Outcomes of patients receiving radical radiation with concurrent chemotherapy for vulva cancer at Universitas Hospital Oncology Department, Free State, South Africa

Researcher:
Dr. C Fourie
Registrar
Department of Oncology
Universitas Hospital

Supervisor:
Prof. A Sherriff
Oncologist
Department of Oncology
Universitas Hospital

Table of Contents

Abstract

Introduction and aim: *Although cancer of the vulva is relatively rare in the developed world, incidence is increasing worldwide. In South Africa, increased incidence is accompanied by a decrease in age at diagnosis. Whereas patients in developed countries are often operable at presentation and undergo surgery, limited resources and the extent of presenting disease in our setting lead to an approach aiming for cure with primary radiotherapy and concurrent chemotherapy in many instances. Even with curable disease, the morbidity and mortality in these patients are high. This study aimed to measure survival outcomes in this group of patients.*

Methods: *This is a retrospective, descriptive cohort study of vulva carcinoma patients receiving radical treatment from 2006 to 2010. We collected demographic, treatment and follow-up data, and date of death where available.*

Results: *A total of 55 patients presented in the trial period, of which 30 met the inclusion criteria. The study population had a mean age 50 years, and 52% were HIV positive, of which 17% were on HAART. Of the HIV positive participants, most had a CD4 count above 400. Most patients had stage 3, moderately differentiated disease. The mean radiation dose received was 66.3 Gy, and nearly all patients completed concurrent chemotherapy. Adequate follow up data was only available for 7 participants, and date of death was only available for four. Survival parameters could thus not be calculated for this cohort.*

Conclusion: *Compared to departmental numbers from 2016 and 2017, the size of our cohort was small, which gives the impression that the incidence of vulva carcinoma is increasing. We concluded that our population is not comparable to international populations, which prompts interest in finding individualized treatment. However, more studies are needed to investigate survival of these patients receiving definitive radiotherapy with concurrent chemotherapy.*

Introduction

Epidemiology

Vulva cancer constituted 3% of all gynecological cancers worldwide in 2002. Of 13 200 new cases, 9000 occurred in developing countries, with fifty percent of patients above 70 years of age.[a]

Vulva cancer is relatively rare in the developed world. In the United Kingdom from 1999 to 2003, the number of cases was reported as 15 per 100 000 females, with most patients above the age of 65. However, there has been an increase in younger women, with the proportion of cases in patients under 50 years rising from 6% in 1975 to 12% in 2003.[b]

In the United States, it is the fourth most common gynecological malignancy.[c] According to the American Cancer Society, the incidence of vulva cancer is increasing in young women due to the increased prevalence of Human Papilloma Virus (HPV), with an estimate of 5950 new cases in 2015/2016.

In Germany, there has also been an increase in incidence in all ages. This is attributed to HPV, smoking, sexual behavior, Human Immunodeficiency Virus (HIV) and organ transplantation.[d]

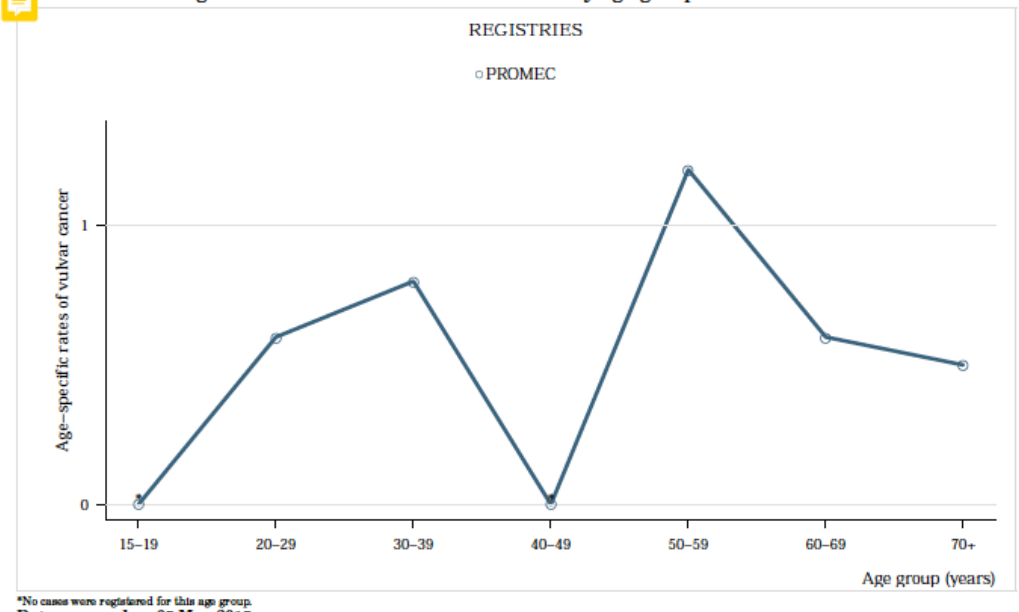
In South Africa, data is unfortunately extremely limited. The Cancer Association of South Africa (CANSA) reports the 2010 statistics for vulva carcinoma in South Africa as 225 total cases, with most patients in their thirties.[e] In 2014, 343 patients were diagnosed with vulva cancer, with age-standardized incidence rate (world standard population) of 1.27 per 100 000.[f] According to 2016 data from the Institut Catala d'Oncologia (ICO) Information Centre on HPV and Cancer PROMEC Registry, the following graph could be extrapolated regarding the incidence rate by age group:

Table 9: Vulvar cancer incidence by cancer registry in South Africa

Cancer registry[1]	Period	N cases[a]	Crude rate[b]	ASR[b]
PROMEC	2003-2007	8	0.3	0.3

Data accessed on 05 May 2015.
ASR: Age-standardized rate, Standardized rates have been estimated using the direct method and the World population as the reference;
[a] Accumulated number of cases during the period in the population covered by the corresponding registry.
[b] Rates per 100,000 women per year.
Data sources:
[1] Forman D, Bray F, Brewster DH, Gombe Mbalawa C, Kohler B, Piñeros M, Steliarova-Foucher E, Swaminathan R and Ferlay J eds (2013). Cancer Incidence in Five Continents, Vol. X (electronic version) Lyon, IARC. http://ci5.iarc.fr

Figure 21: Vulvar cancer incidence rates by age group in South Africa



*No cases were registered for this age group.
Data accessed on 05 May 2015.
Estimate from PROMEC cancer registry
Data sources:
Forman D, Bray F, Brewster DH, Gombe Mbalawa C, Kohler B, Piñeros M, Steliarova-Foucher E, Swaminathan R and Ferlay J eds (2013). Cancer Incidence in Five Continents, Vol. X (electronic version) Lyon, IARC. http://ci5.iarc.fr

Figure 1. Fig 1: Vulvar cancer incidence rates by age group in South Africa. Forman D, Bray F, Brewster DH, Gombe Mbalawa C, Kohler B, Piñeros M, Steliarova-Foucher E, Swaminathan R and Ferlay J eds (2013). Cancer Incidence in Five Continents, Vol. X (electronic version) Lyon, IARC. http://ci5.iarc.fr.

Two clear age peaks can be observed.[g]

Risk factors

There are two proposed pathways by which vulva cancer can develop, which both result in vulva intraepithelial neoplasia (VIN): mucosal HPV infection in younger women,[h] or chronic inflammation due to vulvar dystrophy or autoimmune processes. The genetic variation between the two groups is marked, and they have been described as two distinct diseases.[i] This may explain the two age peaks observed in the PROMEC data.

