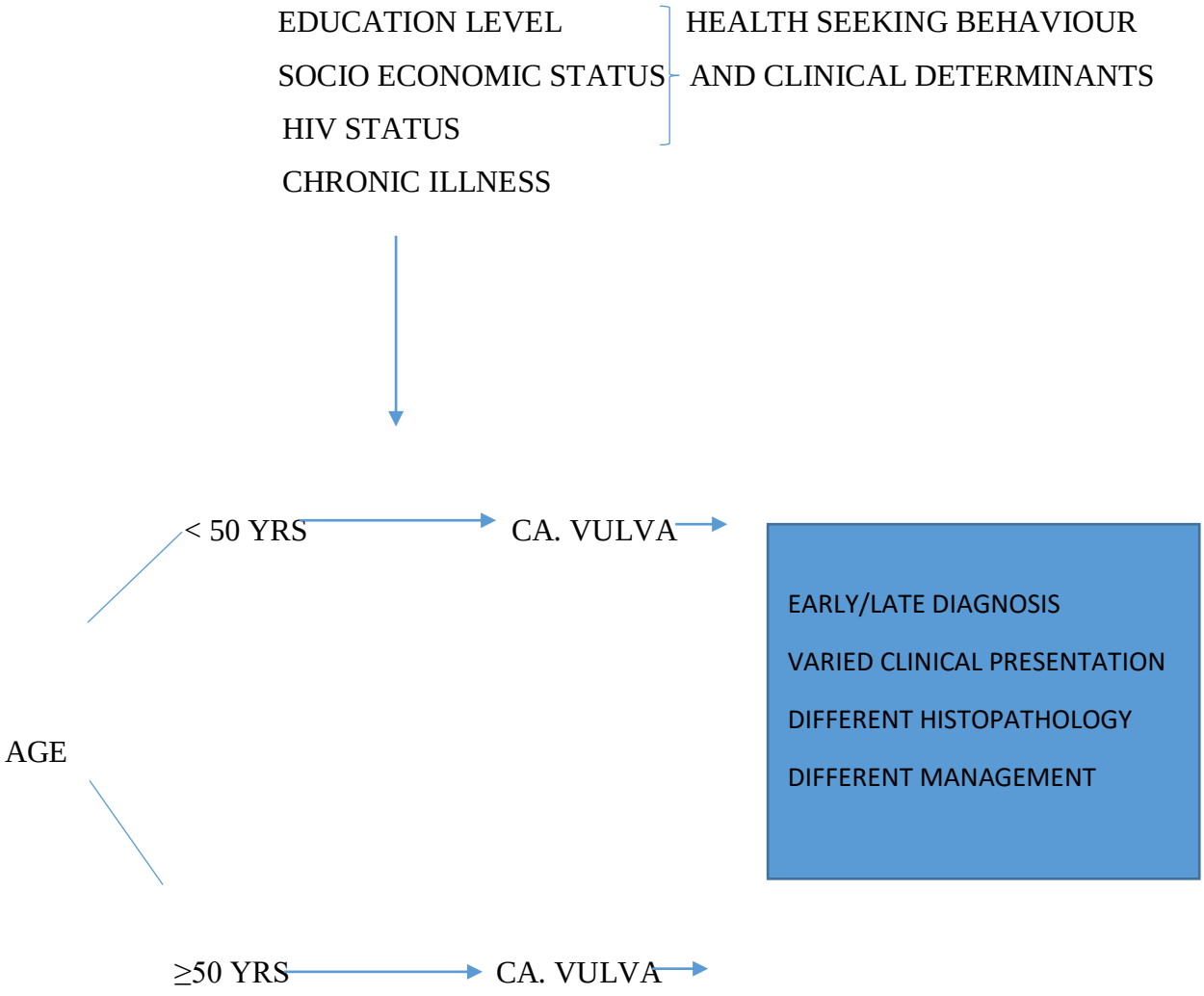
Older patients, those with diabetes, extensive surgery and high output drains after several days post op have been associated with an increased chance of short-term complications, whereas patients who are younger in age or patients who have lymphocele are predisposed to long- term-complications.

CONCEPTUAL FRAMEWORK NARRATIVE

Vulval carcinoma has previously been seen as a disease affecting the elderly. Risk factors appear to have cascaded down to the younger age group but the mystery of predisposing factors and disease characteristics has not yet been elucidated.

Important studied risk factors include age, smoking, sexually transmitted infections, HIV status, Lichen sclerosus, VIN ,and HPV. Lifestyle diseases such as hypertension and Diabetes Mellitus have also been implicated.

By establishing the facts on why younger women are increasingly presenting with vulval carcinoma, it may be possible to state preventive strategies, target early diagnosis and hence improve quality of life and enhance the longevity of life.



JUSTIFICATION OF THE STUDY

Despite being known as a disease of the old coupled with a delay in health-seeking behavior, there is an observation of increasing incidence in younger populations seen over the last ten years at the Kenyatta National Hospital. This study will target the differences in the presentation in both groups with 50 years being the median age.

If this study can elucidate the predisposing factors and disease characteristics in the younger population, then we might come up with prevention strategies and in future even screening modalities. When the presentation is different, management may vary therefore strategy in management offered may reflect on those differences as surrogate indicators.

STUDY QUESTION

Is there a difference in the presentation of vulval cancer at diagnosis at < 50 years and ≥50 years of age?

NULL HYPOTHESIS

There is no difference in the presentation of vulval cancer at diagnosis at < 50 years and ≥50 years of age.

