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DESCRIPTION OF THE CLINICAL CHARACTERISTICS AND PATHOLOGICAL FINDINGS OF VULVAR LESIONS IN WOMEN WHO HAD SURGICAL EXCISION AT CMJAH BETWEEN 2013-2018

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine in Obstetrics and Gynaecology

MMed (O&G)

Johannesburg, September 2022

Declaration

I, Venus Salem, declare that the research reported in this work is completely my own. It is submitted to the Faculty of Health Sciences for the degree of Masters of Medicine in Obstetrics and Gynaecology, at the University of Witwatersrand, Johannesburg.

It has not been submitted before for any other degree or examination at this, or any other university.

Signature: 

Date: 01/09/2022

Dedication

This work is dedicated to my mother for her endless support and patience. To my wonderful grandparents for being my first teachers and my wonderful husband for supporting and encouraging me to believe in myself.

Acknowledgments

I would like to express my gratitude to the following people:

1. My wonderful supervisor, Dr Langanani Mbodi, for his assistance with every aspect of this study. Without his inspiration, coaching, and enthusiasm none of this would have happened.

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3. The staff in the records department who assisted me in retrieving the files electronically.

ABSTRACT

Background:

Vulvovaginal complaints are a common reason for gynaecology consultations. The vulvar conditions may be benign (infections, lichen planus or lichen sclerosus), premalignant (vulvar intraepithelial neoplasia, dVIN), or malignant. Vulvectomy is the treatment of choice in most pre-malignant and malignant lesions and occasionally a vulvectomy may be performed for a benign condition such as condyloma accuminata. In most malignant cases a radical vulvectomy and bilateral lymph node dissection are performed in patients diagnosed with late stage disease. Survivors of vulvar cancer suffer severe morbidity and a decrease in quality of life. Common post-operative complaints include lymphedema, sexual dysfunction, and groin discomfort. This study aimed at characterizing women who had vulvar surgery between 2013 and 2018 at Charlotte Maxeke Johannesburg Academic Hospital.

Methods:

This was a retrospective cross-sectional study that conducted at the Gynaecologic Oncology Unit of Charlotte Maxeke Johannesburg Academic Hospital. The study population was women with a vulvar lesion that needed vulvar excision. This included all women who had any type of vulvectomy performed from January 2013 to December 2018.

In total 113 cases met the inclusion criteria and 36 women were excluded. Data were collected from the patients' records using a data collection sheet. The following data were recorded onto the data sheet: age, parity, symptoms, co-morbidities, tobacco use, surgical procedure, and complications of surgery. The histopathological examination of all specimens was performed at the National Health Laboratory Service.

The data were transferred to an Excel spreadsheet and exported into STATA® (Version 13, Texas 77845, USA) for analysis.

Categorical variables were summarised by frequency and percentage. Continuous variables were summarised using means with standard deviation or medians with inter-quartile ranges. For categorical variable comparisons the Chi^2 test or the Fisher's exact test was used. For

comparisons of continuous variables, the T-test or the Mann- Whitney-U test was used. Significance was set at a p-value of < 0.05

Results:

The mean age of the 113 women in the study was 44.53 years (SD±12.60); of which 101 (89.38%) were of African descent, 11 (9.73%) women were of Caucasian descent and one (0.88%) was Indian. The median parity of women was two (IQR-1-3; range=0-10). Twenty-seven women (23.89%) were post-menopausal.

The most common presenting symptom was a growth in the vulvar region of 107 (94.69%) women, with pain in 11 (9.73%) women, swelling of the vulva in five (4.42%) women, and dyspareunia was a complaint in two (1.77%) women.

There were 20 (17.70%) women with hypertension, and six (5.31%) had diabetes. Eighty-nine (78.76%) women were HIV positive. There were 38 women with a viral load <20 (copies/ml) and two with a viral load <50 (copies/ml). The median CD4 count was 423 (IQR 249-604; range=2-1215), and the median viral load of women who were not virally suppressed was 100 (IQR 100-1570; range=54-260000).

Forty-one (36.28%) women had a radical vulvectomy and a bilateral inguinal lymphadenectomy. Wide local excision was done in 31 (27.43%) women, simple vulvectomy in 26 (23.01%) women and hemi-vulvectomy in 15 (13.27%) women.

The vulvar histopathology reports showed that 52 (46.01%) lesions were benign and 61 (53.98%) were malignant. Squamous cell carcinoma was found in 59 (52.21%) women. The other two malignancies were one melanoma (0.88%) and one Merckel cell carcinoma (0.88%). Fifty-two (88.13%) histology types were invasive moderately differentiated squamous cell carcinoma, four (6.77%) were poorly differentiated squamous cell carcinoma, and two (1.76%) were invasive basaloid type squamous cell carcinoma. There were seven women where a benign lesion (vulvar intraepithelial neoplasia and lichen sclerosus) co-existed with squamous cell carcinoma, six were associated with vulvar intraepithelial neoplasia and one was associated with lichen sclerosis. The benign pathology report showed vulvar intraepithelial neoplasia in 32 (28.31%) women.

Conclusion:

More than half of the women had a malignancy. Most of the women with benign histology had vulvar intraepithelial neoplasia. Women with VIN 2 and VIN 3 were mostly treated surgically. The time from symptom onset and surgical treatment was long. The overall complication rate was high. The presence of lichen sclerosus and vulvar intraepithelial neoplasia together with malignancy were found in seven women.

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List of abbreviations

BMI	Body mass index
CIN	Cervical intraepithelial neoplasia
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
dVIN	Differentiated vulvar intraepithelial neoplasia
FIGO	International Federation of Gynaecology and Obstetrics
HPV	Human papilloma virus
HSIL	High grade squamous intraepithelial lesion
HSV	Herpes Simplex virus
ISSVD	International society for the study of vulvovaginal diseases
LP	Lichen planus
LS	Lichen sclerosus
LSIL	Low grade squamous intraepithelial lesion
NACT	Neoadjuvant Chemotherapy
NHLS	National Health Laboratory Service
NICE	National Institute for Health and Care Excellence
SCC	Squamous cell carcinoma
UVA1	Ultraviolet A1
VIN	Vulvar intraepithelial neoplasia
WHO	World Health Organization

1 INTRODUCTION

Vulvar complaints are experienced by one in seven women. Common symptoms include itching, burning, and dyspareunia. The most common causes of acute complaints are usually infective such as fungal infections, bacterial vaginosis, herpes simplex, and ano-genital warts. Vulvar skin lesions can cause pain, and discomfort, interfere with sexual function and affect a woman's quality of life. At most times the cause of the presenting symptoms is unclear and most patients have a history of using over-the-counter medication or over-washing the affected areas. (1)

A variety of benign, premalignant, and malignant lesions can occur in the vulva. Vulvar disease causes a lot of difficulty for the patients and requires multiple visits by physicians, gynaecologists, and dermatologists. (2)

Conditions such as lichen sclerosus (LS) and human papilloma virus (HPV) infection can cause premalignant lesions in the vulva such as vulvar intraepithelial neoplasia (VIN). Lichen sclerosus is commonly associated with differentiated vulvar intraepithelial neoplasia (d-VIN). The risk of progression of LS to malignancy is about 4-5 %. (3)-(4)

Vulvar cancer represents about 3% of all gynaecologic cancers. In 2002, about 26800 new cases were reported globally. Over the years there has been a decrease in the age group of patients with vulvar pathology. (5) Survivors of vulvar cancer suffer severe morbidity and a decrease in quality of life. Common post-operative complaints include lymphedema, sexual dysfunction, and groin discomfort. (6)

2 LITERATURE REVIEW

2.1 APPROACH TO VULVAR DISEASE

Vulvovaginal complaints are a common reason for gynaecology consultations. Good history taking, examination, and complementary tests are necessary to aid the diagnosis. (7) A full history of the patient's sexual practice, previous surgery on the genital region, and routine care and hygienic habits are of paramount importance. It is advisable to do a thorough physical examination in the dorsal lithotomy position, using good lighting, along with a speculum examination of the vagina. The use of a colposcope can also aid in the Identification of atrophy, erythema, induration, lichenification, erosion, and ulceration. (8) With the aid of a colposcope a magnified view of the vulvar lesion can be obtained for assessment. Unlike cervical dysplasia which often has an aceto-white appearance with atypical vascular changes, vulvar dysplasia may not have significant colposcopic findings, especially in the hair-bearing areas. A mild aceto-white appearance on the vestibule is often normal and should not be confused with dysplasia. (2)

2.1.1 Vulvar biopsy

Indications for vulvar biopsy include lesions that appear malignant, the diagnostic challenge in chronic dermatologic disease, or treatment failure. (2) In many instances, there are delays in the diagnosis of vulvar pathologies. In most cases, a biopsy of suspicious vulvar lesions is indicated except in paediatric patients. A Keyes or punch is the most common tool used for vulvar biopsy. The 5-7 mm size gives a good pathologic specimen without leaving a defect that requires suturing. However, in more superficial disorders such as lichen planus or lichen sclerosus both shave and snip samples of the dermis are sufficient for the diagnosis. (9)

2.1.2 The common causes of benign vulvar disease

In a prospective study conducted by a dermatologist in Australia, 141 adult patients who had vulvar symptoms were evaluated and 89% of them had a vulvar biopsy. As much as 54% of the biopsy results showed chronic dermatitis. The other common condition was lichen sclerosus

in 13% of the patients and vulvovaginal candidiasis was reported in 10%. Further, 9% suffered from dysaesthetic vulvodynia and the least common condition was psoriasis 5%. (10)

2.1.3 Special considerations in vulvar disease

There are different groups of patients who have special characteristics when being evaluated for vulvar complaints.