It is accepted that HPV-related cancers are more prevalent in patients with Acquired Immunodeficiency Syndrome (AIDS) and compromised immunity.[j]

HPV contributes 43% to vulva cancer incidence worldwide.[k] A quarter of the HIV infected population in sub-Saharan Africa are found in South Africa.[l]

Some data suggests that black females with vulva cancer present at a younger age, and more often with disseminated disease.[m] According to the South African National Cancer Registry in 2010, black women in South Africa did not have an increased lifetime risk of vulva cancer compared to other races. However, age and stage at diagnosis were not specified in this document.[e]

As with many other cancers, smoking also contributes to the development of vulva carcinoma.[n]

Anatomy

The vulva forms the external part of the female genitalia, protecting the sexual organs as well as the urethra. It consists of the labia majora (outer folds) and labia minora (inner folds).[o]

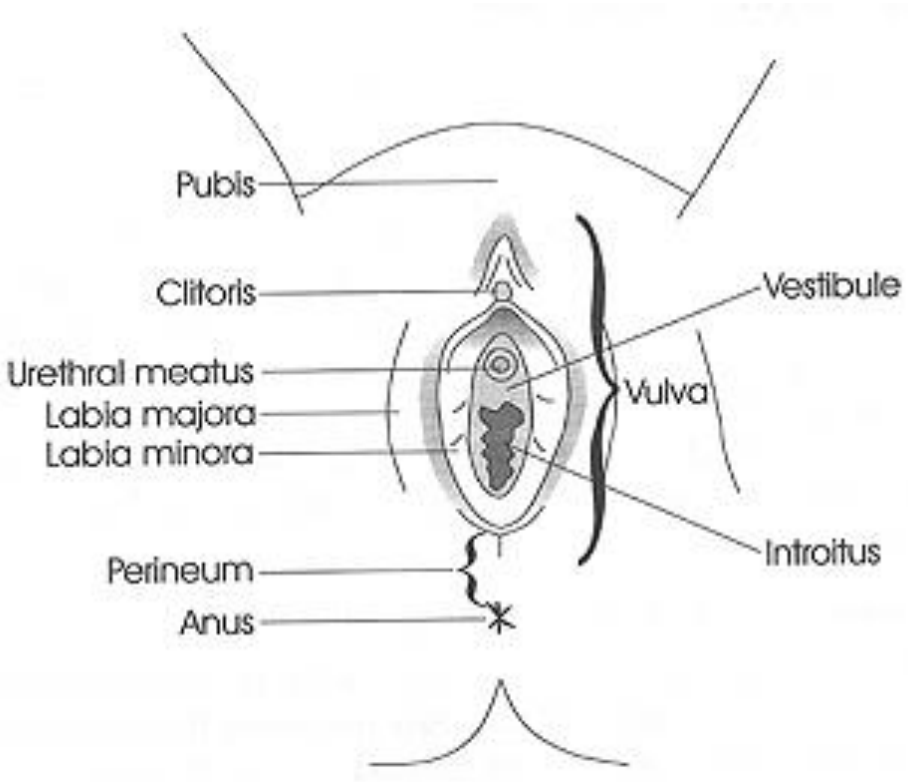


Figure 2. Anatomy. Source: The Interstitial Cystitis Survival Guide by Robert Moldwin, MD, New Harbinger Publications, Inc. © 2000.

Histology

Squamous cell carcinoma accounts for 85 % of all vulva cancer. The remainder consists of melanoma, adenocarcinoma, Paget's disease, verrucous carcinoma, Merkel cell tumors, basal cell carcinoma, transition cell carcinoma and sarcoma.[p]

Staging: Revised FIGO Staging 2009

Patients were originally staged using the original International Federation of Gynecology and Obstetrics (FIGO) system. FIGO staging for vulva cancer was reviewed in 2009, and we restaged the patient based on documented findings on examinations. The American Joint Committee on Cancer (AJCC) TNM classification system and the FIGO staging system for vulvar cancer are provided in Table 1, below.[q]

Table 1. TNM and FIGO Staging for Vulvar Cancer

Primary tumor (T)		
TNM	*FIGO*	
TX		Primary tumor cannot be assessed
T0		No evidence of a primary tumor
Tis[a]		Carcinoma in situ (preinvasive)
T1a	IA	Lesions ≤ 2 cm, confined to the vulva or perineum and with stromal invasion ≤1 mm[b]
T1b	IB	Lesions > 2 cm or any size with stromal invasion > 1 mm, confined to the vulva or perineum
T2	II	Tumor of any size with extension to adjacent perineal structures (distal third of the urethra, distal third of the vagina, anal involvement)

T3	IVA	Tumor of any size with extension to any of the following proximal two thirds of the urethra, proximal two thirds of the vagina, bladder mucosa, or rectal mucosa or fixed to pelvic bone
Regional lymph nodes (N)		
TNM	*FIGO*	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		1 or 2 regional (inguinofemoral) lymph nodes with the following features (see N1a, N1b)
N1a	IIIA	1 or 2 lymph node metastases, each < 5 mm
N1b	IIIA	1 regional lymph node metastasis ≥ 5 mm
N2		Regional (inguinofemoral) lymph nodes with the following features (see N2a, N2b, N2c)
N2a	IIIB	3 or more lymph node metastases, each < 5 mm
N2b	IIIB	2 or more regional lymph node metastases ≥ 5 mm
N2c	IIIC	Regional lymph node metastasis with extracapsular spread
N3	IVA	Fixed or ulcerated regional lymph node metastasis
Distant metastasis (M)		
TNM	*FIGO*	

M0		No distant metastasis
M1	IVB	Distant metastasis (including to pelvic lymph nodes)

Table 2. Anatomic Stage/Prognostic Groups

Stage	TNM		
0[a]	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
IIIA	T1, T2	N1a, N1b	M0
IIIB	T1, T2	N2a, N2b	M0
IIIC	T1, T2	N2c	M0
IVA	T1, T2, T3	N3	M0
IVB	Any T	Any N	M1

[a] FIGO no longer includes stage 0

Treatment

In the 20th century, most patients with vulva cancer died. The survival rate after simple excision was less than 25 %. Basset described extensive surgical techniques to improve outcome in 1912. Thereafter, Way described *en bloc*

dissection radical vulvectomy with inguinal and pelvic lymphadenectomy. Morley reported a 74 % survival with the Bassett-Way method.[r] However, despite the dramatic changes in surgical technique, morbidity remains high.

Current treatment recommendations and techniques

T1 lesions can be treated with wide local excision. T2 lesions can be treated with radical modified vulvectomy with inguinal nodal evaluation (either sentinel lymph node or ipsilateral inguinal lymph node dissection). Surgery for tumors located within 2 cm of or crossing the midline should include bilateral inguinal lymph node dissection. Adjuvant radiotherapy can be added based on margin status, nodal involvement or other risk factors. Positive lymph nodes can be an incentive to give concurrent chemotherapy.

