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ARTICLE

A review of vulvar carcinoma at Groote Schuur hospital for the period 2002 to 2012 with particular emphasis on HPV-related disease

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Background: Vulvar carcinoma is rare and ranks fourth amongst the gynaecological malignancies. GLOBOCAN reported 44 235 new cases in 2018. There has been a rise in the number of cases of vulvar carcinoma in recent years and younger women are being affected by the disease. This rise is thought to be the result of more women being infected with human papilloma virus (HPV). HPV has been implicated in one of the pathways leading to the development of vulvar carcinoma. This study aims to review the cases of vulvar carcinoma at Groote Schuur Hospital and places particular emphasis on HPV-related disease.
Methods: The study is a retrospective descriptive study of patients with vulvar carcinoma at Groote Schuur Hospital for the period 2002 to 2012. The study population included women with vulvar carcinoma who attended the multidisciplinary combined cancer clinic. Data were collected from folder reviews and an existing cancer database. Data were entered into data collection sheets that recorded patient demographics, disease aetiology, HIV status, treatment received, recurrences and multifocal disease. The analysis was performed using the R computing environment (RStudio Version 1.1.463) and MS Excel version 1808. Estimates of patient survival were computed using the Kaplan–Meier estimator.
Results: There were 125 cases included in the study for the period 2002–2012. Data analysis revealed that 119 (95.2%) of the cases were squamous cell carcinomas. Among the squamous cell cancers, 98 (82.4%) had evidence of HPV disease, 18 (15.1%) occurred in patients with lichen sclerosus and 3 (2.5%) of patients had dual pathology. The mean age of the patients was 54.76 (SD 16.59) years. The youngest patient was 21 and the oldest 92 years of age. Of the 125 patients, 101 patients had clinical or histological evidence of HPV disease. In 76 patients (60.8%) the HIV status was known, of whom 75% were HIV negative and 25% HIV positive. Multifocal disease was present in 38.6% of the patients.
Conclusion: This study revealed that there is a high burden of HPV-related disease at this centre, with younger women being affected by the disease. Patients are developing invasive disease despite their HIV status.

Key Words vulvar carcinoma, human papilloma virus, vulvar intraepithelial neoplasm, human immunodeficiency virus, squamous cell carcinoma, multifocal disease

Introduction

Vulvar carcinoma is a rare malignancy worldwide. In the United States it accounts for 6% of gynaecological cancers and 0.7% of all cancers occurring in women.[1] GLOBOCAN 2018 looks at the cancer burden across 20 world regions. In 2018 there were 44 235 new cases of vulvar carcinoma and 15 222 deaths due to this cancer. Vulvar cancer ranked fourth amongst the gynaecological cancers.[2] Vulvar carcinoma is predominantly a disease of the elderly and usually affects women over the age of 60.[3,4] In recent years there has been a rise in the incidence of vulvar carcinoma, especially in younger women.[4–7] This is mainly attributed to the rise in human papilloma virus (HPV) infection.[5–7] Most of the literature reporting an increase in invasive disease has been from developed countries.[7]

Several studies have been conducted in Africa. A study conducted at Tygerberg Hospital found that their patients were 10–15 years younger compared with patients seen in high-income countries. More than half (53.3%) of their patients presented with late-stage disease.[8] A cross-sectional study in Botswana looked at the prevalence of oncogenic viruses in HIV-positive and -negative patients with biopsy-confirmed vulvar cancer. The study revealed that 82.9% of the specimens tested positive for HPV 16, which is much higher than reported worldwide figures.[9] The study demonstrated no significant association with HIV status and prevalence of HPV.[9]

Vulvar carcinoma typically arises on the background of vulvar intraepithelial neoplasm (VIN). More than 90% of vulvar carcinomas are squamous cell carcinomas.[3,10] Two major pathways exist, following a viral-dependent and viral-independent route.[3] The viral-dependent route is associated with persistent infection of the high-risk HPV subtypes, namely 16, 18 and 33.[3] Persistent infection leads to the development of usual type/undifferentiated vulvar intraepithelial neoplasia (uVIN).[3] Invasive warty or basaloid squamous cell carcinoma can develop from the dysplastic epithelium. It is thought that 40% of vulvar carcinomas follow this route.[3,5] HPV is commonly seen in uVIN and only in few cases of differentiated vulvar intraepithelial neoplasm (dVIN).[10] The second pathway is the viral-independent route. This results from chronic irritation and scarring (the itch–scratch cycle) and leads to the development of keratinising tumours from differentiated VIN.[3]