2.1.3.1 Paediatric patients

In paediatric patients, most vulvar abnormalities are related to congenital or abnormal development. Disorders such as ambiguous genitalia, clitoral hypertrophy, hypertrophy of labia minora and majora, imperforated hymen, and transverse or longitudinal vaginal septum are mostly seen in this age group. Young girls may insert foreign objects into the vagina which may be the cause of the vaginal discharge. Organisms such as Candida and *Escherichia coli* can cause infections in pre-pubertal girls. However, the possibility of sexually transmitted diseases should be considered. (11)

2.1.3.2 Post-menopausal women

Women in this age group experience vulvar and vaginal atrophy due to estrogen deficiency. The mucosa of the vestibule is sensitive to estrogen and in menopause, it becomes pale and smooth and the introitus becomes narrow. (2) In severe cases labial adhesion and dyspareunia occur. In such cases, a good response is observed with topical estrogen within two weeks. If the patients are not responding a biopsy is required to exclude lichen sclerosus. (12)

2.1.3.3 Women with HIV

Vulvar infections in immunosuppressed patients appear to be multifocal and resistant to standard treatment. Herpetic lesions may form large ulcers and fungal infections are persistent after standard treatments. There must be a lower threshold to biopsy vulvar lesions or send for cultures to confirm the diagnosis. Infections in immunocompromised patients should be treated

timeously with early intravenous medication. In many patients, optimizing the antiretroviral therapy may show improvement in a lot of dysplasias as the viral load decreases and the CD4 count improves. (2) There is a high rate of HPV infection in HIV-positive women and this is due to immunosuppression and lower clearance of HPV compared to the general population. (13)

2.2 INFECTIOUS DISEASES OF THE VULVA

Infectious diseases are common and should be considered in the differential diagnosis of patients presenting with vulvar complaints.

2.2.1 Candidiasis

Candidiasis is a very common infection in the vulvovaginal area. The common symptoms are itching, burning, dysuria, and dyspareunia. About 90% of vulvovaginal fungal infections are *Candida albicans*. However, infections with *Candida glabrata* are also on the rise. It is important to enquire from patients about previous treatment attempts, and antifungal creams and suppositories. The application of these agents may affect the appearance of the vulva and vagina and the typical white discharge and curd may not be present. (2)

2.2.2 Bacterial vaginosis and Trichomoniasis

These disorders are mainly recognized as vaginal infections causing vaginal discharge, but they may cause vulvar symptoms such as dysuria, burning, and dyspareunia. It is important to do a wet mount and evaluation of vaginal acidity (PH) in all patients with vulvovaginal complaints. Common treatments are oral metronidazole or clindamycin cream. (2)

2.2.3 Genital warts

Condyloma acuminata usually appear as multiple warty lesions on the vulva. They are caused by HPV types 6 and 11. However, most HPV infections may be asymptomatic. (14) Anogenital HPV infection is always acquired by sexual intercourse. A cohort study of 603 college students identified 31 cases that developed anogenital warts. The median time from detection of HPV 6 and 11 and the appearance of the warts was 2.9 months. (15)

Most of the warty lesions are self-limiting in an immunocompetent patient and often resolve without treatment. There are various methods for the treatment of genital warts. Invasive methods such as cryotherapy, laser, trichloroacetic, and bichloroacetic acid are commonly used in the office. (14) Treatments such as podofilox or imiquimod can be applied at home. Imiquimod acts by boosting the immune response. (16)

2.2.4 Other sexually transmitted infections

Primary infection with herpes simplex virus (HSV) causes painful vesicles and ulcers in the vulvar, vaginal, and cervical region, and therefore, testing HSV serology assists in the diagnosis of patients with genital ulcers. (2)

Other sexually transmitted diseases that are less common are syphilis which causes a painless genital ulcer. Granuloma inguinale causes multiple granulomatous ulcers that are usually friable. Chancroid is caused by *Hemophilus ducrayi* and appears with tender vulvar ulcers with a necrotic base. Lymphogranuloma venereum presents with small genital ulcers and later involves the inguinal lymph nodes. Obstruction of ducts of the Bartholin's glands, and Skene's glands cause abscess formation which requires incision and drainage, and antibiotic therapy. (2)

2.3 LICHENOID VULVAR DISEASE

Lichenoid vulvar dermatosis includes lichen sclerosus (LS), lichen planus (LP), and lichen simplex chronicus. These are chronic inflammatory conditions, which present with different symptoms such as pain and pruritus. All these conditions have overlapping clinical characteristics but each condition has unique features and appropriate management requires an accurate diagnosis. (17)

2.3.1 Lichen sclerosus

Lichen sclerosus is a chronic dermatologic condition that is benign and progressive. It is associated with inflammation, pruritus, and pain. Vulvar LS is seen mostly in pre-pubertal girls and post-menopausal women, but it can occur at any age (18). The prevalence of LS ranges from 0.1% to 1.7% and is higher in gynaecologic practice than it is in dermatology practices. (22)

The exact cause of LS is unknown, but it is believed to be an immune-mediated disorder in up to 28% of women. The most common autoimmune disorder concomitant with LS is autoimmune thyroiditis followed by alopecia areata, vitiligo, and pernicious anaemia. (23). Other factors that can predispose women to LS may be low estrogen levels. This could be the reason it is more common in prepubertal girls and post-menopausal women. (25)

Lichen sclerosus is associated with histological changes such as hyperkeratosis, epidermal atrophy, and homogenization of collagen in the papillary dermis (22). There is also an accumulation of lymphocytes in the involved region therefore if the biopsy is not performed in regions with active disease the typical pathological changes will be absent. In cases where the biopsy results are not conclusive but the clinical scenario of pruritus and loss of vulvar architecture is strongly suggestive of LS, treatment should be started. (23) In early LS, the pathological changes are non-specific and may be difficult to differentiate from LP. It is noted that the thickening of the basement membrane and the decrease in the papillary dermis is more prominent in LS (24).

2.3.2 Lichen planus

Lichen planus shares several common features with LS. They both cause severe itching and distortion of the vulvar architecture and only the histological changes can distinguish the two disorders. Lichen planus has three subtypes such as erosive, papulosquamous, and hypertrophic. The erosive type causes more severe tissue destruction which can lead to urinary and sexual dysfunction. It also involves mucosal surfaces such as the oral cavity, nasal mucosa, conjunctiva, and the urethra (25).