OBJECTIVES OF THE STUDY

Broad objective

To describe the difference in the presentation of vulval cancer at diagnosis < 50 years and ≥50 years of age at Kenyatta National Hospital.

Specific Objectives

Of patients with vulval cancer at < 50 years and ≥50 years of age at Kenyatta National Hospital:

1. Describe the difference in socio-demographic factors.
2. Describe the difference in the clinicopathological presentation.
3. Describe the difference in the management strategy offered and complications.

CHAPTER THREE: RESEARCH DESIGN AND METHODOLOGY

Study design

This study was a comparative cross sectional study design .This design, was used since the researcher wished to test the degree of relationship between and among variables dating back ten years.

Study site and setting

This study was carried out at Kenyatta National Hospital (KNH) which is the largest public, tertiary referral hospital in Kenya and located in Nairobi where one is likely to get enough numbers for a relatively rare condition like vulval cancer. It is also the apex of the health system in Kenya. Records on patients diagnosed with vulval cancer from the department of obstetrics and gynecology and oncology unit over a period of ten years from 2008 to 2018 were retrieved from the Records department at KNH.

Study population

The target population for this study included 209 female patients who were diagnosed with vulval cancer over a period of ten years from 2008 to 2018 (KNH, 2018). There was data missing in the years 2011 and 2012.

Inclusion and criteria

The study extracted data from:

i. Patient records with verified histopathological data
ii. Patient records with complete clinical history
iii. Patient records with documented age

Exclusion criteria

The study excluded:

i. Patients with concurrent malignancy i.e. cervical cancer

Sample size

The study sample size was determined using the formula of comparison of two proportions where the upper limit of the sample is required. The sample is computed at a precision level (α) of 5% and a 95% confidence interval as shown below.

$$n = \frac{8}{(p_0 - p_1)^2} = \frac{8}{(0.75 - 0.25)^2} = 32$$

Where

n is the desired sample size

p_0 proportion of patients aged <50 years (0.75)

p_1 proportion of patients aged ≥50 years (0.25)

8 is the multipliers values of power (β) = 0.8 for a two-sided α of .05.

The study sample will include 64 patients' files. Those aged <50 years will be 32 and those aged ≥50 years will be 32; distributed as shown in Table 3.1.

Table 3.1: Population and Sample distribution of patients with vulval cancer at KNH from the year 2008 to 2018.

Year	Population		Sample	
	<50 years	*≥50 years*	*<50 years*	*≥50 years*
2008	10	10	3	3
2009	8	8	2	3
2010	13	3	4	1
2013	8	7	2	2
2014	10	13	3	4
2015	15	14	4	4
2016	12	19	4	6
2017	18	10	5	3
2018 up to Oct	14	17	4	5
Total	**108**	**101**	**32**	**32**

Due to the missing data in 2011 and 2012 we opted to review all the files in the ten year period. This surpassed the original sample size as calculated and increased the power of the study.

Sampling Technique

All complete and available records over the study period formed the chronological sampling frame. The files were then split into two strata – those patients aged below 50 years and those

aged 50 years and above. Convenience sampling was done for all the patient files that fit the inclusion criteria.

Data Collection Methods

Data was collected and recorded from the Records department at KNH. Relevant data was extracted from sampled files by the prinicipal investigator.This included socio-demographics; clinicalpathological presentation; antecedent lesions and concurrent conditions; histological type and management strategies of patients with vulval cancer. Information on complications post-treatment and prognosis was also collected. Extracted information was filled into a structured questionnaire.

Validity and reliability

To ascertain the validity and reliability of the findings of the study, measures of quality control had to applied throughout the study. The study questionnaire was pre-tested for patient records captured years preceding 2008. The pre-test was meant to gauge the comprehension of questions in the questionnaires by the effectiveness of responses collected. All the tools were rechecked as required. The content of the tools was also examined for logical or content validity.

Reliability was ascertained by reducing the variation of external sources and study variables. It was also measured using the split-half technique where a Cronbach Alpha coefficient of 0.7 and above ascertained that the data and findings were trustworthy.

Data Analysis

Data collected was coded, then processed and cleared of any inconsistencies and outliers. Quantitative data recorded from the questionnaires was analysed using SPSS. To reduce dimensions of multivariate variables, factor analysis was carried out. To determine the relationship between variables, correlation and regression, the Chi square test was used. The study delineated and elucidated the differences and similarities between those aged below 50 years and those aged 50 years and above through comparison of proportions chi-square and Fisher's exact tests. Student's t-test was used to compare continuous variables between the groups and analysis of covariance to evaluate between-group differences. All reported P values were two-tailed. Statistical significance was set at $P < 0.05$.

Ethical considerations

Ethical approval was sought from the University of Nairobi, Department of Obstetrics and Gynecology **(250/2018)** and the KNH-UON Ethics and Research Committee **(P559/08/2018).** Upon approval, consent was sought from the Records department. Information collected was treated with utmost confidentiality and no patient names were included in the questionnaire or any presentations arising from the study. Findings from this study were disseminated to the stakeholders and shared with the hospital staff in the form of Continuous Medical Education.