Differentiated VIN usually occurs in the background of lichen sclerosus. This group of tumours occurs in women over the age of 65 and the trigger is thought to be repeated cell damage that leads to mutation and oncogenesis. Lichen sclerosus is a chronic inflammatory condition involving genital and extragenital skin of both men and women. The disorder mainly occurs in the anogenital region with approximately 6% of lesions found in extragenital regions.[11]

It has the potential for destructive scarring and atrophy and also malignant change. Patients usually present with complaints of itching, pain, dysuria, dyspareunia and sexual dysfunction. The cause is unknown, but increasing evidence is pointing to an autoimmune mechanism.[11] Invasive carcinoma is a rare complication of lichen sclerosus with a reported incidence of 0.3% to 4.9%.[11]

Human papilloma virus is the commonest sexually transmitted disease with 80% of women having acquired the infection by the age of 50.[5,12] The virus is transmitted through skin-to-skin contact. It is cleared in most instances by an immune-competent host. If the host is unable to clear the virus, persistence of HPV results in the epithelium undergoing dysplastic change resulting in uVIN. This may occur in different areas of the lower genital tract resulting in multifocal disease.[12] Factors that influence cell-mediated immunity can cause reduced clearance of the virus. Progression of uVIN to invasive disease is relatively low in HIV-negative women.[13] The prevalence of HPV infection is higher in HIV-positive individuals. The main reasons for the higher prevalence are reactivation of latent HPV and reduced clearance of the virus from HIV-infected individuals.[14] Studies have shown HIV-positive women also have a higher HPV burden and more progressive dysplastic change.[12,14]

The aim of this study is to review the population of women with vulvar cancer who attended Groote Schuur Hospital, Cape Town, South Africa. We hope that the review can provide further insight into this rare disease where there is so little reported literature in limited-resource settings such as South Africa, where there is a high prevalence of HPV disease.

Material and methods

Study design

A retrospective descriptive study was performed of the women with vulvar carcinoma who attended the multidisciplinary tumour board clinic at Groote Schuur Hospital, Cape Town, South Africa between 2002 and 2012.

Study population

In South Africa, health services are divided into the public sector, which is government funded, and the private sector, which relies on payment from medical aid insurance schemes and patients who pay privately for services. Groote Schuur Hospital is a tertiary level Government-funded hospital servicing parts of the Western Cape. All women diagnosed with vulvar carcinoma who attended the multidisciplinary combined cancer clinic at Groote Schuur Hospital from 2002 to 2012 were included. A total of 139 women were in the database. Ten of the cases were excluded as it was not possible to retrieve their folders. Two cases were incorrectly entered into the database and two cases of Bartholin gland carcinoma were excluded. In total 125 patient folders were reviewed. Of these patients, 101 had evidence of HPV disease and further data were collected on these cases (see Figure 1).

Data collection

Data were extracted from an existing gynaecological oncology database at Groote Schuur Hospital Research, which has human research ethical approval from the University of Cape Town, as well as from individual patient folders. The data were entered into data collection sheets. If the patient had evidence of HPV-related disease additional data were collected and entered into a separate data sheet. Evidence of HPV disease was based on clinical findings as well as pathology reports. HPV DNA testing was not routinely done at the centre during the study period. The presence of koilocytes and usual type VIN on histology was used as evidence of HPV disease. Clinical evidence of HPV was documented in the folders as the presence of VIN or vulval warts. Data from the collection sheets were entered into an Excel spreadsheet (Microsoft Corp, Redmond, WA, USA) and analysed. Patient demographics and aetiologies were reviewed in all cases. In the HPV group there was specific focus placed on the prevalence of HIV, CD4 counts and antiretroviral regimes, oncological management, disease outcomes, multifocal disease and five-year survival rates of this group.