2.3.2.1 Erosive lichen planus

The erosive type is the most common variant and causes more tissue destruction than the other two types, and can lead to urinary and sexual dysfunction. It also involves mucosal surfaces such as the oropharyngeal mucosa, conjunctiva, and urethra. (25) The common genital areas involved by erosive LP are labia minora, vestibule, and vagina. The vaginal lesions have a fine white lacy pattern. The vaginal involvement causes dyspareunia, post-coital bleeding, and discharge. Chronic disease in the vaginal mucosa may lead to the formation of synechiae and vaginal stenosis. The oral involvement is in the form of glassy red erythema of the gingival mucosa and the tongue. (26)

2.3.2.2 Papulosquamous lichen planus

This form of LP forms small pruritic papules that involve the keratinized and perianal skin. Occasionally it is associated with milky striae on the inner aspect of the labia. (19) After treatment of the papulosquamous lesions the skin may show postinflammatory hyperpigmentation. (28)

2.3.2.3 Hypertrophic lichen planus

This is a rare form of LP and the clinical diagnosis thereof is difficult because it is similar to other hypertrophic vulvar lesions. In many cases, it resembles vulvar intraepithelial neoplasia or invasive squamous cell carcinoma. (27) The clinical picture shows sheets of hyperkeratotic

whitened epithelium involving the vulva and extending to the perianal region. The normal architecture of the vulva is distorted. A biopsy can confirm the diagnosis, showing distortion of the basal layer with dermal lymphocytic infiltrates. Histology shows hyperkeratosis and immunofluorescent studies reveal irregular staining of the basement membrane. (26)
Differentiation between LS and LP may be extremely difficult and a combination of clinical features, histological and immunofluorescent studies, and response to treatment aids the final diagnosis. (26)

2.3.3 Lichen simplex chronicus

This disease appears in all ages. It is associated with pruritus and lichenified plaques which mainly involve the labia majora and the vagina is spared. It does not hold the risk of progression to squamous cell carcinoma. (17)

2.3.4 Associated malignancy

Lichen sclerosus slightly increases the risk of vulvar squamous cell carcinoma. The risk of malignancy is estimated to be 4-5%. (3)-(4) Studies show that early diagnosis of LS and treatment with potent topical steroids and biopsy of the suspicious skin lesions or thickened skin resistant to treatment can reduce the risk of squamous cell carcinoma (SCC) in women with LS. (29)
In a cohort study, 507 women with vulvar LS were followed over six years. They were divided into two groups. The first group comprised women with good adherence and the second group had poor adherence to steroid therapy. The results showed a significant association between treatment adherence and the risk of vulvar malignancy. In the group with good adherence, there were no cases of malignancy out of the 357 patients. The group with poor adherence had 4 cases of vulvar intraepithelial neoplasia and three of invasive SCCs among the 150 patients. (29)
To detect malignancy in an early-stage LS, the patients should be followed up every three months at the beginning of the treatment for two visits. The subsequent visit can be at six months and then yearly on maintenance steroids and they can be referred back to their primary

care physicians. These patients should be counselled, explaining that urgent referral is needed in case of persistent genital ulceration or a new mass. (30)

2.3.5 Treatment of lichen sclerosus

Topical steroids are commonly used as the first-line agents for the treatment of LS. Treatment failure could be due to the patient not being compliant with regular application of topical steroids, the diagnosis may be incorrect or other superimposed conditions could be causing the symptoms such as secondary candidiasis, vulvar intraepithelial neoplasia, psoriasis, or pemphigoid involving the mucous membranes. Conditions such as vulvodynia or vulvar scarring may cause persistent symptoms in women despite adequate treatment of LS. (30)

2.4.5.1 Medical treatment of lichen sclerosus

The first-line treatment for vulvar LS for adults and paediatrics is super potent topical corticosteroids such as clobetasol propionate (4). Evidence shows that topical steroids are highly effective in the treatment of LS (31). Mometasone furoate which is a less potent steroid may be an alternative to the highly potent clobetasol. In a 12-week open-label trial, 54 women with pathology confirmed LS were randomly divided into two groups. One group applied clobetasol 0.05% and the other group used mometasone furoate 0.1% ointment. The ointments were initially applied five days per week and then twice weekly for four weeks. The patients were assessed after the 12-week treatment was completed. Eighty-nine percent of the patients in both groups had responded to treatment. (32)

The patients should be counseled about the importance of adherence to treatment and the gradual tapering regimen of the topical steroids (33). The potent topical corticosteroids can cause various side effects such as atrophy, telangiectasia, and striae. A number of these side effects may occur as early as two to three weeks after daily application. (33) In cases where the use of topical steroids is not showing therapeutic effects or is poorly tolerated, the treatment of choice is tacrolimus and pimecrolimus which are calcineurin inhibitors (34).

Other therapies used for vulvar LS include oral retinoids, phototherapy, and photodynamic therapy (35). Ultraviolet A1 (UVA1) phototherapy can be an alternative to topical steroids. In

a randomized trial, one group of patients received home-administered medium-dose UVA1 phototherapy four times a week and a second group received once-daily clobetasol 0.05% ointment. The results showed that both therapies were effective. (36)

2.4.5.2 Surgical treatment of lichenoid disease

Surgical treatment is reserved for cases where there is disease progression despite medical treatment. (37) These procedures include dissection of the buried clitoris, the division of the fused labia, and dilatation of the narrowed introitus. (38) Simple vulvectomy is not recommended for the treatment of patients with LS where there is no underlying malignancy. (21)

2.4 OTHER VULVAR DERMATOSIS

Other rare chronic dermatologic diseases such as pemphigoid and pemphigus Vulgaris which can cause blisters can involve the vulvar region. Crohn's disease which usually has intestinal manifestations may also involve the vulvar region and cause ulcers and fissures in that region. (39)

2.4.1 Vulvar dermatitis

Vulvar dermatitis can be either endogenous or exogenous. The endogenous type is atopic dermatitis which begins in childhood and rarely involves the vulvar area (40). The exogenous type is a result of contact dermatitis and is mainly triggered by exposure to irritant agents, for instance, soaps, sanitary pads, fragrances, sweat, and urine (41). The key in the treatment of all types of eczema is educating the patients on avoidance of irritant agents. These patients respond well to mild to moderately potent topical steroids. (40)

2.4.2 Vulvar psoriasis

Psoriasis often presents in the form of erythematous plaques with silvery dry scales in other skin areas but because the vulvar region is usually moist it gives the lesions a fissuring appearance. The plaques often extend from the mons to the buttocks. Treatment options are the application of aqueous cream and moderately potent corticosteroids. (42)

2.4.3 Behcet's syndrome

This syndrome can cause painful ulcers of the vulva as well as oral ulcers and ophthalmologic inflammation (42). It is a multisystem disorder and the eye lesions are mostly uveitis and retinitis. Vulvar lesions respond to topical steroids, however, severe cases require oral steroids, colchicine, and immunosuppressants. (45)

2.5 VULVAR SQUAMOUS INTRAEPITHELIAL LESION

Vulvar squamous intraepithelial lesion (SIL), formerly referred to as vulvar intraepithelial neoplasia (VIN) is a vulvar premalignant condition. It refers to the squamous lesions that may lead to vulvar neoplasia. The latest classification system of vulvar disease was published in 2015 by the International Society for the Study of Vulvovaginal Disease (ISSVD) According to the 2015 ISSVD low grade squamous intraepithelial lesion (LSIL) of the vulva is the flat condyloma and this was previously referred to as VIN1. This shows cytologic atypia and increased mitotic activity in the basal and parabasal epithelium, and mature squamous cells in the upper two-thirds of the epithelium (44)

The high grade squamous intraepithelial lesion of the vulva (HSIL) shows loss of maturation in the middle and upper third to full-thickness of the squamous epithelium which is classified as VIN2 and VIN3 respectively. The cytological changes are significant with atypical mitotic figures and pleomorphism. Vulvar HSIL is often multifocal and can involve extensive areas of the vulvar region such as the interlabial grooves, the posterior fourchette, and the perineum. About two-thirds of the patients show multifocal lesions. (45) The HSIL lesions are divided into two histologic categories of the basaloid and the warty subtype. In the basaloid subtype,

the epithelium is flat and smooth, and histologically immature para-basal cells and mitotic figures are seen. The warty subtypes show spiking at the surface, have a condylomatous appearance and the histology shows numerous mitotic figures and abnormal maturation. (46)

Research shows that almost 90 percent of VIN lesions test positive for HPV, even though routine HPV testing is not done in clinical settings. (48) Low-risk HPV subtypes (6 and 11) are mostly detected, although a minority of lesions show high-risk types such as 16, 18, and 31. (47)

2.5.1 Differentiated VIN

Differentiated VIN comprises less than 5% of VIN cases and is mostly seen in postmenopausal women. It is usually unifocal and is often associated with lichen sclerosus. The d-VIN is commonly found adjacent to keratinizing squamous cell carcinoma. The differentiated type refers to lesions where the epithelium is thickened and parakeratotic with elongated and anastomosing ridges. The atypical cells are confined to the parabasal and basal parts with little or no atypia above them. (48)

2.5.2 The treatment of VIN

The aim of treatment in patients diagnosed with VIN is the prevention of progression of the disease to SCC and at the same time preserve the anatomy of the vulva. (49)