Larger T2 lesions and T3 lesions are treated as per National Comprehensive Cancer Network (NCCN) guidelines, with radiotherapy to primary, groin and pelvis, and concurrent chemotherapy. The NCCN recommends dosages of 59.4-64.8 Gy to inoperable tumors, with a boost to 70Gy for large nodes.[s] Perez *et al.* also reported that 60-70 Gy can control tumor growth in 75-80 % of patients with advanced disease.[t] Metastatic vulva carcinoma can be radiated for local control and symptom relief, with concomitant chemotherapy or best supportive care.[s]

Prognosis

In the United States the five-year survival has been shown to be 86 % for local disease (stages I and II), 54 % for regional disease (stages III to IVA), and 16 % for distant disease (stage IVB). However, our patient profile differs markedly from this population.[u]

South Africa

According to NCCN guidelines, the treatment for vulva cancer preferably starts with surgery.[s] The little available research is focused on this approach. However, patients in developed countries present earlier and in a better general condition to receive surgery. In our setting, patients frequently present late, in poor physical condition. Limited theatre time also hinders surgeons from addressing even operable vulva cancer patients.

Our institution protocol is based on the NCCN guidelines[s] for inoperable patients, but the study population is unique regarding immunity, nutritional status and tumor burden. Patients must overcome many hurdles of a crippled peripheral healthcare system. Staff shortages are a major problem in primary public health care in South Africa, with only 30 % of healthcare practitioners working in the public sector to provide services to 80 % of the population.[v] Another problem overloading primary health care is the large number of patients suffering from chronic diseases such as tuberculosis (TB) and HIV, weighing heavily on resource-limited primary healthcare clinics.[w] Butt *et al.* published on survival of patients with all stages of vulva cancer research at Tygerberg Hospital in the Western Cape in 2017. They found overall five-year survival for all stages and treatment modalities to be 58.8 %. A small percentage (in total 7 patients) received definitive chemoradiation with external beam radiotherapy (EBRT) of 45 Gy, with additional electron therapy to the vulva administered with sensitization using cisplatin, or mitomycin C and 5-fluorouracil. Four of these patients were free of disease at follow-up; two died of their disease, and one defaulted further care. Most patients in the study received surgery as primary treatment.[x]

Opakas *et al.* also published on radiotherapy as treatment for vulva cancer at Tygerberg Hospital in 2015. They studied all radical vulva cancer patients in their department between January 2007 and December 2012 (n=25), separating all patient factors and outcomes into two groups, with and without HIV. The median age at presentation differed, with HIV-positive patients presenting at a median age of 39 years versus HIV-negative patients at 58 years. Most patients in the study received surgery (with only two who did not). They also found patient follow-up challenging, and could not perform an in-depth analysis of survival or patterns of failure.[y]

A case report by Majeed *et al.* from Pietersburg Hospital in Limpopo in 2006 describes a patient with vulva cancer and HIV having an excellent response to palliative radiotherapy, but does not comment on survival.[z] Three other papers from African countries which investigated vulva cancer are available. A case series published in 2016 by Amavi *et al.* in Togo described surgical management of vulva cancer using total vulvectomy and superficial and deep bilateral inguinal lymphadenectomy, and survival was found to be was 62.1 %.[aa] A second paper f by Medhi *et al.* describes epidemiological, clinical and pathological features of vulvar cancer in Tunisia 76 patients. They found the mean age to be 65.4 years. Most patients were FIGO stage 2 or 3 at the time of presentation. All patients had primary surgical management. Twenty-two patients had adjuvant

radiotherapy. They state that no patients had a history of immunosuppression, but do not state whether HIV testing was done. Five-year relative survival rates were 46.1 %.[bb] Finally, Kroeber *et al*. conducted a cohort study of 86 patients with vulva cancer in Ethiopia. Median age was 39 years, which included patients receiving surgery, radiotherapy and chemotherapy, with a median follow-up period of only 17 months. The two-year survival rate was 51 %.[cc] Although the abovementioned research was conducted on analogous African population groups, it predominantly focuses on outcomes after surgery as the primary therapy. Due to the uncommon nature of vulva cancer, these were all small studies. Five-year survival rates specifically for patients with vulva cancer after definitive chemoradiotherapy have not been thoroughly studied in our population.

Aim

As a primary outcome, we aimed to determine the five-year progression-free survival of patients with vulva carcinoma who were treated with radical chemotherapy and radiotherapy from 2006 to 2010. Secondary outcomes were HIV status, age, stage at presentation, total dose of radiotherapy, and number of chemotherapy cycles tolerated. The general condition of patients was documented using the Eastern Cooperative Oncology Group (ECOG) Performance Status score, and measured serum albumin.

Methodology

Study design

A retrospective, descriptive cohort study was performed. Patients were selected according to the following criteria:

Inclusion criteria:

a) Minimum of 18 years of age.
b) Histological diagnosis of Squamous Cell Carcinoma of the vulva.
c) Radical treatment attempted for vulva carcinoma at the Oncology Department of Universitas Hospital Annex in Bloemfontein, Free State according to the established protocol (see Appendix 2) from 2006 to 2010.

Exclusion criteria:

a) Younger than 18 years
b) Other histology, or carcinoma in situ
c) Patients receiving treatment other than radical chemoradiation, such as surgery, palliative radiotherapy or best supportive care.

Study Participants

All new patients diagnosed with vulva carcinoma that presented from 2006 to 2010 to the Radiation Oncology Department of the Free State and received radical radiation with concurrent chemotherapy were eligible to participate in the study. Patient information remains confidential and a study number was assigned to each candidate. Thirty patients met inclusion criteria.

Patients were admitted for the duration of the treatment for maximum nutritional and symptom support. They received daily radiotherapy in 1,8 Gy fractions Monday to Friday, with a goal to administer a total of 59.4-70 Gy (as per departmental protocol). Day 1-4 and Day 29-33 chemotherapy was given. Cisplatin 80mg/m^2 in 2 L Saline/Dextrose/Mannitol was administered D1 and D29, and 5-Fluorouracil 1000 mg/m^2 in 1 litre saline over 24 hours daily for 4 days after fluids. Patients' white cell count, hemoglobin, platelets, neutrophil count and renal function were evaluated before chemotherapy was administered.

Measurements

Our institutional electronic medical information system (Meditech) only holds information from 2012 onward, with our department only recently commencing its use for discharge summaries. Hence, no information on study participants was available in this system. Furthermore, the National Health Laboratory system was also recently instituted, and did not hold any information on study participants, with the previous system no longer available. Therefore, the following data was collected manually from our departmental patient files:

- Age:
  Age at presentation.

- HIV status and CD4 count:
  HIV is a major contributing factor to an increased incidence of vulva cancer in younger patients, in keeping with the increase in all HPV-related cancers in the HIV population.[j,h] CD4 lymphocyte count is an indication of patient immunity, and response to antiretroviral therapy.[dd] A CD4 count of 200 or less confirms the diagnosis of AIDS. Normal CD4 values range between 500-1000, with higher values associated with improved immunity.[ee] It was documented in cells per microliter or cells per mm^2.

- Cancer Stage:
  The staging system used from 2006-2010 was the old FIGO staging system which was reviewed in 2009. Staging was changed based on documented clinical findings to the new FIGO staging (as described above) for the purposes of this study.