CHAPTER FOUR: RESULTS

STUDY FLOW CHART

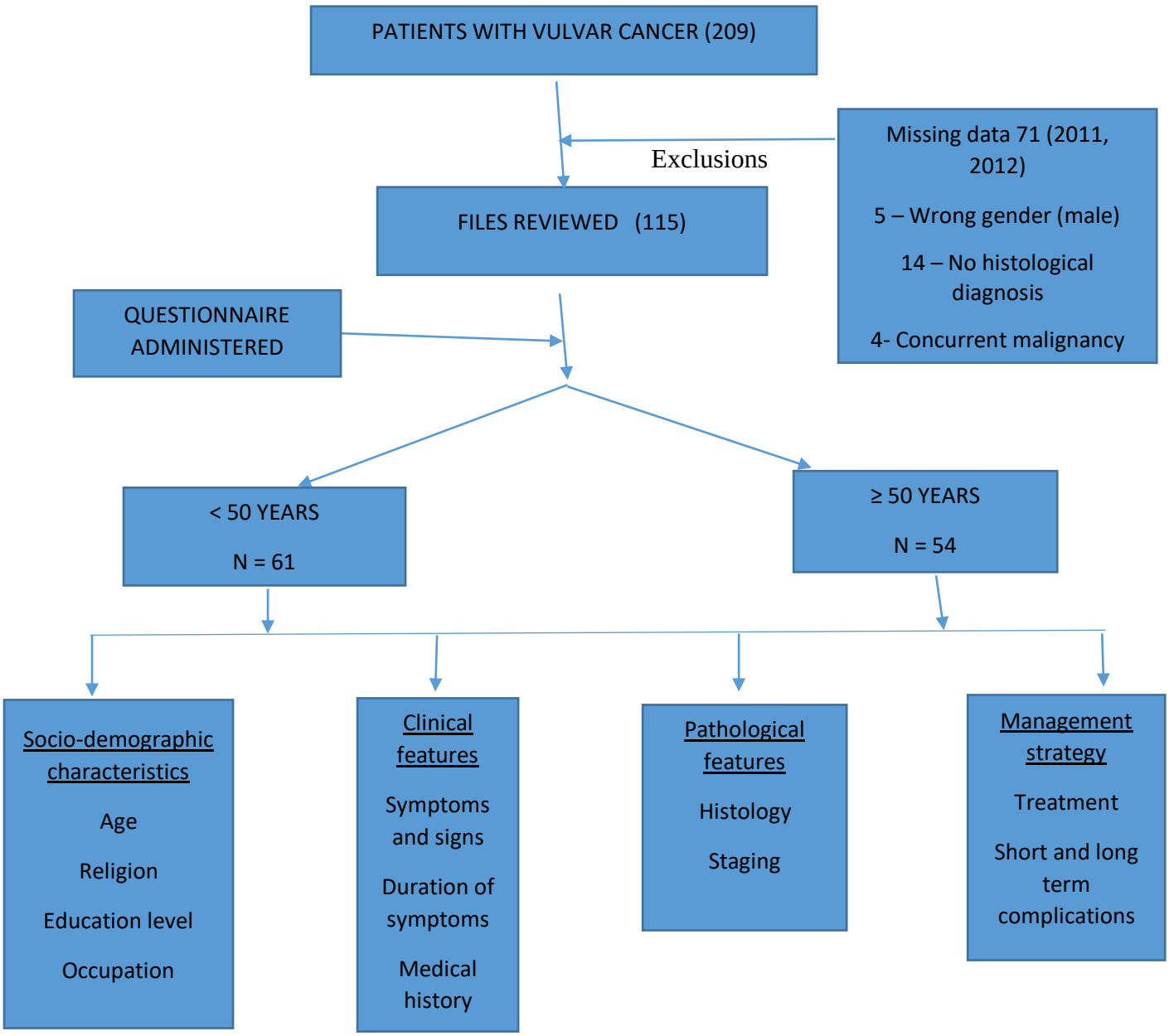