Ethical considerations

The study was approved by the Human Research Ethics Committee of the University of Cape Town. Institutional as well as departmental approval was obtained to access and collect data from patient folders. The oncology database that was used in the study has existing ethics approval as mentioned earlier. The study was conducted according to guidelines from the declaration of Helsinki.[15]

Objectives

Primary objectives

The number of cases of vulvar carcinoma during this period as well as the demographics of the patient population was reviewed. The percentage of cases with lichen sclerosis and HPV disease was documented. In the HPV group, further data on prevalence of HIV, CD4 count, antiretroviral treatment, disease outcomes and treatment were collected.

Secondary objectives

The secondary outcomes included the five-year survival rate of the patients at the unit. The study also placed emphasis on multifocal disease. (This refers to intraepithelial lesions present in two or more sites of the anogenital region.)[12]

Analysis

The analysis was performed using the R computing environment (RStudio Version 1.1.463; R Foundation for Statistical Computing, Vienna, Austria, https://www.r-project.org/) and MS Excel version

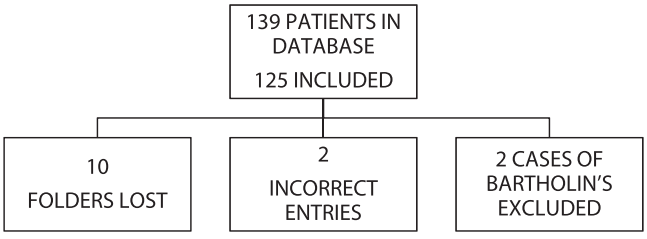

Figure 1: Flow diagram of study population.

1808. Additional packages (ggplot, plotly, dplyr) were also installed on the R. Estimates of patient survival were computed using the Kaplan–Meier estimator.

Results

Number of cases

Data from 125 cases were extracted and analysed. Of these cases, 101 patients had evidence of HPV disease.

Demographics

The mean age of the patients was 54.76 (SD 16.59) years of age. The youngest patient was 21 and the oldest 92 years. Figure 2 demonstrates the distribution of age amongst the patients. The data collection focused on specific co-morbidities. Fifty-one (40.8%) patients were hypertensive, 18 (14.4%) had diabetes, 20 (16%) had active or previous tuberculosis and 12 (9.6%) had cardiovascular disease. Among the 125 patients, 39 (31.2%) were smokers and 26 (20.8%) had no smoking history. These results are limited as 60 (48%) of patients had no smoking history documented. Eighty (64%) of the patients were menopausal and 45 (36%) of the women still had reproductive potential. In 27 (60%) of the 45 women no documentation regarding contraception use was made, 7 (15.6%) patients were not making use of any contraceptive method and 11 (24.4%) were using contraception. Figure 3 depicts the source of financial income for the patient population.

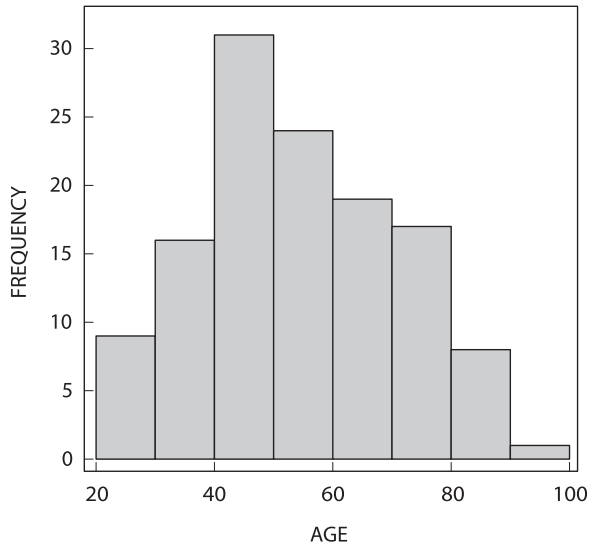

Figure 2: Histogram of patient age.

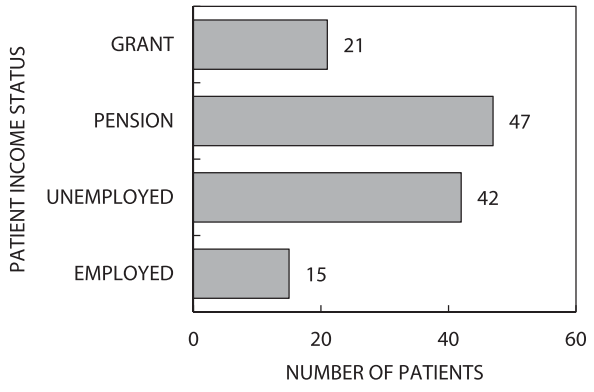

Figure 3: Source of patient income.