Surgical excision is the treatment of choice although ablative therapy and topical treatment have been used. There are limited studies to guide us in terms of the efficacy of the various methods. In a study of 1905 patients who were treated surgically, the recurrence rate after vulvectomy, local excision, and laser ablation were 19%, 18%, and 22% respectively over 12 to 75 months. (50)

Wide local excision is defined as the excision of an individual lesion with a 1cm margin and a re-approximation of the defect. In some cases, it is difficult to accomplish the 1cm margin and preserve vulvar anatomy. (51) In a simple vulvectomy, the entire vulva and the perineal tissue are resected. This is performed for benign and malignant conditions. (52)

The medical treatment of choice for VIN is imiquimod cream. It is an immune response modifier and has antitumour and antiviral effects. It stimulates local cytokine production and

cell-mediated immunity. It has been effective for high-grade VIN. In a systematic review including two randomized trials and eight observational studies, treatment with imiquimod showed full regression of the lesion in 51% of women, partial regression in 25%, and a recurrence rate of 16%. The overall results showed that Imiquimod is significantly more effective than the placebo (53). Imiquimod is applied topically to each lesion and does not need to be applied to the entire vulva. The therapeutic course is 16 weeks and it should be applied two to three times a week. The side effects are local erythema, inflammation, and irritation of the skin. However, most patients complete their course of therapy. (54)

Patients should be closely followed up because of a high recurrence rate. In a study on women with high-grade VIN, a 26% recurrence rate was observed, 8% of those progressed to malignancy, and 25% of the cases showed a late recurrence between 44 to 196 months. It is recommended to do a six-monthly follow-up on the patients for five years and a yearly follow-up after. (57)

2.6 VULVAR CARCINOMA

Vulvar carcinoma often presents with suspicious lesions or changes in the vulvar epithelium such as swelling, a lump, ulcer, colour, and persistent warts. The diagnosis is confirmed histologically by biopsy of the lesions. (56) The most common histologic subtype is SCC in 75% of cases. The other histologic types include melanoma, basal cell carcinoma, Bartholin gland adenocarcinoma, sarcoma, and Paget disease. (57) Histologically, the stromal response and inflammation involving nests of squamous epithelium determine the invasiveness of the lesion. Lesions with HPV involvement often appear warty or basaloid but the non-HPV invasive carcinoma show areas of differentiation and areas of keratinization. (2)

The risk factors for vulvar carcinoma are vulvar or cervical intraepithelial neoplasia, prior history of cervical cancer, cigarette smoking, vulvar lichen sclerosus, immunodeficiency syndromes, and European ancestry (58). Two pathways lead to SCC, one seen in younger women is related to HPV infection which often presents with basaloid and warty lesions while the lesions that are not related to HPV are well differentiated with keratinization and may be associated with lichen sclerosus and squamous cell hyperplasia. (59)

2.6.1 Epidemiology

Vulvar carcinoma is the fourth most common gynaecologic malignancy after uterine, ovarian, and cervical carcinoma. (60). Statistics from the US show 6100 new cases of vulvar cancer and 1500 deaths every year (61). Data from 2010 to 2014 showed non-Hispanic whites had an incidence of 2.7 per 100 000, non-Hispanic blacks 1.8, Asians 0.9 and Hispanic Americans 1.8 per 100 000 cases. The average age of vulvar cancer in the US is 68 years. Most of the women are diagnosed at an early stage with only 6% with distant metastasis. (62)

In a study by Brinton *et al*, the average age of women diagnosed with vulvar carcinoma was over 70 years old.(58) A South African study by Butt *et al*, reported that the mean age of women with vulvar carcinoma was 52.50 years, which showed an increase in the prevalence of vulvar carcinoma in younger women where the average age of diagnosis is 10-15 years younger compared to higher-income countries. (63) These findings may be attributed to the high rate of HPV infection in the Southern African region. A large meta-analysis including 78 studies showed the overall HPV prevalence in 157 879 women with normal cervical cytology estimated to be 10.4% (95% CI 10.2-10.7), however, the estimates in the African region were 22.1%. Human papilloma virus prevalence in Northern America was 11.3%, and in Asia 8.0%. This analysis further showed that HPV prevalence was highest in women in the age group of 35 years. (65) The latest FIGO update in 2021 has estimated the worldwide HPV prevalence in healthy women above the age of thirty years to be approximately 11.7% while the highest prevalence is 24% in sub-Saharan Africa. (65)

A study by Jonathan *et al*, in 2016, is the largest study to report the prevalence of LS in patients with vulvar SCC. This study showed that in 29% of women who had wide local excision for vulvar carcinoma, LS pathology was adjacent to the excised SCC, and 36% had previous histology of LS in their former outpatient visits. The data also suggested that at least one in three vulvar SCCs in this institution had LS as a predisposing factor. (66)

2.6.2 Vulvar carcinoma staging

The staging of vulvar cancer has been done using the International Federation of Gynecology and Obstetrics (FIGO) since 1988. It has had various modifications and was updated in 2009. (67) The FIGO staging of vulvar carcinoma was updated in 2021, more simplified and is now rather evidence-based compared to the previous versions. The United States Cancer database

prospectively analyzed data on vulvar carcinoma from 2010 to 2017 and Kaplan-Meier survival curves showed how different stages of vulvar carcinoma affect survival. The depth of invasion has been a topic of controversy over the years and in 1984, the International Society for the Study of Vulvovaginal Disease (ISSVD) had defined it from the most superficial dermal papilla to the deepest point of invasion, however in the latest FIGO staging system, it is measured from the basement membrane of the deepest, adjacent tumour free rete ridge to the deepest point of invasion. This staging system is used for all different types of vulvar cancers except for malignant melanoma. In the new FIGO staging system, variations in the depth of rete ridges or hyperkeratosis of the tumour will not alter the depth of invasion. The FIGO Committee for Gynaecology Oncology will assess the prognosis and survival of patients with the new depth of invasion measurements and the results are expected to be released in the next 10 years. (64) FIGO staging is presented in Appendix 1.

2.6.3 Other histologic types of vulvar malignancies

2.6.3.1 Basal cell carcinoma

This malignancy is common in the skin of other parts of the body and only represents 2-3% of vulvar carcinomas (68). This tumour tends to be locally invasive and rarely metastasizes unless more aggressive histologic types such as basosquamous, the morphea form, metatypical, or micronodular are present. (69)-(71). Vulvar basal cell carcinoma usually occurs on the labia majora and is commonly seen in Caucasian women 70 years and older (70).

2.6.3.2 Melanoma

Melanoma is rarely seen in clinical practice but it is the second most common vulvar malignancy after squamous cell carcinoma (71). It is important to biopsy pigmented vulvar lesions. The prognosis depends on the depth of the invasion and early diagnosis is very important. Surgery is the mainstay of treatment. The depth of invasion is measured from the most adjacent dermal papilla which is different in squamous cell carcinomas. (76)

2.6.3.3 Paget's disease of the vulva

Extramamilary Paget's disease involving the vulva appears as velvety red lesions with overlying white plaques. These lesions often present with burning, pruritis, and pain. Histologically large eosinophilic Paget cells appear in the basal layer of the epithelium. Paget's disease of the vulva may also be a manifestation of underlying adenocarcinoma of the sweat glands.(76) A study by Parker *et al,* on 76 cases of Paget's disease of the vulva showed that patients with intraepithelial Paget's disease with coexisting cancer and underlying adenocarcinoma have poorer prognosis compared to patients with intraepithelial Paget disease and patients with clitoral involvement may require more aggressive treatment (73).

2.6.3.4 Metastatic tumours to the vulva

Other gynaecologic malignancies such as the endometrium, ovary, and cervix have been reported to metastasize to the vulva (72). Neoplasms originating from the gastrointestinal, urinary tract, and breast may also metastasize to the vulva (74). These lesions may appear similar to primary vulvar carcinoma. Treatment should be directed to the primary malignancy (72).

2.6.4 Treatment of vulvar carcinoma

2.6.4.1 Wide local excision

For malignancies confined to the vulva and not extend to the adjacent perineal structures, wide local excision is recommended. The depth of resection must be adequate to avoid recurrence. (75) Dissection of groin nodes is recommended if the depth of invasion is more than 1mm or the size of the lesion is more than 2cm (76).