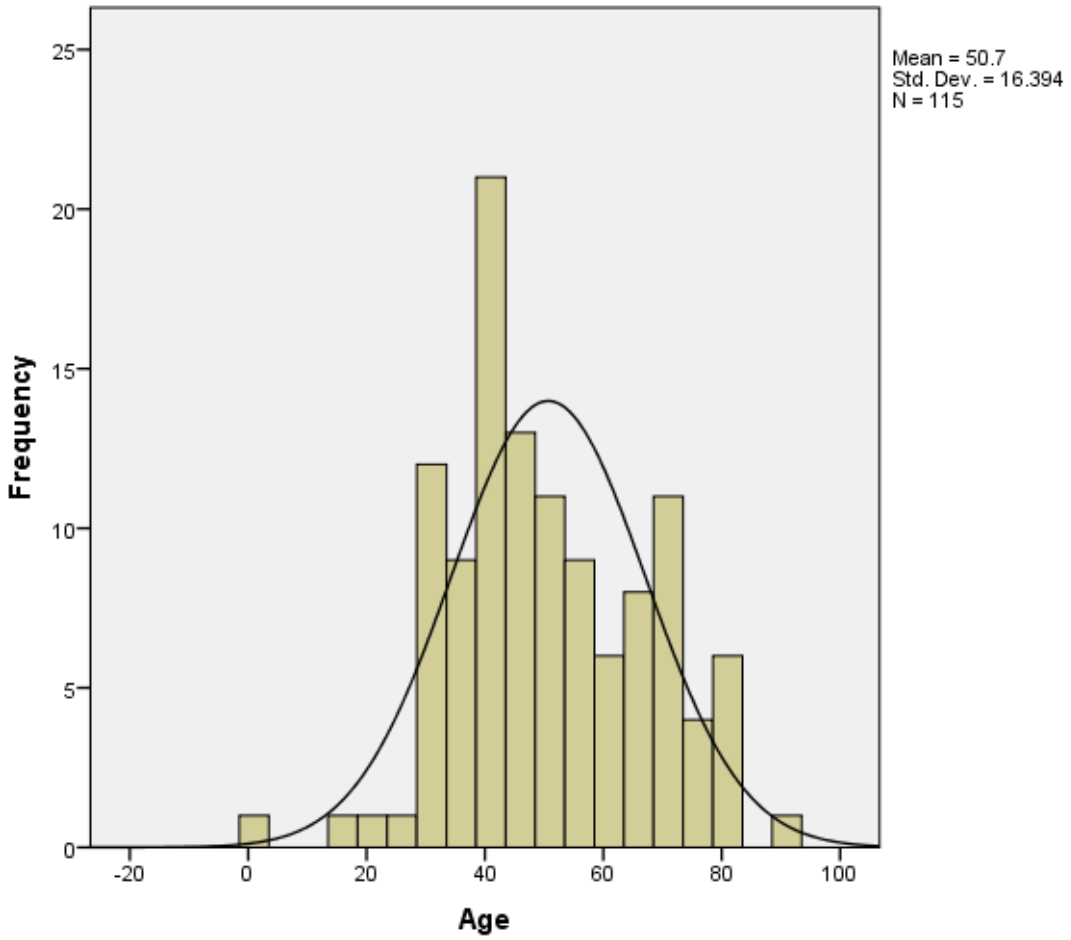
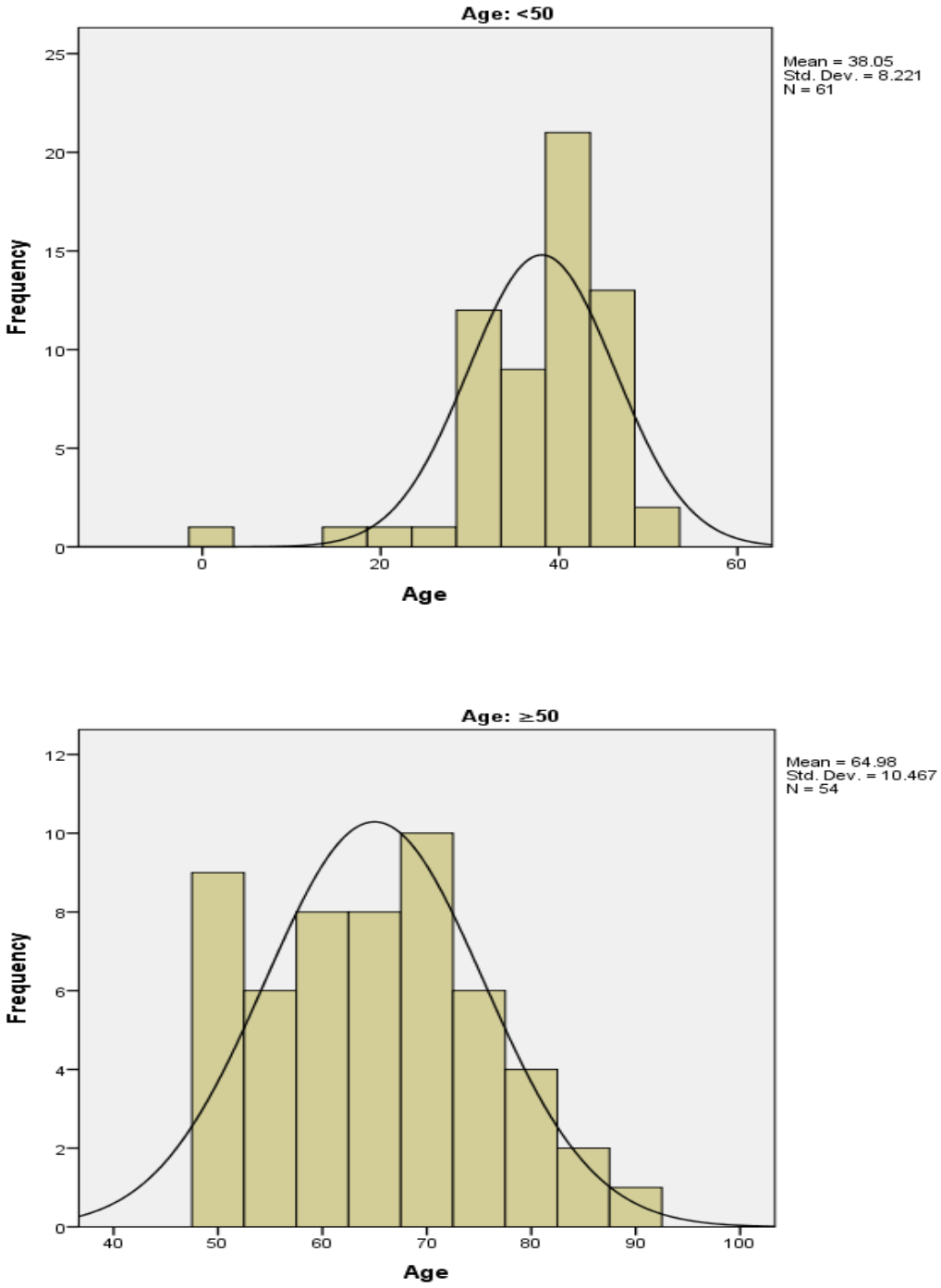