Aetiology

Of the 125 patients with vulvar carcinoma, 119 (95.2%) were squamous cell carcinomas. The remaining six (4.8%) had other histology, including two patients with melanoma, two patients with adenocarcinoma, one patient with basal cell carcinoma and one patient with a sarcoma. Of the 119 patients with squamous cell carcinoma, 98 (78.4%) had HPV-associated disease, 18 (14.4%) had lichen sclerosus and 3 (2.4%) had dual pathology. Figure 4 depicts the aetiology of the squamous cell cancers.

HPV-associated disease

HIV status

Separate data sheets were collected in the group of patients with HPV documented disease. Of the 101 patients, 76 (75.2%) had documented evidence of HIV status, with 25 (24.8%) women having an unknown HIV status. Of the 76 patients in whom status was known, 57 (75%) were HIV-negative and 19 (25%) were HIV-positive.

CD4 counts and antiretroviral treatment

Table 1 presents CD4 count ranges of the 19 HIV-positive patients. In one patient the CD4 count was unknown. Of the HIV-positive patients 13 (68.4%) were on antiretroviral treatments with 11 on first-line treatment and only two patients on a second-line regime. Six of the patients were not on antiretroviral treatment at time of diagnosis.

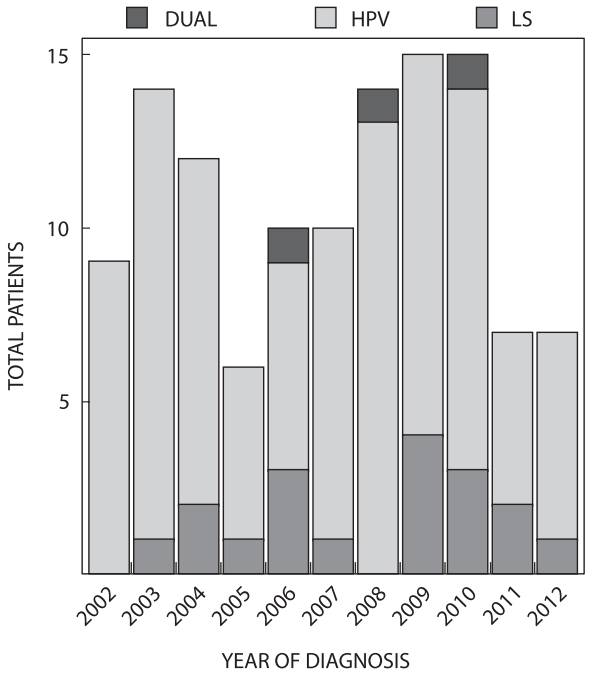

Figure 4: Aetiology of squamous cell cancer in study population.

Table 1: Range of CD4 counts.

CD4 count	Patient number
< 200	5
200–349	4
350–499	4
≥ 500	5

Disease outcomes and treatment

Stage and treatment

This unit used the FIGO staging criteria according to international standards. The patients were staged according to the year of diagnosis; as a result a combination of the 2006 and 2009 FIGO staging criteria were included. Thirty-eight (37.6%) patients presented with stage one disease, 19 (18.8%) stage two disease, 26 (25.8%) stage three disease and 18 (17.8%) stage four disease. Figure 5 represents the treatment of vulva received at the facility. Fifty-two (51.5%) patients were treated with radical wide local excision and 34 (33.7%) received primary chemoradiation with 5 patients requiring both modalities of treatment. Two of the patients received no treatment; both had advanced disease with poor prognosis. The treatment to groins is separately documented in Table 2.

Adjuvant treatment and recurrence

After primary treatment to vulva and groin, 12 (11.9%) patients received adjuvant therapy and 3 patients declined adjuvant therapy after primary treatment. Eighty-six (85.1%) patients did not require any further therapy. Adjuvant chemoradiation was given to nine patients and three required re-excision. The patients were followed up for at least five years after primary treatment. In 16 (15.8%) patients, recurrence of disease was documented, in 84 (83.2%) patients no recurrence occurred and one patient defaulted follow-up. The vulva was the main site of recurrence, with 12 (75%) women having recurrent disease in this site. Two patients had distant site recurrences and two recurred in groin nodes. Of the 16 patients with documented recurrences, 15 of them presented within four years of treatment.