2.7.3.2. Radical vulvectomy and inguinal lymph node dissection

Radical vulvectomy is a surgical procedure that removes the entire vulva down to the level of the deep fascia of the thigh, the periosteum of the pubis, and the inferior fascia of the urogenital diaphragm (77). In case of involvement of inguinal lymph nodes, bilateral inguinal

lymphadenectomy is indicated (76). Vulvar reconstruction is a challenge and it often requires skin flaps and grafts. (56) If tension-free closure of the skin is not possible, the small defects can heal by secondary intention. Local flaps such as a rhomboid flap or lotus petal flap are taken from the adjacent vulvar tissue, which helps cover the larger defects. In the case of previous vulvar surgery or radiation, local flaps do not have a reliable blood supply, therefore, skin grafts from the buttocks and thighs can be used. In most of these cases, plastic surgeons need to be involved. (78)

It is important to individualize patient care, try to perform less radical surgery, reduce morbidity and maintain a high cure rate. Some of the complications of vulvectomy and inguinal lymphadenectomy are wound breakdown, thromboembolic disease, pressure ulcers, introital stenosis, urinary incontinence, faecal incontinence, and inguinal lymphocyst (79).

A lateralized vulvar lesion is one where wide local excision with a 1cm margin does not cross a midline structure such as the clitoris, urethra, perineal body, or anus. The groin lymph node dissection can be initially done on the ipsilateral side because the lymphatic cross-over is unlikely. If those nodes show cancer involvement the nodes on the contralateral side need to be excised or irradiated. (80)

Sentinel lymph node detection is mostly applicable for patients with early vulvar cancer. The benefit of this approach is to avoid bilateral inguinal lymphadenectomy and to decrease morbidity. The sentinel node is the lymph node that primarily drains the tumour. This should be done in unifocal tumours confined to the vulva, tumours less than 4cm, stromal invasion more than 1mm, and in cases in which clinically groin node involvement is negative and there are no safety issues for using Patent Blue dye or Technetium-99. (81)

2.7.3.4 Radiotherapy

Primary radiotherapy is recommended in cases of advanced vulvar cancer, with or without chemotherapy. The patients who receive radiotherapy pre-operatively may be able to have less invasive surgery with sphincter preservation (82).

The pathological findings such as surgical margins and groin node positivity determine the need for adjuvant radiotherapy. Routine radiotherapy is used post-operatively in patients with close surgical margins. Adjuvant radiotherapy is indicated when two or more groin lymph nodes are involved. (83)

2.6.4.5 Chemotherapy

Neoadjuvant chemotherapy is commonly used for patients with advanced, recurrent, or metastatic vulvar carcinoma. The common chemotherapy agents such as cisplatin, fluorouracil (5FU), and bleomycin are used for metastatic squamous cell carcinoma arising from other sites. (84)

2.6.5 Follow up

The follow-up plan for women after treatment of vulvar cancer is initially every three months for the first year, six monthly in the second year, and yearly thereafter. The prognosis is improved if the recurrence is found at an early stage and treated by excision or radiotherapy. Late recurrence is relatively rare but the patients should be advised to return if they experience any new symptoms or masses in the vulvar region. (78)

2.6.6 Recurrence and survival

In patients diagnosed and treated for invasive SCC, the recurrence rate ranges from 15% to 33%. The common sites of recurrence are in the vulva (69%), groin nodes (24.3%), and pelvis (15.6%). Distant metastasis occurs in 18.5% of the cases. (85)

The survival of the patients following recurrence is relatively poor therefore attempts must be made to cure the disease during primary treatment. The outcome of the patients following the local recurrence of vulvar cancer is better than other gynaecologic malignancies. (86) In cases where the recurrent disease is treated surgically the survival rate of the patient is about 45%. In cases in which excision of the involved area may lead to sphincter dysfunction, the option of radiotherapy should be considered. In patients who previously received a maximum dose of radiation, the excision of the recurrent lesion should be considered. (87)

2.7 CONCLUSION

Patients with vulvar disorders should be managed by a multidisciplinary team involving both gynaecologists and dermatologists (88). Vulvar dermatitis is a common condition that occurs at any age. It is well known that certain vulvar dermatosis may predispose to vulvar cancer. Clinicians need to have a low threshold for biopsy of suspicious lesions. (89) For an accurate diagnosis the biopsy should be taken correctly. In palpable vulvar lesions, the biopsy should contain the tumour mass with the surrounding normal skin to be able to comment on the extent of invasion (91,92).

Over the years there has been a decrease in the age group of patients with vulvar pathology (5). Conditions such as lichen sclerosus and HPV infection can cause premalignant lesions in the vulva such as (VIN). Research on these premalignant lesions has led to the discovery of the different pathways that may cause vulvar malignancies (3).

3 PROBLEM STATEMENT

Vulvovaginal complaints are a common reason for gynaecology consultations and are experienced by one in seven women. (1) Vulvar disease ranging from benign, malignant and premalignant conditions can cause a lot of distress for the patients and it may have diagnostic challenges for physicians, dermatologists and gynaecologists.

Vulvectomy is the treatment of choice in most pre-malignant and malignant lesions and occasionally a vulvectomy may be performed for a benign condition such as condylomata accuminata. In most malignant cases a radical vulvectomy and bilateral inguinal lymph node dissection are performed in patients diagnosed with higher stage disease. Survivors of vulvar cancer suffer severe morbidity and a decrease in quality of life. Common post-operative complaints include lymphedema, sexual dysfunction, and groin discomfort.

4 AIM OF THE STUDY

To describe the types of vulvar lesions and clinical characteristics in women treated with surgical excision at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from January 2013 to December 2018.

5 OBJECTIVES

1. To describe the clinical characteristics and demographics of patients who underwent surgical treatment for vulvar disease.
2. To describe the histopathological types of lesions in both benign and malignant.
3. To describe the prevalence of benign lesions associated with malignancy.

6 RESEARCH METHODOLOGY

6.1 STUDY SETTING

This study was conducted at the Gynaecology Oncology Unit of CMJAH. This unit is managed by an oncologist and accepts referrals from three regional hospitals and local clinics.

6.2 STUDY DESIGN

This was a retrospective cross-sectional study involving patient record reviews.
The study population was any woman with a vulvar lesion that needed a surgical excision. This included all types of vulvectomies. Some of the women already had a diagnosis and some came for diagnostic purposes.

Inclusion criteria:

Any woman who had a confirmed surgical excision.

Exclusion criteria.:

Unavailability of files at the hospital records stores.

Unavailability of the pathology report.

Those who only had a punch biopsy or Keyes biopsy.

6.3 SAMPLE SIZE

The study sample included all women who underwent surgical treatment for vulvar lesions (malignant or benign). This was a descriptive study so no sample size calculation was performed.

6.4 DATA COLLECTION

Data included in the study were identified by using theatre records and gynaecology ward admission books. In total, 113 cases met the inclusion criteria and 36 women were excluded due to the unavailability of histology reports or files in the hospital records.

Data was collected from the patient's records using a data collection sheet (Appendix 2). The patient's information was retrieved from the hospital records where they were stored electronically in a PDF format. The records contained each patient's clerking notes (history and examination), investigations, and copies of their pathology reports. If the pathology report could not be found in the records it was traced by using the National Health Laboratory Service database (NHLS). No further histological reporting or analysis was requested and no patient was interviewed, either directly or through a self-administered questionnaire.

The variables that were extracted were demographics (age, race), clinical (parity, menopausal status, presenting features, examination findings), and histology (cell type, margins, lymph node involvement). The reporting of the vulvar disease, margin status, lymph nodes, and histological subtype was as per the Pathology Department reporting protocols.

6.5 DATA ANALYSIS

The collected data was cleaned and coded for statistical analysis and transferred from the datasheet to the Excel data collection tool to STATA® (Version 13, Texas77845, USA) program for analysis.

Categorical variables were summarised by frequency and percentage. Continuous variables were summarised using a mean with standard deviation (SD) or a median with Interquartile ratio (IQR). A comparison between benign and malignant lesions was made. VIN and LS were considered benign lesions and for all SCC, melanoma was categorized as malignant. Comparisons were made using a Chi^2 test. A Fisher's exact test was used for categorical variables. For comparisons of continuous variables, a T-test or a Mann-Whitney-U test was used. A P-value of less than 0.05 was considered statistically significant.