Figure 1: Age distribution of patients diagnosed with vulvar cancer between the period 2008-2018 at Kenyatta National Hospital



Theaverage age of the patients was found to be 50.7 years (±16) with a range of 1 to 92 years as shown in Figure 1 above.

Figure 2: Disease ocurrence of vulvar cancer patients by age category at Kenyatta National Hospital



During the study interval the mean presenting age of these patients declined from 64 to 38 years.

Table 1: Sociodemographic characteristics of patients with vulvar cancer by age category at Kenyatta National Hospital

CHARACTERISTIC	CATEGORY					
	<50yr (N= 61)		≥50yr(N=54)			
	No	(%)	No	(%)	OR	P value
Marital status						
Single/Separated	27	(44.3)	24	(44.4)	0.96	0.913
Married	34	(55.7)	29	(53.7)		
Religion						
Christianity	59	(96.7)	51	(94.4)	1.735	0.664
Islam	2	(3.3)	3	(5.6)		
Education						
None	4	(6.6)	9	(16.7)	**0.34**	**0.008**
Primary	21	(34.4)	26	(48.1)		
Secondary	23	(37.7)	13	(24.1)		
Post - Secondary	7	(11.5)	0	(0.0)		
Occupation						
Unemployed	21	(18.3)	27	(23.5)	0.503	0.084
Gainfully Employed	34	(29.6)	22	(19.1)		

Proportions of education level significantly varied between patients aged <50 and ≥50 years (p value =0.008) as shown in Table 1 above. Proportions of patients' marital status, ethnicity, religion, and occupation did not significantly vary between those aged <50 and ≥50 years, that is, the proportions were similar.

Table 2: Clinical features of patients with vulvar cancer by age category at Kenyatta National Hospital

SYMPTOMS	CATEGORY					
	<50yr (N= 61)		≥50yr(N=54)			
	No	(%)	No	(%)	OR	P value
Pruritus						
No						
Yes	36	(59.0)	26	(48.1)	1.44	0.344
	23	(37.7)	24	(44.4)		
Vulvar mass						
No						
Yes	19	(31.1)	12	(22.2)	1.5	0.344
	40	(65.6)	38	(70.4)		
Bleeding						
No	**35**	**(57.4)**	**43**	**(79.6)**	**0.237**	**0.002**
Yes	**24**	**(39.3)**	**7**	**(13.0)**		
Ulcer						
No	26	(42.6)	24	(44.4)	0.850	0.681
Yes	33	(54.1)	26	(48.1)		
PV Discharge						
No	36	(59.0)	31	(57.4)	0.96	0.916
Yes	23	(37.7)	19	(35.2)		
Vulvar pain						

No	47	(77.0)	40	(74.1)	1.10	0.874
Yes	12	(19.7)	11	(20.4)		
Other						
Abscess	1	(1.6)	0	(0.0)	-	0.472
Anal discharge	1	(1.6)	0	(0.0)		
Constipation	1	(1.6)	0	(0.0)		
Dysuria	7	(11.5)	3	(5.6)		
Leg swelling	1	(1.6)	0	(0.0)		

Proportions of bleeding women significantly varied between women aged <50 and ≥50 years (p value =0.008). Proportions of patients with and without pruritus, vulval Swelling, ulcer, vaginal discharge, and vulval pain did not significantly differ between women aged <50 and ≥50 years, that is, the proportions were similar.

Table 3: Medical history of patients with vulvar cancer by age category at Kenyatta National Hospital

HISTORY	**CATEGORY**					
	<50yr (N= 61)		**≥50yr(N=54)**			
	No (%)		**No**	**(%)**	**OR**	**P value**
HIV						
Negative	12	(19.7)	28	(51.9)	0.068	**<0.001**
Positive	44	(72.1)	7	(13.0)		
Diabetes						

No	56	(91.8)	36	(66.7)	1.166	**<0.001**
Yes	2	(3.3)	15	(27.8)		
Hypertension						
No	53	(86.9)	32	(59.3)	4.732	**0.001**
Yes	7	(11.5)	20	(37.0)		
Sexually Transmitted Infections						
Absent	59	(96.7)	53	(98.1)	-	0.531
Present	1	(1.6)	0	(0.0%)		
Smoking						
No	60	(98.4)	51	(94.4)	-	0.464
Yes	0	(1.6)	1	(1.9)		
PAP smear						
Normal PAP Smear	4	(6.6)	3	(5.6)	-	0.205
Abnormal PAP smear	5	(8.2)	0	(0.0)		
Lichen sclerosus						
Absent	60	(98.4)	50	(92.6)	4.800	0.185
Present	1	(1.6)	4	(7.4)		

Majority of patients <50 years were HIV positive (P<0.001) as opposed to those ≥ 50 years who had diabetis and hypertension as significant co-morbidities as shown above.

Table 4: Site of lesion of patients with vulval cancer by age category at Kenyatta National Hospital

SITE OF LESION	CATEGORIES				
	<50yr (N= 61)		≥ 50yr (N=54)		
	No	(%)	No	(%)	p value
Anal area					
Absent	56	(91.8)	47	(87.0)	0.404
Present	5	(8.2)	7	(13.0)	
Clitoris					
Absent	44	(72.1)	43	(79.6)	0.35
Present	17	(27.9)	11	(20.4)	
Lt Majora					
Absent	28	(45.9)	20	(37.0)	0.336
Present	33	(54.1)	34	(63.0)	
Rt Majora					
Absent	28	(45.9)	17	(31.5)	0.114
Present	33	(54.1)	37	(68.5)	
Lt Minora					

Absent	37	(60.7)	25	(46.3)	0.123
Present	24	(39.3)	29	(53.7)	
Rt Minora					
Absent	40	(65.6)	30	(55.6)	0.272
Present	21	(34.4)	24	(44.4)	

Relative of proportions of sites were independent of age (p value<0.05). Proportions of patients with and without different sites did not significantly differ between women aged <50 and ≥50 years, that is, the proportions were similar.

Table 5: Duration of symptoms of patients with vulval cancer by age category at Kenyatta National Hospital

	Duration in years				
Age	**Mean**	**SD**	**SEM**	**95% CI**	**P value**
<50	1.86	2.43	.341	-0.70 -1.23	0.591
≥50	1.59	2.37	.350		

Levene's Test for Equality of Variances		**T-test for Equality of Means**						
F	**Sig.**	**t**	**df**	**Sig. (2-tailed)**	**Mean Difference**	**Std. Error Difference**	**95% Confidence Interval of the Difference**	
							Lower	Upper
.009	.92	.54	95	.59	.2645	.4901	-.708	1.237

The mean duration of symptoms did not significantly vary between women aged <50 and ≥50 years (p value =0.591) as shown above.

Table 6: Appearance of lesion of patients with vulval cancer by age category at Kenyatta National Hospital

APPEARANCE	Age <50yrs N = 61		≥50yrs N = 54		P value
	No	(%)	No	(%)	
Fungating	8	(13.1)	5	(9.3)	0.528
Haemorrhagic	1	(1.6)	0	(0.0)	
Nodular	2	(3.3)	1	(1.9)	
Ulcerated	8	(13.1)	5	(9.3)	
Warty	22	(36.1)	22	(40.7)	

Relative of proportions of appearance were independent of age (p value=0.528). Proportions of patients with and without fungating, hemorrhagic, nodular, and ulcerated appearances did not significantly differ between women aged <50 and ≥50 years, that is, the proportions were similar as shown in Table 6 above.

Table 7: Pathological presentation of patients with vulvar cancer by age category at Kenyatta National Hospital

HISTOLOGICAL TYPE	CATEGORY				
	Age <50yrs N = 61		≥50yrs N = 54		P value
	No	(%)	No	(%)	
Squamous cell	43	(70.5)	45	(83.3)	0.291

Melanoma	0	(0.0)	1	(1.9)
Basal cell carcinoma	4	(6.6)	2	(3.7)
Sarcoma	2	(3.3)	1	(1.9)
Others	3	(4.9)	0	(0.0)

Relative of proportions of histology were independent of age (p value=0.291). Proportions of patients with and without Squamous cell, Melanoma, Basal cell carcinoma, and Sarcoma did not significantly differ between women aged <50 and ≥50 years, that is, the proportions were similar as shown above in Table 7.

Table 8: Presence of lymph nodes in vulvar cancer patients by age category at Kenyatta National Hospital

Lymph nodes	**Age <50yrs N = 61**		**≥50yrs N = 54**		**P value**
	No	**(%)**	**No**	**(%)**	
Absent	13	(21.3)	12	(22.2)	0.517
Present	39	(63.9)	33	(61.1)	

Relative of proportions of Lymph nodes were independent of age (p value=0.517). Proportions of patients with and without Lymph nodes did not significantly differ between women aged <50 and ≥50 years, that is, the proportions were similar as indicated in Table 8 above.

Table 9: Staging of vulvar cancer patients by age category at Kenyatta National Hospital

STAGE	CATEGORY				
	Age <50yrs N = 61		≥50yrs N = 54		P value
	No	(%)	No	(%)	
I	6	(9.8)	4	(7.4)	0.479
II	4	(6.6)	7	(13.0)	
III	29	(47.5)	28	(51.9)	
IV	18	(29.5)	11	(20.4)	

Relative of proportions of stage were independent of age (p value=0.479). Proportions of patients in different stages did not significantly differ between women aged <50 and ≥50 years, that is, the proportions were similar. However majority of patients presented at stage III of illness.

Table 10: Modalities of treatment of patients with vulvar cancer by age category at Kenyatta National Hospital

MODALITIES OF TREATMENT	CATEGORY				
	Age <50yrs N= 61		≥50yrs N = 54		P value
	No	(%)	No	(%)	
None	4	(6.6)	4	(7.4)	0.941
Radical vulvectomy and bilateral lymphadenectomy	8	(13.1)	5	(9.3)	
Radical vulvectomy/ bilateral lymphadenectomy/	8	(13.1)	8	(14.8)	

Radiotherapy				
Radical vulvectomy/ bilateral lymphadenectomy/	2	(3.3)	2	(3.7)
Radio/ Chemotherapy				
Chemotherapy	1	(1.6)	1	(1.9)
Radiotherapy	9	(14.8)	12	(22.2)
Chemoradiotherapy	7	(11.5)	6	(11.1)
Simple vulvectomy and chemotherapy	1	(1.6)	0	(0.0)
Simple vulvectomy and chemoradiotherapy	4	(6.6)	1	(1.9)
Simple vulvectomy	12	(19.7)	9	(16.7)
Simple vulvectomy and radiotherapy	3	(4.9)	4	(7.4)

Relative of proportions of treatment were independent of age (p value=0.941). Proportions of patients using different treatments did not significantly differ between women aged <50 and ≥50 years, that is, the proportions were similar as shown above.