- Albumin
  Albumin is used as an indication of general nutritional health, composing 50-60% of plasma proteins. Normal values are 35-55 g/L.[ee,ff]

- ECOG Performance status score:

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

- Total dose of radiation received
  Recommended total dose for definitive radiotherapy is 59.4-64.8 Gy in 1.8 Gy fractions. Large nodes may require 70 Gy.[s]

- Whether chemotherapy was completed as per departmental radical treatment protocol (see Appendix 2). Department protocol at the time was to give chemotherapy D1-4 and D29-33, however 3 patients received chemotherapy as per current protocol which is a weekly Cisplatin dose of 25mg/m2.

- Overall survival at five years

- Progression free survival

A data form was used for documentation of all relevant measurements for each patient. (See Appendix 1)

Analysis of data

Data were captured from the Patient Data Forms and were entered onto an Excel (Microsoft Corporation, Redmond, USA) spreadsheet by the researcher, and analyzed by the Department of Biostatistics of the University of the Free State. Numerical variables such as the mean and median were determined, and categorical variables were summarized in frequencies and percentages. Survival analysis to determine five-year survival could unfortunately not be performed due to poor follow-up of patients.

Ethics

This study was approved by the Ethics Committee of the University of the Free State, and reviewed by the Department of Health of the Free State. (HSREC 152/2016 and UFS-HSD2016/1319 respectively.)

Results

A total of 55 files representing all new patients with vulva cancer presenting to our department from 2006 to 2010 were screened. Only 30 patients were identified as eligible to participate. The patients excluded had received palliative treatment, surgery or had histology other than squamous cell carcinoma, and therefore could not be included.

The mean (range) age of patients was 50 (27-79) years. (Figure 3)

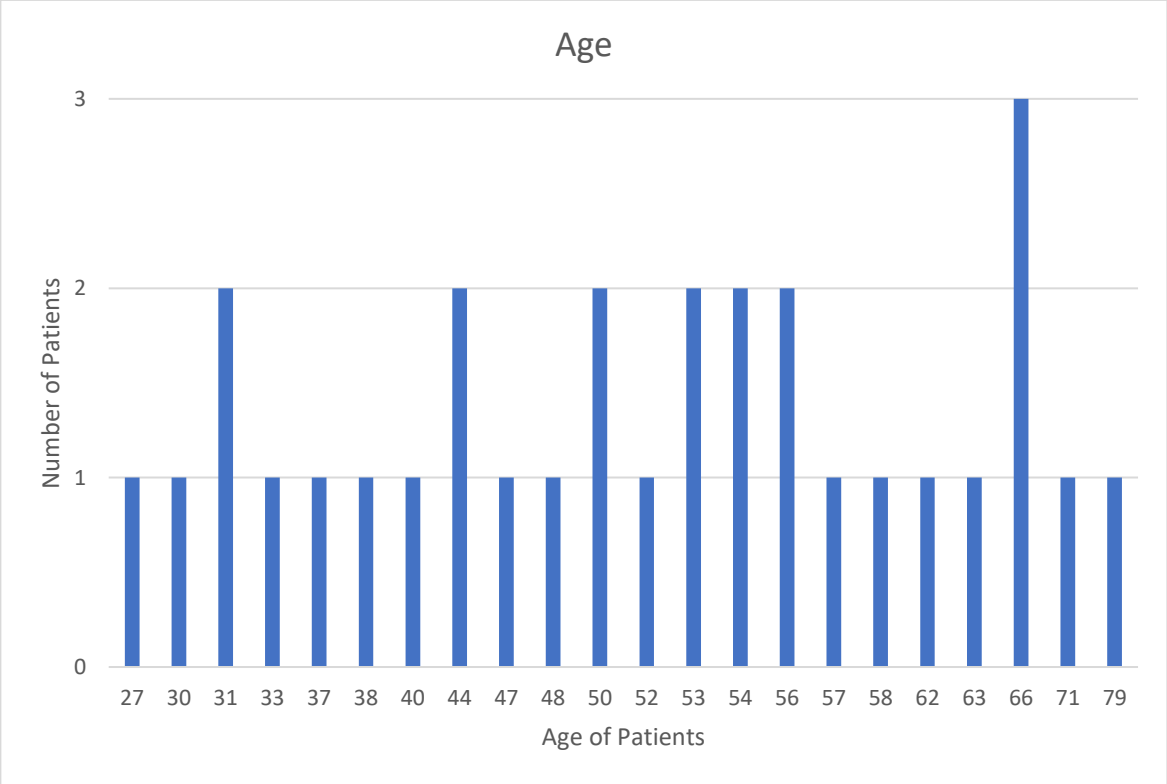


Figure 3. Patient age distribution.

ECOG Performance status was recorded for 91% (50/55) of patients, with 73% ECOG 1, 13% ECOG 2 and 13% ECOG 3. (Figure 4) The performance status of the remaining 5 patients is was unknown, as it was not documented in patient files.

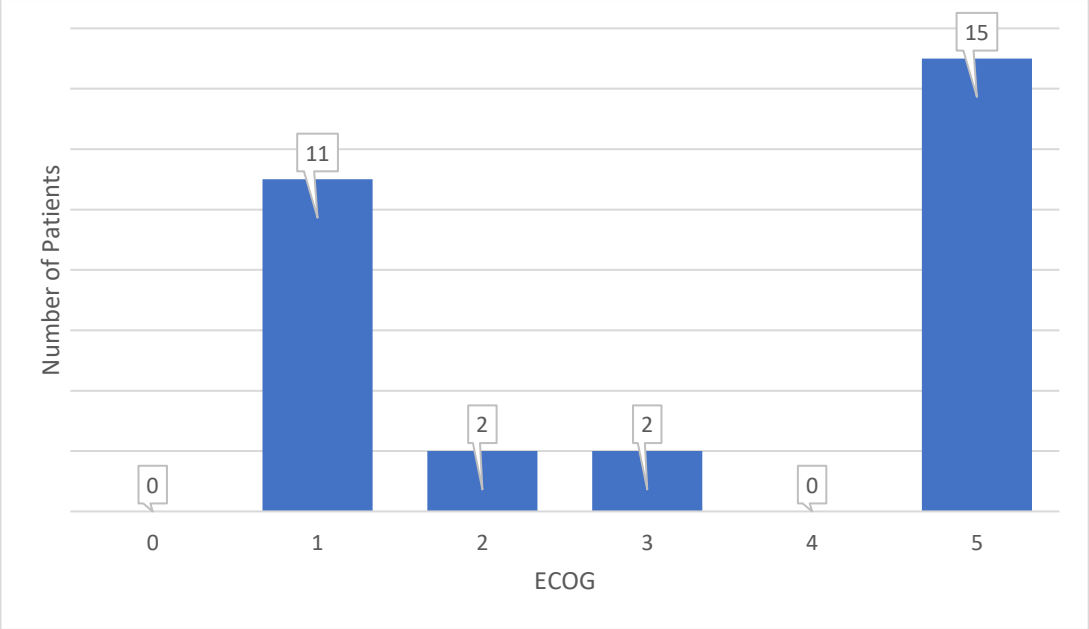


Figure 4. ECOG Performance Status

HIV status was unknown in 17% of patients. Of patients where HIV status was known, 52% were HIV positive and 48% HIV negative. (Figure 5) Amongst those known to be HIV positive, 17% were documented to be on highly active antiretroviral therapy (HAART); 39% were known not to be on HAART, with the remainder undocumented. Of the HIV positive patients in our study group, only 69 % had a known CD4 count. (Figure 6)