6.6 ETHICS CLEARANCE AND THE HOSPITAL PERMISSION FOR THE STUDY

The protocol for this study was approved by the post-graduate assessors' group (Obstetrics & Gynaecology, Faculty of Health Sciences, University of the Witwatersrand) for a Masters of Medicine project. Permission to conduct this study was obtained from the following departments; the clinical head, Department of O&G, CMJAH; the Department of Anatomical Pathology, NHLS/the University of Witwatersrand; the Chief Executive Officer of CMJAH. Approval from the Human Research Ethics Committee (HREC) of the University of the Witwatersrand was obtained on 05/04/2019. The clearance certificate number is M190313 (Appendix 3).

6.7 FUNDING

This was a retrospective study that required access to the patient's records. A data collection sheet was used and data were stored and processed electronically. This study was done with a small budget for stationary. There were no funds required to undertake the study and no sponsorship or financial assistance was received from any company or institution.

7 RESULTS

One hundred and forty-nine women who had undergone surgical treatment for the vulvar disease were identified from the theatre books at CMJAH from January 2013 to December 2018. Of these, 36 (24.16%) women were excluded from the study for the following reasons: six had cauterization of warts in theatre and no specimen was sent for histology, a simple vulvar biopsy was done in theatre for four women, and in 26 women either the histology results could not be traced or the file could not be identified in the hospital records department. The final number of women thus included in the study was 113.

7.1 THE DEMOGRAPHICS

The mean age of the women in the study was 44.53 years (SD±12.60) and this included women with both benign and malignant pathology. The mean age of women with vulvar cancer was 44.33 years (SD±12.39). The mean age of women with the benign disease was 43.53 (SD±17.31). One hundred and one (89.38%) women were of African descent, 11 (9.73%) women were of Caucasian descent and one (0.88%) was Indian. The median parity of women was two (IQR 1-3; range=0-10). There were 27 (23.89%) women who were post-menopausal and most women were in the 4^{th} decade of life. Four (3.54%) women had a history of tobacco use. The demographic description is shown in Table 7.1.

Table 7.1 Demographic characteristic categories

Age groups	**Number (%) n=113**
20-30 years	7(6.20)
31-40 years	46 (40.71)
41-50 years	35 (30.97)
51-60 years	13 (11.50)
61-70 years	6 (5.31)
71-80 years	4 (3.54)
81-90 years	2 (1.77)
Tobacco Use	
History of any tobacco use	4 (3.54)
No Tobacco use	109 (96.46)
Menopausal status	
Pre-menopausal	86 (76.11)
Post-menopausal	27 (23.89)
Parity	
Median parity	2 (IQR 1-3)

7.2 THE PRESENTING SYMPTOMS

The most common presenting symptom was a growth in the vulvar region, which was reported in 107 (94.69%) women. Pain was reported in only 11 (9.73%) women. Swelling in the vulva was a symptom in five (4.42%) women and dyspareunia was a complaint in two (1.77%) women. Some women had more than one symptom. The median duration of symptoms was 12 months (IQR 8-18; range=2-36).

7.3 THE CO-MORBIDITY CONDITIONS

There were, 20 (17.70%) women with hypertension, and six (5.31%) women had diabetes. Eighty-nine (78.76%) women were HIV positive. Of those who were HIV positive, 38 (33.62%) women had VL<20 (copies/ml), two had VL<50 (copies/ml), and the remainder had a VL of more than 50 copies /ml. The median CD4 count was 423 (IQR-249-604; range=2-1215), and the median viral load of women who were not virally suppressed was 100 (IQR 100-1570; range=54-260000). The co-morbidity conditions are summarized in Table 7.2.

Table 7.2 Description of the co-morbidities

Co-morbidity	**Number (%) n=113**
Hypertension	22 (19.47)
Diabetes	6 (5.31)
HIV	89 (78.76)

7.4 SURGICAL PROCEDURE

The median duration of the surgical procedure was 70 minutes (IQR 50-105; range 11- 300). With regards to groin surgery, bilateral inguinal lymphadenectomy was done in 61 (53.98%), and unilateral lymphadenectomy in eight (7.08%) women. In 44 (38.94%) women, no lymphadenectomy was performed. Table 7.3 gives a description of the overall surgical procedures done.

Table 7.3 Surgical procedures

Surgical procedure	**No lymphadenectomy** **N (%)**	**Unilateral lymphadenectomy** **N (%)**	**Bilateral lymphadenectomy** **N (%)**
Wide local excision 31(27.43%)	25 (22.12)	3 (2.65)	3 (2.65)
Hemi-vulvectomy 15(13.27%)	7 (6.19)	5 (4.42)	3 (2.65)
Simple vulvectomy 26(23.00%)	12 (10.61)	0	14 (12.38)
Radical vulvectomy 41(36.28%)	0	0	41(36.28)

Table 7.4 shows the different reconstruction flaps used after vulvectomy in those women whose primary repair was not possible due to the large defect. In 3 (20%) women the reconstruction flaps were done by plastic surgeons.

Table 7.4: Reconstruction flaps

Type of reconstruction flap	**Number (%) n=15**
V-Y advancement flap	8 (53.33)
Rhomboid flap	4 (26.67)
Other flaps (lotus petal, angel wing, unidentified)	3 (20.00)

There was one patient with an intraoperative complication of excessive bleeding with an estimated blood loss of 1500 ml. The median hospital stay postoperatively was six days (IQR-3-10; range 1-72). No women with reported with bleeding during the postoperative period. Table 7.5 reports the postoperative complications recorded.

Table 7.5: Postoperative complications after vulvectomy and groin surgery

Post-operative complications	**Number (%) n=38**
Wound sepsis	19 (50.00)
Wound breakdown	16 (42.10)
Flap necrosis	2 (5.26)
Lymphocyst	1 (2.64)

7.5 VULVAR PATHOLOGY

The vulvar histopathological reports showed that 52 (46.01%) women had benign pathology and 61 (53.98%) had malignant pathology. The most common malignant pathology was SCC reported in 59 (52.21%) women. There was one woman with vulvar melanoma who was treated with wide local excision and right inguinal lymphadenectomy. She was an 86-year-old Caucasian woman, who was HIV negative and with parity of 10.

One other woman had an invasive small cell neuroendocrine carcinoma (Merckel cell carcinoma) and underwent a vulvectomy and bilateral lymph node dissection. She was a 35-year-old African woman, with a parity of two. She was HIV positive with a CD4 count of 64 and a viral load lower than the detectable level.

Fifty-two (88.13%) histological subtypes were invasive moderately differentiated SCC, four (6.77%) were poorly differentiated SCC, and two (1.76%) were invasive basaloid type SCC. The margin status in women with SCC showed that 15 (17.44%) had positive margins for malignancy and 7(6.19%) had VIN III on the margins.

Seven women where the SCC was associated with the pathology of VIN [6 (5.30%)] or Lichen sclerosis [1(0.88%)]. The pathology reports of the 6 (5.30%) women with SCC showed that the malignant lesions were arising from a bed of VIN III and 1 (0.88%) arising from VIN II pathology. The woman where the SCC co-existing with LS was a 39-year-old African woman who had radical vulvectomy and bilateral lymph node dissection for vulvar malignancy.

There were three women who had vulvar malignancy that had previous cervical carcinoma. Two of them had been treated by radiation therapy and one had a radical hysterectomy. Nine out of 10 women had advanced vulvar carcinoma and were treated with another non-surgical modality before surgery and one woman had suspected recurrence of vulvar carcinoma and who underwent a wide local excision after previous vulvectomy and inguinal lymph node dissection. The histology showed benign pathology in 52 (46.01%). Vulvar intraepithelial neoplasia was found in 32 (28.31%) women. In the VIN II histology reports, one had positive margins, and 7 histology reports of the VIN III lesions showed positive margins.

There was a 68-years-old Caucasian woman with a clinical suspicion of lichen sclerosus and inconclusive biopsies. The wide local excision showed lichen sclerosus pathology.

Two women's histology showed inflammation. One was a 34-year-old woman with parity of three, HIV positive and virally suppressed with a vulvar lesion suspicious for malignancy with an inconclusive biopsy and who underwent a wide local excision which showed non-specific inflammatory changes. The other woman was 55 years old, with a previous history of cervical carcinoma, who had received radiation. She presented with a vulvar mass and a wide local excision was done which showed HSV infection. She had a parity of three and was HIV positive. The other four (3.54%) pathological categories were seborrheic keratosis, and three specimens showed no malignant changes. Table 7.6 shows the various vulvar pathologies.