Table 11: Short term complications of vulvar cancer patients by age category at Kenyatta National Hospital

SHORT TERM COMPLICATIONS	**CATEGORY**				
	Age <50yrs N= 61		**≥50yrs N = 54**		**P value**
	No	**(%)**	**No**	**(%)**	
DVT	2	(3.3)	6	(11.1)	0.373
None	21	(34.4)	15	(27.8)	
Wound breakdown	3	(4.9)	2	(3.7)	
Wound breakdown, wound infection	1	(1.6)	3	(5.6)	
Wound infection	11	(18.0)	13	(24.1)	
Wound infection, DVT	1	(1.6)	0	(0.0)	

Relative of proportions of short term complications were independent of age (p value=0.373). Proportions of patients' short term complications did not significantly differ between women aged <50 and ≥50 years, that is, the proportions were similar as shown above.

Table 12: Long term complications of vulvar cancer patients by age category at Kenyatta National Hospital

LONG TERM COMPLICATIONS	CATEGORY				
	Age <50yrs N= 61		≥50yrs N= 54		P value
	No	(%)	No	(%)	
Pressure sores					
Absent	18	(29.5)	14	(25.9)	0.383
Present	1	(1.6)	0	(0.0)	
Introital stenosis					
Absent	18	(29.5)	14	(25.9)	0.383
Present	1	(1.6)	0	(0.0)	
Urinary and fecal incontinence					
Absent	18	(29.5)	14	(25.9)	0.442
Present	3	(4.9)	5	(9.3)	
Rectocele					
Absent	18	(29.5)	14	(25.9)	0.501
Present	2	(3.3)	0	(0.0)	
Lymphedema					
Absent	18	(29.5)	14	(25.9)	0.966
Present	4	(6.6)	3	(5.6)	
Hernia					
Absent	18	(29.5)	14	(25.9)	0.18
Present	1	(1.6)	4	(7.4)	
Recurrence					
Absent	18	(29.5)	14	(25.9)	0.219

Present	7	(11.5)	1	(1.9)	
Death					
No	18	(29.5)	14	(25.9)	0.79
Yes	12	(19.7)	8	(14.8)	

Relative of proportions of long term complications were independent of age (p value>0.05). Proportions of patients' long term complications did not significantly differ between women aged <50 and ≥50 years, that is, the proportions were similar.

DISCUSSION

In the last decade, there has been an increasing trend of younger women presenting with vulval cancer. The mean age of the patients presenting with vulval cancer at diagnosis was 50.7 years at Kenyatta National Hospital with the average presenting age decreasing from 64 to 38 years. This is similar to the RCOG guidelines of 2014 where in the last 30 years, the incidence in women diagnosed with vulvar cancer aged 40 – 49 years increased 2 fold. Messing Gallup (USA) also found that the average presenting age dropped from 69 to 55 years and Zongo (Burkina Faso) found the average presenting age to be 55 years.

In this study, patients aged <50 years mainly had secondary and university education. Some patients aged ≥50 years were not educated while others had primary education. Education among women aged <50 years lowered their probability of presentation with vulval cancer by 66% compared with their counterparts. Though not significant, women aged <50 years who are single, muslim, and unemployed are less likely to present with vulval cancer compared with their counterparts. Munhoz et al (Brazil) found that most of their patients (median age 70 yrs) with vulvar cancer had little or no schooling. China Xiao et al (2017) surmised that patients at ≥50 years had a low level of education. There was however no statistical difference in socioeconomic status of patients < and ≥ 50 years of age. However, Lanneau et al found that vulval cancer patients <45 years had a low SES.

Vulvar bleeding significantly varied between women aged <50 and ≥50 years whereby women

<50 years presented most with vulvar bleeding and those ≥ 50 years presented mostly with a vulvar mass. In contrast Alkatout et al found pruritus was the most common reported symptom of vulvar cancer. Women aged ≥50 years and bleeding were 23.7% less likely to present with vulvar cancer compared to their counterparts.

Women with and without HIV, and chronic illnesses i.e. diabetes and hypertension significantly varied between women aged <50 and ≥50 years whereby most of the women aged <50 years were HIV positive. This is similar to Lanneau et al who found immunosuppression to be a predisposing factor to developing vulvar carcinoma. In contrast, Al Ghamdi et al found HIV to be the lowest predisposing factor at 4% while VIN and HPV were found in 95% and 80% respectively in patients below 40 years of age. Women aged ≥50 years and HIV positive were 6.8% less likely to present with vulvar cancer compared with HIV positive women aged <50 years.

Women ≥ 50 years with diabetes and hypertension seemed to have a higher incidence of vulvar cancer similar to Stroup et al who found older women diagnosed with vulvar cancer with two or more comorbidities. Patients with diabetes, high blood pressure, and elevated BMI seem to have an association with of vulvar cancer, but do not appear to have a direct implication.(37) Women <50 years with diabetes and hypertension were 11.7 and 4.7 times respectively less likely to be diagnosed with vulval cancer in comparison to their counterparts.

Patients with and without sexually transmitted infections, smoking history, Pap smear history and lichen sclerosus did not significantly differ between women aged <50 and ≥50 years, that is, the proportions were similar. This is in contrast to Lanneau et al who found a strong correlation between smoking, STI history, multiple sexual partners and age at coitarche and vulvar cancer in patients below 45 years. Most of this information was however not documented in the patients' files. Messing in a similar comparative study found that a history of cigarette use was not significantly different across the age groups in his study.

Patients with and without squamous cell carcinoma, basal cell carcinoma, melanoma and sarcoma did not significantly differ between women aged <50 and ≥50 years.

Overall however, in this study, SCC remained the commonest histological type followed by basal cell and the least was sarcoma. This was similar to Alkatout et al who found that SCC was the commonest, followed by melanoma then sarcoma.

Clinical stage at presentation did not significantly differ between women aged <50 and ≥50 years. Overall however, all patients with vulvar cancer presented in advanced stage disease regardless of age. (stage III). Messing et al (USA) found that patients >45 years mostly presented in advanced stage disease while the younger patients presented in early stage disease. This was similar to Al Ghamdi et al where patients < 40 years of age presented in stage I/II disease.

Neither the site of the tumor nor the time duration from onset of symptoms differed by age in our study. This is surprising because younger women are expected to be more sexually active thus hastening the time to presentation or are more comfortable with self examination.

There was no difference in management strategy and outcome by age. Management was largely based on stage and presence or absence of lymph nodes. Proportions of patients using different treatments, short and long term complications, did not significantly differ between women aged <50 and ≥50 years. In our setup, the approach was more individualized and less radical in most patients. This was similar to Deppe et al (USA) treatment for early stage disease was wide excision and was largely individualised.

The main limitations of this study were convenience sampling, incomplete records and incomplete data. The strengths were a larger sample size that surpassed the intended sample thus increased the power of the study. The non invasive nature of the study was also a strength as there was no patient contact or interventional procedures involved.

CONCLUSION

Carcinoma of the vulva in younger female patients may result from either the natural history of the disease being hastened or the development of a different disease with different risk factors. Human immunodeficiency virus appears to be more preponderant as a factor in its aetiology. Vulvar bleeding has also been seen as a common presenting symptom in patients below 50 years of age. Young women with vulval carcinoma may constitute a unique group sharing a common diagnosis but have a different disease than their older counterparts. Despite these factors, the ultimate treatment and prognosis appears to be unaffected by age.

RECOMMENDATIONS

1. General education in the society to encourage early detection and prevention of HIV might alter the rising incidence of this disease in younger women.
2. Given the late stage at presentation of vulvar cancer there is a need for public health education on signs and symptoms of the disease.
3. Young female patients who are HIV positive with vulval bleeding should undergo thorough screening for diagnosis of vulvar cancer.

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APPENDIX I: DATA COLLECTION WORKSHEET

Date…… Identification number…….....

Patient characteristics	
Age in years	
Ethnicity	
Religion	Christian □ Muslim □ Other: (specify)
Education level	Primary □ Secondary □ University □
Occupation	Employed □ Unemployed □
Duration of symptoms (months)	0-3 □ 4-6 □ 7-9 □ 10- 12 □ 13 □ Other □
Symptoms	Pruritus□

	Swelling □ Vaginal discharge □ Vaginal bleeding □ Vaginal ulceration□ Dysuria □ Others …….
Relevant past medical history	HIV status: Positive□ Negative □ Diabetes: Yes □ No □ Hypertension: Yes □ No □ Antecedent lesions: (specific) History of STI: (specific) History of smoking: Yes □ No □ Others: ……..
Examination findings	Vulval mass/ulcer: Present □ Absent □ -Appearance of mass Warty □ Bowenoid □ Nodular □ Keratinized □ -Site of mass Lt Labia Majora □ Rt Labia Majora □ Lt Minora □ Rt Minora □

	Clitoris □ Other……. -Size of mass in cm…… -Lymphadenopathy: Present □ Absent □ Others: ……
Histological type	Squamous cell □ Melanoma □ Basal cell carcinoma □ Paget's disease of the vulva □ Sarcoma □ Others: (specify)……..
Stage	I □ II □ III □ IV □
Treatment	Radical vulvectomy and bilateral lymphadenectomy □ Simple vulvectomy □ Radiotherapy □ Chemotherapy □ Simple vulvectomy and chemotherapy □ Radiotherapy and chemotherapy □

	No treatment □
Complications – short term	Wound breakdown □ Wound infection □ DVT / PE □
Long term	Pressure sores □ Introital stenosis □ Urinary and fecal incontinence □ Rectocele □ Inguinal lymphocyst □ Lymphedema □Hernia □

APPENDIX II: ETHICAL 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

KENYATTA NATIONAL HOSPITAL APPROVED 16 OCT 2018 KNH/UON-ERC P.O Box 20723-00202 NBI

Ref: KNH-ERC/A/371

16th October 2018

Dr. Susan Diane Akinyi Adongo
Reg. No.H58/80615/2015
Dept.of Obs/Gynae
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Adongo

RESEARCH PROPOSAL – A COMPARATIVE STUDY ON PRESENTATION OF VULVAL CANCER IN PATIENTS BELOW AND ABOVE 50 YEARS OF AGE AT KENYATTA NATIONAL HOSPITAL (P559/08/2018)

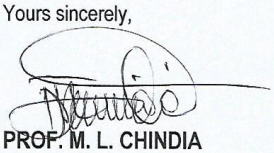
This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 16th October 2018 – 15th October 2019.

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.

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 Chairperson, Dept. of Obstetrics and Gynaecology, UoN
Supervisors: Prof. Koigi Kamau, Dr. Medhat Amin

APPENDIX III: STUDY TIME FRAME AND BUDGET

Study time frame

ACTIVITY	May 2018	June 2018	Jul 2018	Aug 2018	Sep 2018	Oct 2018	Nov 2018	Dec 2018	Jan 2019	Feb 2019	Mar 2019	Apr 2019
Proposal development												
Ethical Approval												
Data Collection												
Data Analysis												
Dissertation Writing and presentation												

Budget

Item	**Amount (Kshs)**
Statistician	30,000
Stationery	15,000
Contingencies	20,000
Research fee	2,500
Research assistant	30,000
Printing and binding	15,000
Total	**112,500**

The study will be funded by the principal investigator.