Table 2: Treatment to groin nodes

Treatment to groin	Number of patients	%
Bilateral groin node dissection	19	18.81
Unilateral groin node dissection	12	11.88
Primary chemoradiation	39	38.61
Adjuvant radiotherapy	3	2.97
Palliative radiotherapy	5	4.95
No treatment required: surgical excision adequate	23	22.78

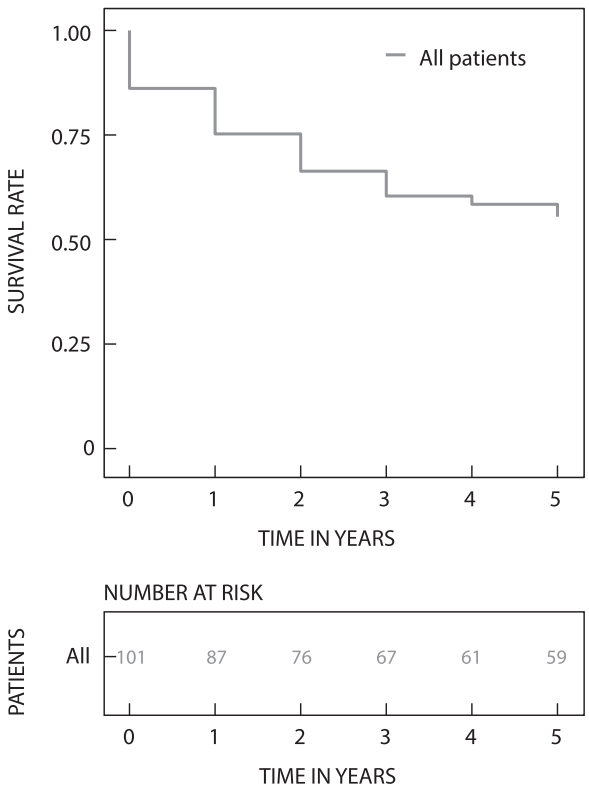

Figure 6: Five-year survival all stages.

Five-year survival curves

Figures 6 and 7 depict our five-year survival rates. Overall survival in all stages was 58.4%. Figure 6 depicts five-year survival rate at each stage of the disease, which was 89.5% for stage 1, 73.7% for patients with stage 2 disease, 38.5% for stage 3 and 5.6% for patients with stage 4 disease. Only 30 patients died as a result of cancer- or treatment-related causes. Eighteen patients died as a result of unrelated causes with one patient having an unknown cause of death documented. Three patients died as a result of malignancies unrelated to vulvar cancer. Among the deaths, six deaths occurred after the five-year follow-up period.

Multifocal disease

Of the patients with HPV-related disease, 39 (38.6%) of them had documented multifocal disease. Multifocal disease was documented in the form of cervical, vaginal or anal involvement of

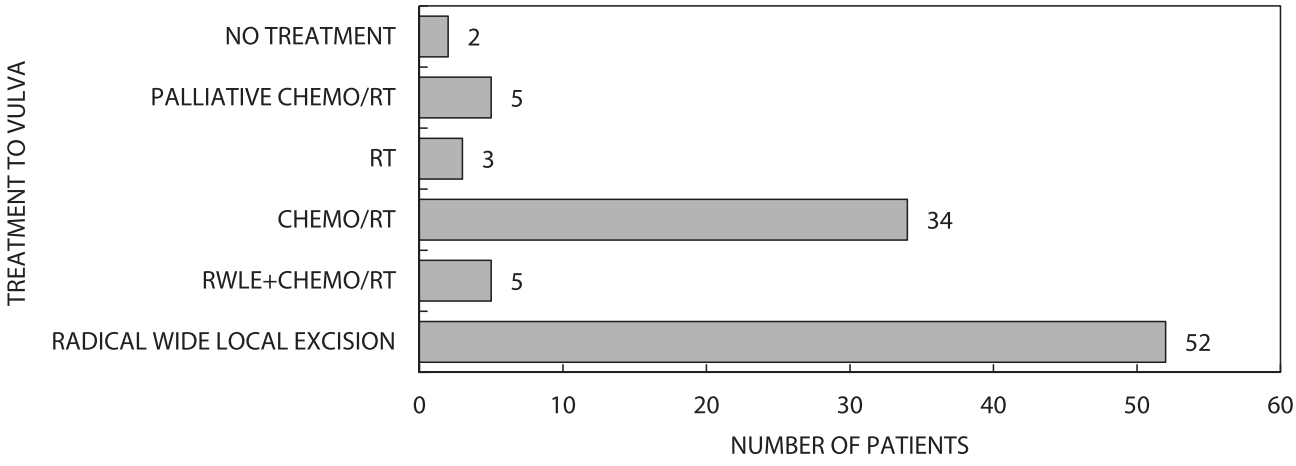

Figure 5: Treatment to vulva.

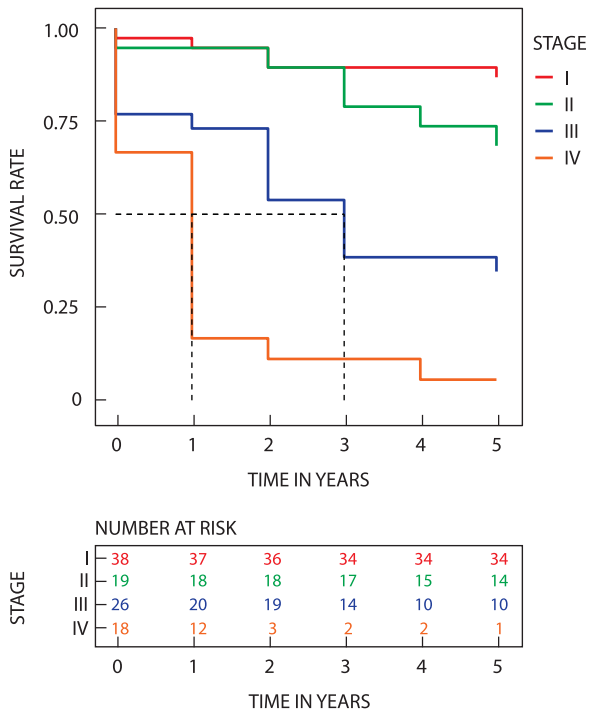

Figure 7: Five-year survival by stage.

HPV-related precancerous or cancerous, in addition to vulvar carcinoma. The cervix was the most common site of involvement with 32 (82%) patients showing evidence of HPV disease in this site. Eleven patients (28.2%) had evidence of anal or peri-anal involvement and 2 (5.1%) patients had vaginal involvement.

Of the 39 patients with multifocal disease, six of the patients had both cervix and perianal involvement. Twenty-two (56.4% of all women with multifocal disease) patients required intervention for this. In the subgroup of patients with multifocal disease, 19 (48.7%) were HIV-negative, 13 (33.3%) were HIV-positive and in 7 (18%) patients the HIV status was unknown.

Discussion

This review revealed that the majority of the patient population at this centre were younger than 60 years of age with a peak in women between 40 and 50. This is in keeping with literature from developed countries, which report a shift towards younger women presenting with the disease.[4–7] This is supported by additional literature.[16,17]

Smoking history was poorly documented with nearly half of the patients not having this risk factor documented in their records. In this review, 64% of the patients were menopausal with 36% still in their reproductive years. Of the patients who were still able to conceive there was poor documentation with regard to contraceptive use and only 24.4% were using contraception. This is an important consideration in women diagnosed with any gynaecological malignancy. Special attention should be paid to this aspect as pregnancy can complicate or delay surgical and oncological management of these women.

These patients mainly relied on pension and disability grants for financial support. A large proportion of the patients were unemployed. This centre is government funded and most of the patients have no source of income. Patients do qualify for temporary/permanent disability grants depending on the stage of their disease.

The large majority of cancers were of squamous cell histology, which is in keeping with current evidence; only six of the patients had other histologies.[3] The majority of disease burden at the centre is related to HPV disease.

HPV-related disease was present in 80.8% of the patients in this review, with only a few cases of lichen sclerosis documented. This is in contrast to the literature, which shows HPV being present in about 40% of cases.[3,5] Review of the cases of vulvar carcinoma at Groote Schuur Hospital shows a higher disease burden than reported in the literature.

Only 76 of the 101 patients with HPV-related disease had their HIV status documented; 75% of the documented cases were HIV-negative. This is an unexpected finding as it is known that HIV co-infection leads to reduced clearance of HPV and persistent disease.[14] We do not know if this is a true reflection of our HIV-negative population as 24.8% of our patients did not have their status documented. We may need to further investigate the possibility of genetic or immune factors that may lead to reduced clearance of HPV in this population. Patients seem to be developing invasive disease despite being HIV-negative. Only 19 of the patients were documented to be HIV-positive, of whom 13 were on antiretroviral therapy. Five patients had CD4 counts below 200. The viral loads of these patients were not documented as this test was not routinely available at the centre during the period.

More than half the patients presented with stage 1 and stage 2 disease and the majority of these women received primary surgery as the main modality of treatment. In developing countries patients are more often diagnosed with advanced disease, which is not the case in our setting. Of the patients treated at the unit, 85.1% required no adjuvant treatment. The patients adhered well to follow-up and a recurrence rate of 15.8% was documented. The main site of recurrence was the vulva and the majority of recurrences occurred within four years of treatment.

Recurrence rates according to the literature range from 12% to 37%, despite treatment.[18] The main site for recurrence is local followed by groin recurrence, which is in keeping with the study results.[18] Of the 16 patients with recurrence, 15 patients had recurrence within 4 years after treatment. The literature reports that 40–80% of recurrences occur within the first two years following treatment.[18] A prospective study of 143 patients reported local recurrence of up to 28.6% within the first two years following treatment.[19] This highlights the importance of follow-up for at least five years in patients with vulvar carcinoma.

A follow-up of the GROINSS-VI study reported a local recurrence rate of 27% after five years.[18] Overall the incidence of isolated local recurrence is 20–23%.[20–22] The rate of local recurrence at this unit was 11.9%.

There was an overall five-year survival rate of 58.4%, with a high five-year survival rate of 89.5% in patients with stage one disease. Figures from data collected by FIGO report five-year survival rates of around 80% for stage 1, around 60% for stage 2, more than 40% for stage 3 and more than 15% for stage 4 disease.[23] These reports are old and it is difficult to collect data due to small numbers of patients with the disease. The five-year survival rates for stage 1, 2 and 3 disease are in keeping with these figures, but the rate for stage four disease is much lower.

This study found that 38.6% of the patient population had multifocal disease present at the time of diagnosis. The

cervix followed by the anal area were the most common sites where multifocal disease occurred. This can be expected as both the cervix and anal areas have transformation zones, which are vulnerable to dysplastic change. Twenty-two of the 39 patients required treatment of the multifocal disease. A third of the patients with multifocal disease were HIV-positive. A retrospective review conducted in Europe included 998 patients treated at a colposcopy centre. This study reported that multifocal disease was present in 4.4% of the patients treated at their facility.[24] This is much lower that the percentage found in the patients of the present study. There is limited evidence on rates of multifocal disease in patients with invasive carcinoma.

Ideas for future research should focus on studies including HPV DNA testing. Further studies focusing on multifocal disease and HPV genotyping and immune factors may be warranted. A review looking at contraceptive use in patients with malignancy may be helpful in managing these patients. Studies looking at disease outcomes in HIV-positive patients with focus on CD4 counts and viral suppression may assist with treatment planning in cancer patients.

Limitations

Our results are limited by the retrospective nature of our study. Our study looked at vulvar cancer over an 11-year period with only 125 cases included in our study. We had a small number of patients for the time period, but vulvar carcinoma is a rare disease.

Conclusion

Through this review valuable knowledge regarding the nature of vulvar carcinoma at this unit has been gained. There is a high burden of HPV-related disease in a younger population at this unit. These patients are presenting with early disease and the recurrence rates at the unit are in keeping with current literature. A large proportion of women in this patient population have multifocal disease present. Limited international literature is available on this aspect of the disease. Patients presenting to the unit at Groote Schuur Hospital also seem to be developing invasive disease irrespective of their HIV status. Patients need thorough examination of the entire genital tract if HPV-related disease is identified at one site. This unit needs to focus on particular areas such as documentation of risk factors and contraceptive counselling. With the rise in the number of younger women presenting with the disease, contraceptive counselling and lifestyle modification plays an important role in counselling and treatment of these patients.

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