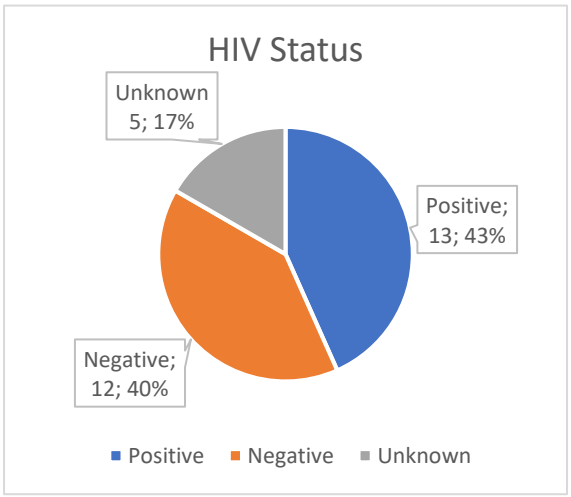


Figure 5. HIV status

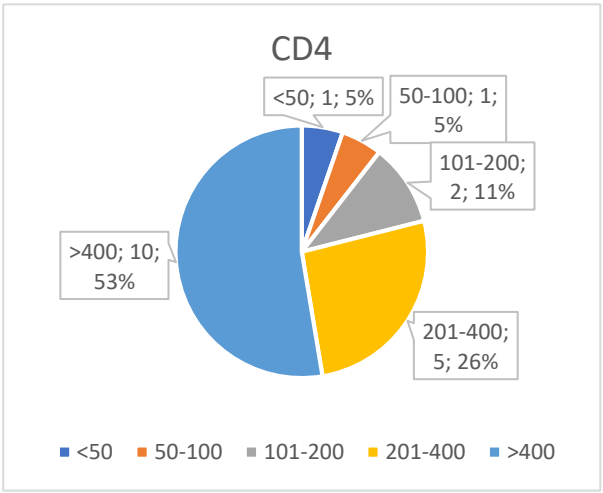


Figure 6. CD4 count

Four patient's albumin levels were unknown, with 7% having an albumin level below 20, 30% between 20 and 30, 46% between 30 and 40 and 7% more than 40 g/L. (Figure 7)

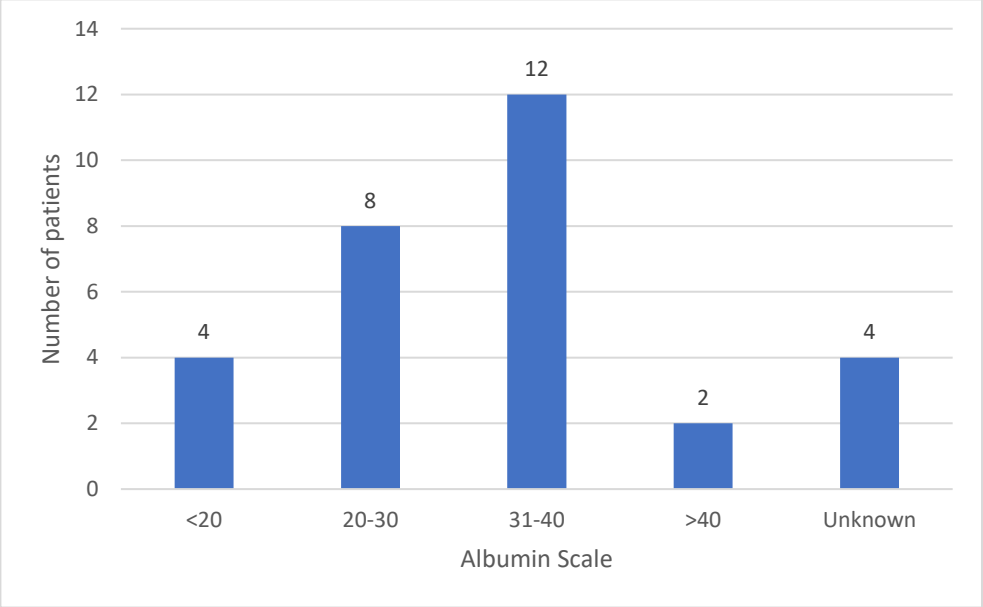


Figure 7. Albumin levels

According to the new FIGO staging system, 33.3 % had Stage 4 disease, 53,0 % had Stage 3 disease, and 3.3% of patients had Stage 2 and Stage 1 disease each. (Figure 8) Most patients had a T3 local tumor and most had N0 disease. (Figures 9 and 10)

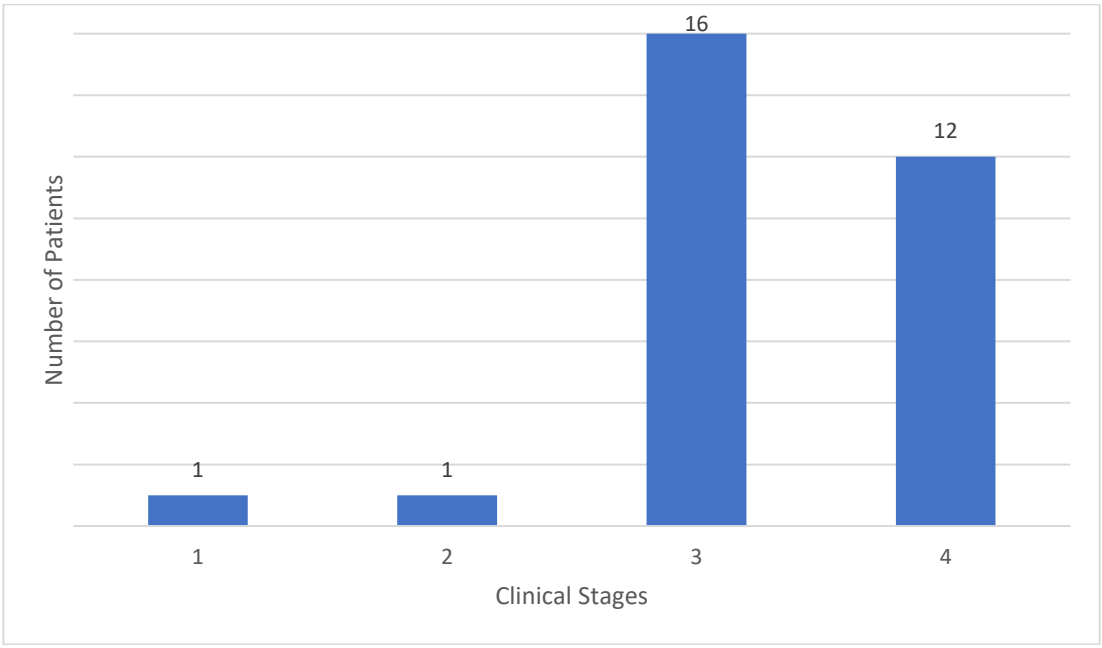


Figure 8. FIGO Clinical Staging

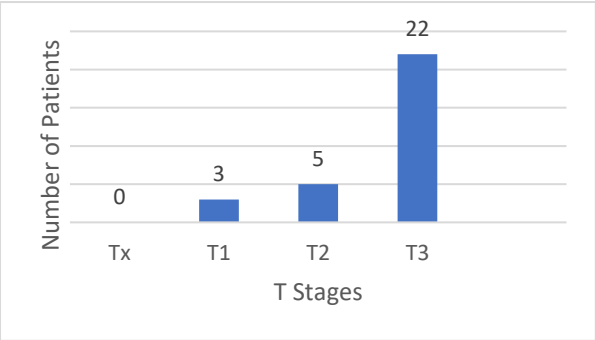


Figure 9. T stages

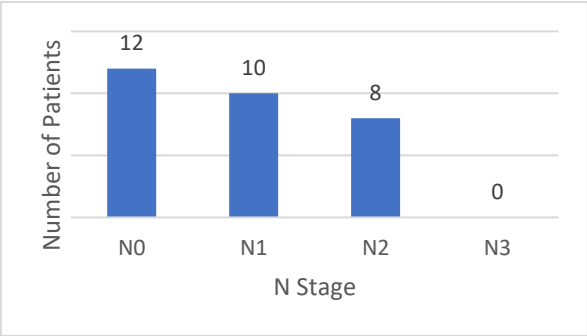
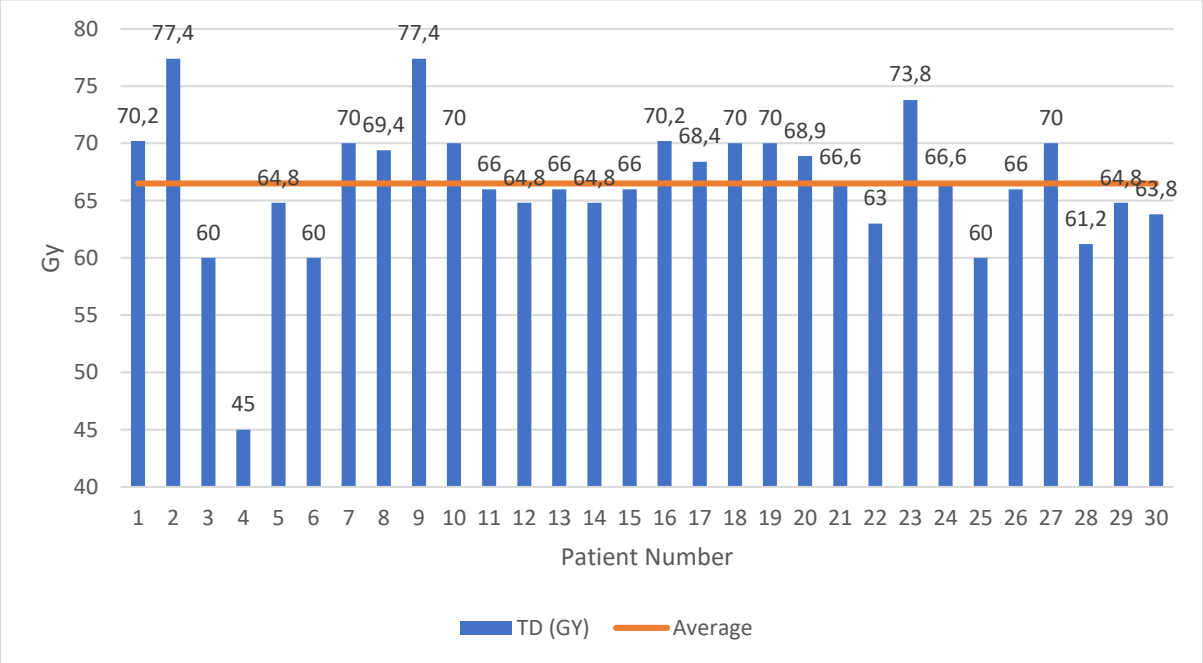


Figure 10. N stages

In 93.3% of patients the grading was known from the histology. 23% had well differentiated, 60% moderately differentiated and 10% poorly differentiated tumors.

Most (93.3%) of the patients received concurrent chemotherapy. Of these, 82.1% completed D1-4 and D29-33 chemotherapy as per protocol. 3 patients received weekly concurrent Cisplatin alone. 2 completed 7 weeks and 1 only 2 weeks due to a drop in CD4 count. Radiation dosages varied. The minimum dose was 45 Gy and the maximum 77.4 Gy.



Median follow-up was only 156.5 days (approximately 5 months). The minimum follow-up was 0 days, with the longest at 3567 days (approximately 10 years).

Discussion:

In this study, 55 potential participant's records were screened. This figure represents all new patients who presented to our department from 2006 to 2010, and was disappointing in the sense that a larger cohort was expected, with an original estimation of 120 patients anticipated. Although not the aim of the study, if compared to the numbers from 2016 (38) and 2017 (47), it can be concluded that incidence appears to be increasing. This is likely due to an increase in HPV and HIV.[j] One can also speculate that the peripheral health clinics are identifying more patients.

The mean age of patients was 50 years, with a range from 27 to 79 years. This places 40 % of our study population under 50 years, which appears to be much younger than international statistics. For instance, the American Cancer Society reports less than 20% of patients to be below 50 years, and more than 50 % above the age of 70 years.[hh] In our study, only 6% were older than 70. In the UK, 44 % of vulva carcinoma patients were aged 75 years and older. Comparison to other African countries is difficult due to lack of data. However, the research performed in Tunisia reports that their mean age at diagnosis is 65.4 years, and 86,9% of patients are more than 55 years old.[bb] In contrast, the data from Ethiopia displays an even younger population than ours, with a mean age of 39.[cc] Therefore, our data does not appear to be similar to any published in other African countries.

The high rate of HIV infection in South Africa is a contributing factor to the incidence of vulva cancer; emphasized by the fact that 52% of the study population was known to be HIV positive. According to UNAIDS Data from 2017, the South African National HIV prevalence is 18.9 %, with only 56% on HAART.[k] In our cohort, less than a third (30 %) of patients were on HAART. This could be a direct reflection of a failing peripheral health care system, as this is where patients should be educated on, tested and treated for HIV with antiretroviral drugs. It is unfortunate that a proportion of patients had no record of HIV status in either paper files or on the electronic systems available. Stigmatization of HIV may play a role, although to what extent we cannot postulate. The author hopes that awareness will increase over time, and patients will have opportunities to become more educated.

A large proportion of our population comes from poor socioeconomic circumstances, with underlying poor general health, which is reflected in their albumin levels. Contributing factors are known to be malnutrition, poverty,

substance abuse and comorbid diseases. It is noteworthy that 12 patients had an albumin of less than 30 g/L. 5-Fluorouracil, one of the chemotherapies used, binds to albumin, which is thus essential for optimal utilization of this treatment. Unfortunately, no comparative data is available to compare our population's albumin levels to patients in developed countries.

Among the 50% of the cohort who had a documented ECOG PS, 73% of patients had score of 1. This can be attributed to the fact that patients included in this study were those selected for attempting curative treatment, and those with a ECOG PS of 3 or 4 would most likely have been treated palliatively.

According to the research at Tygerberg Hospital, 53.3% of their patients had stage 3 or 4 disease. In our study population, 93.3% had advanced disease. As our study did not include patients who received surgery, it is therefore difficult to make a comparison. However, our numbers reflect the high prevalence of advanced vulva cancer patients treated at our institution. Seven of the 25 patients who were excluded from our study received surgery.

Regarding treatment, we were pleased to find that 93.3 % (51/55) of this study population received concurrent chemotherapy, with the majority (82.1%) receiving D1-4 and D29-33 chemotherapy as per our protocol. The 7 patients who could not receive both D1-4 and D29-33 were deemed unfit, either due to worsening general condition or renal insufficiency. Three patients received weekly cisplatin, which forms part of our new departmental protocol, and appears to be better tolerated. Two completed 7 weeks of treatment and one only 2 weeks due to a dramatic drop in CD4 count.

We found that patients received an adequate radiation dose, with dose administered comparable to international guidelines. (NCCN recommendations are dosages of 59.4 - 64.8 Gy to inoperable tumors, with a boost to large nodes to 70Gy.[5]) The reason why two patients received 77.4 Gy is unknown, and constitutes overtreatment according to NCCN guidelines and our protocol. Only one patient received less than 60 Gy. This patient had to stop treatment at 45 Gy due to deterioration of general condition.

The primary outcome in this study was unfortunately not met due to poor patient follow-up. Mean follow-up duration was only 655.2 days (approximately 1.8 years), although the longest follow up was 3567 days (approximately 9.7 years).

Patient compliance and follow-up poses an enormous problem when conducting research. The socioeconomic factors and distances patients need to travel need to be considered. Lack of understanding of the importance of follow-up, lack of income and infrastructure also hinder follow-up visits. In our study, determination of five-year survival is an impossible task, as only 5 patients (16.6 %) attended follow-up visits for at least 5 years. Four (13%) patients did not follow up at all. (It is possible that these patients attended follow-up in the Northern Cape Province). The inclusion of patients from another province is a limitation of this study. While this could possibly have been foreseen, and these patients excluded from the study, this would have reduced total numbers and would probably not have changed the outcome, seeing that the majority of local patients were also lost to follow-up.

One patient did not complete her treatment due to dramatic decline in general condition. No patients died during treatment. One patient presented with a second primary cancer (adenocarcinoma of the ovary), which was subsequently treated. Three patients had proven recurrence, which constitutes a 10% recurrence rate in our study population. These recurrences occurred in the 3rd to 8th months of follow-up, and were proven on biopsy. Two patients had residual disease after treatment. Of all patients, 63 % had a good outcome and no recurrence until last follow-up, although this varied from 4 days to 10 years.

Analysis of the 25 patients who were excluded revealed that 7 were treated with primary surgery. Four patients had non-squamous cancers. Six patients were planned to get radical radiotherapy but defaulted treatment before it was commenced. Eight patients were treated with palliative radiotherapy. The reasons for palliation were: albumin of 16 g/L, chronic illness, ECOG 3 or 4, renal failure, and rectovaginal fistula.

Poor record keeping and undocumented data was a major limiting factor. This was encountered with records of ECOG PS, HIV status, CD4 count, and whether patients were on antiretroviral drugs. In our context, record keeping has recently been addressed, and has improved. A standardized admission booklet which reminds the clinician of essential information is now used for each patient. Although the National Health Laboratory System has updated their website, previous patients laboratory records are not available anymore. The Free State Department of Health uses an electronic medical record (Meditech), in which different patient identification methods at different institutions limits information tracking.

Conclusion:

In this small cohort study, most patients were HIV positive, with advanced disease. Loss to follow-up, which is commonplace in a resource-limited setting, hinders conclusions on recurrence and survival.

Regular viral load testing and documenting for HIV positive patients currently assists in treatment decisions, and may to an extent predict how well (or poorly) treatment will be tolerated.

More studies are needed to investigate 5-year survival statistics in South African patients with vulva cancer receiving radical definitive radiotherapy and concurrent chemotherapy. Follow-up research in our department can be conducted to reflect the current incidence and outcomes.

References:

a. Ferlay J. 2006. Worldwide burden of gyneacological cancer: The size of the problem. *Best Practice & Research Clinical Obstetrics and Gynaecology,* 20(2):207-225
b. Cancer research UK.Vulva and vagina cancers. CancerStats. Available from: www.cancerresearchuk.org/. [March 2007]
c. Siegel RL, Miller KD, Jemal A. 2017. Cancer Statistics 2017. CA Cancer J Clin;67(1):7.
d. Buttman-Schweiger N, Klug S, Luyten A, Hollczek B, Heitz F, Du bois A, Kraywinkel K. Incidence Patterns and Temporal Trends of Invasive Nonmelanotic Vulvar Tumors in Germany 1999-2011. A Population-Based Cancer Registry Analysis. Available from: PLoS ONE; 10(5):e0128073. [May 28,2015]
e. Herbst MC, Cancer Assosiation of South Africa (CANSA). Available from: www.cansa.org.za. [April 2015]
f. National Cancer Registry. *Summary statistics of cancer diagnose histologically in 2014.* Available from: http://www.nicd.ac.za/wp-content/uploads/2017/03/2014-NCR-tables-1.pdf. [March 2017]
g. Forman D et al. *Cancer Incidence in Five Continents.* Available from: http://ci5.iarc.fr [May 2014]
h. Halec G, Alemany L et al. 2017. Biological relevance of human papillomaviruses in vulvar cancer. *Modern Pathology*; 30(4):549.
i. Weberpals JI, Lo B, Duciaume MM et al. 2017. Vulvar Squamous Cell Carcinoma (VSCC) as Two Diseases: HPV Status Identifies Distinct Mutational Profiles Including Oncogenic Fibroblast Growth Factor Receptor 3. *Clin Cancer Res*; 23(15):4501.
j. Chaturvedi AK, Madeleine MM et al. 2009. Risk of human papillomavirus-associated cancers among persons with AIDS. *J Natl Cancer Inst.* Aug 19;101(16):1120-30
k. de Martel C, Ferlay J et al. 2012. Global burden of cacers attributable to infection in 2008: a review and synthetic analysis. *The Lancet Oncology*; 13(6):607-15
l. *Joint United Nations Programme on HIV/AIDS. The Gap Report.* 2014. Available from: http://www.unaids.org. [May 20, 2015]
m. Rauh-Hain JA, Clemmer JT et al. 2013. Racial disparities in cervical cancer survival over time. *Cancer*; 119(20):3644.
n. Madeleine MM, Daling JR et al. 1997. Cofactors with human papillomavirus in a population-based study of vulvar cancer. *Journal of the National Cancer Institute*;89(20):1516-23.

o. Anatomy of the vulva. 2000. Available from: www.nva.org.
p. Perez CA & Brady LW (eds) 2013. *Perez and Brady's Principles and Practice of Radiation Oncology.* Sixth Edition p1502-1515 Philadelphia. Lippincott Williams & Wilken.
q. Edge S, Byrd D et al. 2010. *AJCC Cancer Staging Manuel.* New York; Springer Verlag
r. Morley GW. 1976. Infiltrative carcinoma of the vulva: results of surgical treatment. *American Journal of Obstetrics Gynecology;* 124:874-878
s. National Comprehensive Cancer Network. Vulva Cancer. Available from: www.NCCN.org.
t. Perez CA, Grigsby PW, Chao C et al. 1998. Irradiation in carcinoma of the vulva: factors affecting outcome. *International Journal of Radiation Oncology Biology Physics*; 42(2):335-44.
u. U.S. Department of Health and Human Service. National Institute of Health. National Cancer Institute. SEER data. Available from: www.USA.gov.
v. Keeton, Claire et al. 2010 Bridging the Gap in South Africa. *Bulletin of the World Health Organization;* 88(11): 803-804.
w. Maillacheruvu P, McDuff E. 2014. South Africa's Return to Primary Care: The Struggles and Strides of the Primary Health Care System. *Journal of Global Health*. Available from: www.ghjournal.org.
x. Butt JL et al. 2017. Vulvar cancer is not a disease of the elderly: Treatment and outcome at a tertiary referral center in South Africa. *South African Medical Journal*;197:1000-1004
y. Opakas JE et al. 2015. Radiotherapy in the Management of Carcinoma of the Vulva in HIV positive and negative patients: An Institutional experience. Available from: https://scholar.sun.ac.za
z. Majeed U, Sekowski A, Ooko F. 2006. Vulvar cancer in HIV-positive young women – a treatment challenge. *South African Journal of Obstetrics and Gynecology*; 12(3)156-162.
aa. Amavi AK, Kouadio L, Adabra K et al. 2016. Surgical management for squamous cell carcinoma of the vulva. *Pan African Medical Journal*; 24:145.
bb. Mehdi Kehila MD et al. 2017. Vulva cancer in Tunisia: Epidemiological and clinicopathological features multicentric study. *Journal of Egyptian National Cancer Institute;* 29(2):95-98
cc. Kroeber ES, Mathewos A, Wondermagegnehu T et al. 2018. Vulvar cancer in Ethiopia: A cohort study on the characteristics and survival of 86 patients. *Medicine;* 97:9 Available from: www.ncbi.nim.nih.gov

dd. Graham NM, Park LP, Piantadosi S et al. 1995. Prognostic value of combined response markers among human immunodeficiency virus-infected persons: possible aid in the decision to change zidovudine monotherapy. *Clin Infect Dis*; 20(2):352.

ee. United States Department of Veterans Affairs: HIV/AIDS. Avalable from: www.hiv.va.gov

ff. Burtis CA, Ashwood MD. 1999. *Tietz Textbook of Clinical Chemistry 3rd ed.* Available from: Saunders. [14 October 2012]

gg. McPherson RA, Pincus MR. 2011. *Henry's Clinical Diagnosis and Management by Laboratory Methods: Expert Consult 22nd ed.* Available from: Saunders [2 August 2011]

hh. American Cancer Society publication, Cancer Facts & Figures 2016. Atlanta: American Cancer Society. Available from: www.cancer.org

Appendix 1: Example of Patient Data Form

Patient number (given by researcher to each pt)		1-3
Data		
Patient's profile		
Age		4-5
Baseline ECOG (0=0, 1=1, 2=2, 3=3, 4=4, 5=unknown)		6
HIV status (positive=1, negative=2, unknown=3)		7
HAART (Yes=1, No=2, unknown=3)		8
Albumin (1=<20, 2=20-30, 3=31-40, 4=>40, 5=unknown)		9-10
Clinicopathological characteristics		
CD4 prior to chemo/RT initiation(cells /microlitre or mm^3)		
(1=<50, 2=50-100, 3=101-200, 4=201-400, 5=>400, 6=unknown)		11-14
Clinical stage (1=1, 2=2, 3=3, 4=unknown)		15
T stage (Tx=0, T1=1, T2=2, T3=3, T4=4)		16
N stage (N0=0, N1=1, N2=2, N3=3)		17
Differentiation (1=Well, 2=Moderately, 3=Poor, 4=Unknown)		18
Therapy		
Chemotherapy (yes=1, no=2)		19
D1-4 completed (yes=1, no=2)		20
D29-33 completed (yes=1, no=2)		21
Radiation therapy		22
Total dose received (Gy)		23-26
Final outcome		
Date of completion of treatment		
Estimated date of death		27
Progression free survival (1=<6mo, 2=6-12mo,3=1-2yrs, 4=2-3yrs,		
5=3-4yrs, 6=4-5yrs, 7=>5yrs, 8=unknown)		28
Lost to follow up (yes=1, no=2)		29

Appendix 2 : Vulva Cancer Protocol

DEPARTMENT OF ONCOLOGY – Universitas Annex, Free State
VULVA CANCER PROTOCOL

WORK-UP
History and full clinical exam
Biopsy (histological confirmation of invasive CA)
Papsmear or biopsy of suspicious cervix lesions
CXR
Sonar (abdomen +pelvis)
HIV (CD4 + viral load if +)
RPR/U&E/LFT/Albumin/CMP/FBC

STAGING: TNM/FIGO
SURGERY (Gynae CC)
All carcinoma in situ or microinvasion (</= 5mm): wide local excision
Lateralised T1aN0M0 /IA: Wide local excision or simple vulvectomy
T1b N0M0 /IB and T2 N0M0/ II: Radical vulvectomy with lymph node dissection
Stage III: Radical vulvectomy + lymph node dissection
Stage IVA: pelvic excenteration (NB: most of our patients will not qualify due to comorbidities &ECOG)

Adjuvant chemoradiotherapy
Primary tumour >/=4cm
Positive surgical margins or close margins (< 1cm)
Positive lymph nodes (> one node)
Lymphovascular invasion
Extracapsular extension of lymph nodes
Elective nodal irradiation (clinically negative and no nodal dissection done)

Adjuvant Radiotherapy doses
Primary surgical bed (negative margins): 45-50Gy
Negative nodes: 45-50Gy
Positive resected nodes: 50-54Gy
Positive nodes with ECE: 54 -66Gy
Definitive chemoradiotherapy TD 66 -70Gy (if OAR within tolerance)

CT-scan (as per SOP)
All patients are scanned with bolus over palpable inguinal nodes and over primary tumour.
Some patients may need to lie on superflab (depends on the posterior extent of the tumour)
Wires on surgical scars (Post-op)

Delineation
Gross Tumor Volume (primary + nodal)
Organs at Risk:

Small bowel bag
Rectum
Bladder
Femoral heads

Large Fields (AP/PA) 45 Gy
Superior: L5/S1
Inferior: 2cm below GTV
Laterals: cover the nodal region

Small Fields (True Pelvis) 5.4Gy
Inferior: unchanged
Superior: below SI-joints
Laterals: off femoral heads
Electron Fields: inguinal area (size + energy measured on CT)

Boost: 9Gy-15.6Gy/19.6Gy
Primary + positive nodal electron field

Concurrent chemotherapy
Weekly Cisplatin 25/30 mg/m2 OR
Cisplatin 80mg/m2 (D1&D29)
5FU 1g/m2 (D1-4 & D29-32)

Palliation
ECOG 2 or more
Albumin < 2
340cGy x 11
300cGy x 10
400cGy x 5

Follow-up
Clinical @ 1month then 3-4 monthly for first two years;
6 monthly up to 5 years;
Annually

Disease recurrence
Discuss at Gynae CC for histological confirmation of recurrence and evaluation of resectability.

Irresectable local recurrence /metastatic disease
Cisplatin/5FU (NOT on NCCN)
Cisplatin/Vinorelbine
Cisplatin/Gemcitabine
Carboplatin/Paclitaxel
Carboplatin (single agent)

PLANNING PALLIATIVE TREATMENT

- Field sizes are the same as for LARGE fields
- Dose: 200 cGy x 12 #'s
  Rest 4 weeks
  200 cGy x 8 #'s
  Re-assess
- For very palliative patients: 300 cGy x 10 #'s, 340 cGy x 11 #'s 4x/week or 400cGy x 5#'s