Table 7.6: Vulvar pathologies

Malignant **Number (%) n=61**		**Benign** **Number (%) n=52**	
Squamous cell carcinoma	59(52.22)	Condyloma accuminata	12(10.62)
Melanoma	1(0.88)	VIN I	3(2.66)
Small cell neuroendocrine	1(0.88)	VIN II	3(2.66)
		VIN III	26(23.00)
		Infective	2(1.77)
		Lichen sclerosis	2(1.77)
		Others	4(3.54)

A comparison of women with benign and malignant diseases was made. This is shown in Table 7.7. The only comparison that was statistically significant was the duration of hospital stay.

Table 7.7: Comparison of benign and malignant disease

	Malignant disease 61(53.98%)	Benign disease 52(46.01%)	P-value
Mean age	44.33 (SD±12.39)	43.53 (SD±12.31)	0.44(T-test)
Tobacco use	3 (75%)	1 (25%)	0.623 (FE)
Menopausal 27(23.89%)	15 (55.56%)	12 (44.44%)	0.851 (Chi2)
HIV positive 89(78.76%)	46 (51.69%)	43 (48.31%)	0.345 (Chi2)
Median duration of symptoms in months	12 (IQR 2-8)	4 (IQR-0-12)	0.173 (MWU)
Median duration of hospital stay in days	8 (IQR 4-11)	4(IQR-2-8)	0.003 (MWU)
Post-op wound breakdown	10 (62.50%)	6 (37.50%)	0.591 (FE)
Post-op infection	12 (63.16%)	7 (36.84%)	0.454 (FE)

8 DISCUSSION

8.1 THE DEMOGRAPHICS

This was a cross-sectional study that evaluated the benign and malignant vulvar pathologies in women who were treated surgically at CMJAH over a period of six years.

The mean age of women in our study was 44.53 years (SD±12.65; range 23-90). These results include women with both benign and malignant vulvar disease and the mean age of participants with vulvar SCC was 44.33 (SD±12.39). The women in our study are significantly younger than the average age of women with vulvar carcinoma in African studies and other studies outside of the African continent with different demographics.

In a South African study by Butt *et al*, conducted in 2017 the mean age of women with vulvar cancer was 52.5 years (SD±15.5; range 24-102) (63). Another South African study conducted in the gynaecology oncology unit of a referral hospital in KwaZulu-Natal over a four year period showed the mean age of women with vulvar cancer was 48.2 years (SD±12.5) (92). A Nigerian study by Okolo *et al*, over 28 years showed the mean age of women with vulvar and vaginal cancer to be 49.7 years (93).

In a large cohort study by Brinton *et al*, the mean age of women in the study was 61.8 years, with most of the study population being white, educated, married, and parous. They were followed up for a mean of 13.8 years. During this period, women diagnosed with vulvar carcinoma had a mean age of 71 years old and women with VIN III had a mean age of 67.5 years. (94) The studies conducted in African countries show an increase in the prevalence of vulvar carcinoma in younger women where the average age of diagnosis is 10-15 years younger compared to in higher-income countries. These findings may be attributed to the high rate of HPV infection in Southern Africa which is estimated to be (22.1%). (68) Studies show that women with HPV-related vulvar cancer are younger compared to those with cancers originating from chronic epithelial disorders such as lichen sclerosus. (96) A study that compared HPV-related and HPV negative vulvar cancers was done by Gargano *et al*. They found that the median ages of women were 61 years in the HPV positive group and 75 years in the HPV negative group. In the study, testing the tissue specimens for HPV was not possible but histological findings showed HPV infection changes in the specimen of 82 women. The statistics showed that the HPV group with a mean age of 50.4 years was significantly younger

than the non-HPV group (68.6years $p < 0.001$). (97) Perhaps the prevalence of HIV (79.6% positive) in our setting played in role in that the study population with vulvar cancer and other non-cancer pathologies was younger.

8.2 THE PRESENTING SYMPTOMS

The most common presenting symptom was the growth of a lesion with the median duration of symptoms of 12 months. The study done by the University of KwaZulu-Natal reported the duration of symptoms before diagnosis was more than 12 months in 73% of women and 43% presented with advanced disease (92). Another study conducted in Tygerberg Hospital between 2001 and 2014 reported the median duration of symptoms before diagnosis was six months with a lot of cases having an incidental diagnosis in the gynaecology clinic or referral for an abnormal Pap smear (seven women) to a duration of 10 years in two women with lichen sclerosus. The most common presenting complaint was a lesion on the vulva (67.0%), pain (41.5%), and itching (21.6%). Within 18 days of diagnosis up to 50% of women were seen by a Gynaecologist Oncologist. One woman treated the lesion with traditional medicine for two years and presented with advanced disease. (67) These findings differ from those of Lanneau *et al.*, where the study population had different demographics, who found that only 28.6% of patients had symptoms for more than 12 months before the diagnosis of vulvar malignancy was made. This was a study that reviewed patients younger than 45 years who had vulvar cancer between 1994 and 2006. Only two (3.6%) of 56 women were HIV positive in this study. (98) These findings show that there have been major delays in patients seeking medical help when they have vulvar lesions as well as delays due in part to inappropriate diagnosis and referrals by health care professionals. Such appears to be universal in patients with vulvar lesions and is not an isolated finding from our study.

8.3 RISK FACTORS AND CO-MORBIDITIES

Factors such as high parity, tobacco, alcohol, HPV and HIV infection, and lichen sclerosus are risk factors for vulvar malignancy. In our study 89 (78.76%) women were HIV positive, 22(19.47%) were hypertensive and six (5.31%) were diabetic. The HIV infection rate was significantly higher in our study compared to the 2017 study by Butt *et al*; where the HIV infection rate was 23.7%, the median parity of women was three, and the mean BMI was 25.40 (SD ±6.6) and 87% were married. Hypertensive disease was 40% whilst 13.3% were diabetic (63). In our study four (3.54%) women were smokers which were lower than the studies on vulvar malignancies. In the study from Tygerberg Hospital Oncology Unit on 180 women with vulvar malignancies, 103 (64.2%) were smokers (63). Our study was a retrospective study and the patient's BMI was not available on the records and the HBA1c levels in the diabetic patients were not documented. According to the study by Brinton et al a BMI ≥ 30 is a risk factor for vulvar carcinoma (58).

The rate of HIV infection in our study was 78.76% and the median CD4 count was 423 (IQR-249-604; range=2-1215. These numbers are comparable to another retrospective study conducted in South Africa that evaluated 86 women with histology of vulvar carcinoma where 70 (81.4%) women tested positive for HIV, 14 (16.7%) negative and two had undocumented HIV status. The CD4 count was documented in 53 (75.7%) and 47 (89%) had a CD4 count of more than 200. Only 30 (42.9%) had a record of their viral load and 25 (36%) had a suppressed viral load.(92)

High HIV infection in a population is linked to higher HPV infection, where many women with HIV infection do not clear the HPV. According to a South African study, the incidence of HPV infection in HIV-positive women was 85% compared to the HIV-negative women with a rate of 42% (p= 0.00001). This evaluated the IgA response to HPV and a decreased serum IgA response was correlated with progression to HPV-related malignancies.(99) With only 40 (35.39%) women in our study having a documented viral load lower than the detectable level and two women who were newly diagnosed, the need for better management of women who are currently on antiretroviral treatment in terms of monitoring and adherence is emphasized.

The other less common pathway for vulvar malignancies is LS which was not common in our study population with only two cases (1.77%) that correlate with international literature. Globally, lichen sclerosus is a rare pathological finding in vulvar lesions. A study done by Goldstein *et al,* in 2005 estimated the prevalence of LS to range from 0.1% to 1.70%. (19) A

study by Davick *et al*. is the largest study to report the prevalence of LS in patients with vulvar SCC. This study showed that in 29% of women who had wide local excision for vulvar carcinoma, LS pathology was adjacent to the excised SCC, and 36% (95% confidence interval, 0.28-0.45) had confirmed histology of LS in their previous outpatient visits. The data from their study suggested that at least one in three vulvar SCCs in this institution had LS as a predisposing factor. (66)

8.4 SURGICAL PROCEDURES

The most common surgery performed was vulvectomy with or without inguinal lymph node dissection (59.27%). Amongst the cases with postoperative complications, sepsis was seen as the commonest followed by wound breakdown. The most common reconstruction flap used was the V-Y flap perhaps because it is easy to perform. Eisner *et al*, suggested that in patients with stage I and II vulvar malignancy a conservative surgical approach, rather than radical vulvectomy, should be implemented to reduce morbidity as it does not affect survival (100). Less radical surgery aims to reduce the morbidity of patients without affecting survival. The common complications associated with vulvectomy and lymph node dissection are wound breakdown, thromboembolic events, urinary incontinence, faecal incontinence, lymphocyst, hernia, and psychosexual complications (78). A cohort study of 164 patients on the short- and long-term complications of vulvar surgery showed a greater amount of drain production on the last day before drain removal was associated with an increased risk of post-operative complications, while young age and lymphocele were risk factors for long term complications. The possible reason for this is that a younger woman is more mobile which increases the risk of postoperative complications after vulvar surgery. The use of drains is common in gynaecology oncology surgery but there are no protocols for their management. However, most centres keep drains post-operatively for up to five days or until they drain less than 50-100mls per day. The study also showed that extensive dissection of lymph nodes does not increase the rate of complications. (79)

Nine women had previously received other treatment preoperatively due to advanced disease. With such a small number, it is likely that for patients who received radiotherapy before surgery was the studies by Hacker et al and Rotmensch *et al*, it is suggested that neo-adjuvant radiotherapy in women with advanced vulvar cancer decreases the need for stoma surgery which decreases the quality of life significantly. However, performing surgery on the vulvar

area post-radiation therapy has its challenges and it should be individualized and the risks and benefits has to be discussed with the patients. (101) The incidence of vulvar recurrence is related to the disease margins in the histology specimens. The tissues undergo contraction after excision and fixation, therefore, if the disease margins are less than 8mm the patient is at high risk for recurrence and the aim should be at least a 15mm margin on the fresh surgery. (77)(102)

8.5 VULVAR PATHOLOGY

The vulvar histopathological reports from women in our study showed that 88 (77.87%) of the vulvar histologies were neoplastic (premalignant and malignant). The most common non-benign pathology was SCC, with one case of vulvar melanoma and another case of small cell neuroendocrine carcinoma. Various factors amongst women with benign and malignant vulvar lesions were compared. The HIV infection rate, the mean age, and the median duration of symptoms were not statistically significant. However, the median duration of hospital stay was eight (IQR 4-11) in women with malignant disease versus four (IQR-2-8) days for women with benign disease which was significant.

Histological evaluation of women with SCC showed that 15 (17.44%) had positive margins for malignancy and six (5.30%) had VIN III in the margins. In the VIN II histology reports, one had positive margins while seven histology reports of the VIN III lesions showed positive margins. A retrospective study by Mohan *et all* which was conducted in India looked at vulvar pathologies, biopsy, or vulvectomies between 2005 to 2012. A total of 170 biopsies and two vulvectomies were performed. Ninety-four (55.29%) of the lesions were non-neoplastic and 50 (29.41%) were neoplastic. The commonest benign lesion was lichen sclerosus in thirty-six (38.30%) cases. From the neoplastic category 17 (62.96%) were SCC and 6 (22.22%) were VIN.(103) This study has a higher prevalence of LS compared to our study (3.52% versus 1.77%) even though their neoplastic (malignant and premalignant) lesions were only 13.52% of the total histologies which is significantly lower in our findings. However, in this study, there were only two vulvectomies in 172 women compared to 67 vulvectomies in 113 women in our study. Therefore, a lot of pathologies could have been missed.

A study by Davick *et al,* on the histology reports of women with SCC between 2009 and 2013, with a mean age of 66 years, reported 25 (22.5%) women who had a history of LS and 36% with vulvar SCCs were associated with LS. These cases were most likely related to the

dVIN/non-HPV-related category of vulvar SCC. The pathogenesis of the 64% of SCCs was not clear although it is likely to be HPV-related. (66)

9 LIMITATIONS

This was a retrospective and cross-sectional study assessing patient's records for six years and the sample size was relatively small. Patients were not all followed up postoperatively and the survival and the recurrence rate of vulvar malignancies could not be assessed.

Certain information such as the patient's BMI, diabetic control, and HbA1c levels was not available or was incomplete in the records.

10 CONCLUSION

More than half of the women had a malignancy. Most of the women with benign histology had VIN. Women with VIN II and VIN III were mostly treated surgically. The time of symptom onset and surgical treatment was long. The overall complication rate was high. The presence of LS and VIN together with malignancy was found in seven women.

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APPENDIX 1: FIGO 2021 staging of carcinoma of the vulva

FIGO stage	Description
I	Tumour confined to the vulva
IA	Tumor size ≤2 cm and stromal invasion ≤1 mm (Depth of invasion is measured from the basement membrane of the deepest, adjacent, dysplastic, tumor-free rete ridge (or nearest dysplastic rete peg) to the deepest point of invasion)
IB	Tumor size >2 cm or stromal invasion >1 mm
II	Tumor of any size with extension to lower one-third Of the urethra, lower one-third of the vagina, lower one-third of the anus with negative nodes
III	Tumor of any size with extension to upper part of adjacent perineal structures, or with any number of nonfixed, nonulcerated lymph node
IIIA	Tumor of any size with disease extension to upper two-thirds of the urethra, upper two-thirds of the vagina, bladder mucosa, rectal mucosa, or regional lymph node metastases ≤5 mm
IIIB	Regional lymph node metastases >5 mm (Regional refers to inguinal and femoral lymph nodes)
IIIC	Regional lymph node metastases with extracapsular spread
IV	Tumor of any size fixed to the bone, or fixed, ulcerated lymph node metastases, or distant metastases
IVA	Disease fixed to the pelvic bone or fixed or ulcerated regional lymph node metastases
IVB	Distant metastases

APPENDIX 2: Data collection sheet

Patient code……

Demographic data

Age (in years): ……..

Race…African…White….Coloured….Indian….Other……Unknown….

Parity:…….. Country of origin (if not South African) ……..

Menopausal status... Premenop……Postmenop……Unknown……

Weight……

Risk factors

Tobacco use Yes…..No…..Unknown….

Previous benign vulva disease….Yes….No……Unknown……

If yes, specify…….

Previous malignancy vulva disease Yes……No……Unknown……

If yes, specify……

Duration of symptoms:…… Tobacco use:……..

Patient comorbidities

Hypertension Yes….No….

If yes, Treatment..Yes…No....Controlled. .. Yes…No…..

DM Yes….No…..

If yes, Treatment..Yes…No....Controlled. .. Yes…No…..

HIV Yes….No

If yes, Treatment..Yes…No....Controlled. .. Yes…No…..CD4……VL…..

Other malignancies…..Yes……No

If yes, the Organ system…….. Treatment Yes…No....If yes, modality……..…..

Known Lichen disease pre-op? Yes….. No…… Unsure……

Presenting symptoms (tick any relevant**)**

Skin discolouration…Skin lesion/mole…Tumour/growth…….

Pain…Swelling…Bleeding…… Dyspauenia…. Groin swelling….Others…….

Surgical procedure done

Wide local excisional biopsy……..

Simple Vulvectomy …..Radical Vulvetomy……Hemivulvectomy…..

Inguinal lymphadenectomy…..Yes….No… If yes, Unilat….Bilat…….

Reconstruction flap…Yes….No…… If yes, specify type……

Duration of surgery in minutes…… Total blood loss (ml)……

Days in Hospital post-surgery……..

Intra-op complications…Yes… No… Unknown….

If yes, Bleeding…….Vein injury, ... Nerve injury….Others……..

Post-op complications….Yes…. No….. Unknown…….

If yes., Sepsis……Wound breakdown…Bleeding…Flap necrosis…….

Lymphocyst……. Others……

The period from surgery to complications (weeks)…….

Pathology report

Vulva pathology….Benign……Malignant……Subtype……

Lichen Planus Yes….No……..

Lichen sclerosis Yes…..No…..

Other pathologies including parasites……

Margins status… Free…. Involved…If yes... Lichen…..VIN….Malignancy….

Survival

Recurrence: Yes….No….Unknown……Treatment to recurrence (weeks)…….

New pathology Yes….No……

If yes, Histological type……..

Dead Yes…..No……Unknown……..

If dead, period from surgery to death(weeks)…….

If not known or still alive, last time seen (date)..……

APPENDIX 3: Ethics Approval

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr Venus Salem

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190313

NAME: (Principal Investigator)	Dr Venus Salem
DEPARTMENT:	Obtetrics and Gynaecology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Lichen disease in patients with vulvar pathology
DATE CONSIDERED:	29/03/2019
DECISION:	Approved
CONDITIONS:	Permission to access NHLS AARMS
SUPERVISOR:	Dr Langanani Mbodi
APPROVED BY:	Doctor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	05/04/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in March and will therefore be due in the month of March each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

23/06/2019
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES