Radiotherapy in the Management of Carcinoma of the Vulva in HIV positive and negative patients: An Institutional experience

By

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DECLARATION

I, ***Jesse Elungat Opakas,*** hereby declare that this report is my own work, except where otherwise acknowledged. It is being submitted in partial fulfillment for the degree of Master of Medicine in Radiation and Clinical Oncology at the University of Stellenbosch, Tygerberg, Cape Town. South Africa.

This study has received ethical approval from the University of Stellenbosch's Ethical Committee for Research on Human Subjects (HREC): PROTOCOL NUMBER S13/02/024

No data collection was carried out prior to ethics approval received on the 8th of March 2013 (Addendum).

In compliance with the Western Cape Provincial Administration and Tygerberg Hospital Research Policy, permission to conduct research as per Protocol S12/02/024, was requested and obtained on 11th April 2013. (Addendum)

CONFLICT OF INTEREST

No personal financial gain is anticipated from this thesis or any related article. I hereby declare no conflict of interest

Signed at: ***Tygerberg*** on this 29th day of ***October 2014.***

Signed:

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LIST OF ABBREVIATIONS AND SYMBOLS

AIDS:	Acquired Immune-Deficiency Virus
CD4:	Cluster of differentiation 4: a glycoprotein predominantly found on the surface of T-helper cells
ELISA:	Enzyme-Linked Immunosorbent Assay
ECOG:	Eastern Co-operative Oncology Group
FIGO:	International Federation of Gynecology and Obstetrics
GOG:	Gynecological Oncology Group
Gy:	Gray
Hb:	Hemoglobin
HIV:	Human Immune-Deficiency Virus
HAART:	Highly Active Anti-Retroviral Therapy
IMRT:	Intensity modulated Radiation Therapy
IGRT:	Image Guided Radiation Therapy
n:	Number of Patients
NE:	Not Evaluable
PR:	Partial Response
PTB:	Pulmonary Tuberculosis
RECIST:	Response Evaluation Criteria In Solid Tumours
RT:	Radiation Therapy
5-FU:	5-Fluorouracil

ABSTRACT

Radiotherapy in the Management of Carcinoma of the Vulva in Human Immune-Deficiency Virus (HIV) Positive and Negative Patients: An Institutional Experience.

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Background: Radiotherapy and chemotherapy are integral parts of the effective and optimal management of patients with vulva cancer, especially when initiated early in the course of this disease. Often, surgical resection alone cannot effect total removal of the tumour or may not be feasible.

Human Immune-Deficiency Virus (HIV) infection has been an epidemic in sub-Saharan Africa. Highly Active Antiretroviral Therapy (HAART) is available in public health facilities in the region to arrest and control HIV infection, delaying the progression to AIDS and death. Infection with HIV has now been transformed into a manageable, chronic disease and this has allowed patients to live longer, healthier and more productive lives.

Human Immune-Deficiency Virus (HIV) infection may further complicate the management of vulva cancer disease as patients are immunocompromised and may have difficulty in completing treatments prescribed.

This study aims to identify and assess the outcomes, tolerances, toxicities and factors influencing treatment completion in both HIV positive and negative patients with vulva cancer treated at Tygerberg Academic Hospital.

Study Design and Methods: This is a retrospective, observational, cross-sectional review of the factors influencing the completion of radical radiotherapy in the treatment of locally advanced cancer of the vulva. Patients are classified as either HIV positive or HIV negative. The period of the study was between 1st. January 2007 and 31st December 2012 and it was conducted at the Division of Radiation Oncology, Tygerberg Academic Hospital, Cape Town, South Africa.

All the HIV positive patients were already on antiretroviral therapy at the outset. The disease and treatment characteristics are described as well as toxicities of treatment of patients undergoing radiotherapy and chemo-radiation.

Treatment completion for the two groups is evaluated. The toxicities that led to treatment interruptions for these groups are also listed.

Results: Of the 68 patients screened, 25 met inclusion criteria; of these patients, seven (28%) were HIV positive while the other 18 (72%) were negative. Vulva cancer patients infected with HIV presented at a younger age and with more locally advanced tumours compared to HIV negative patients. There is no statistically significant difference between the two groups in treatment completion rates and tumour failure rates.

Conclusion:

This retrospective study concludes that HIV positive patients with vulva cancer presented with a more locally advanced disease and at a younger age when compared to HIV negative patients. There was no statistically significant difference in overall therapeutic outcomes although cutaneous toxicities were more pronounced in the HIV positive subset. Chemo-radiotherapy sequentially or concurrently can be regarded as a standard of care in both HIV positive and negative patients provided that the HIV patients are on antiretroviral therapy.

Chapter 1:
Introduction and Background

This paper provides a retrospective review of the profile of patients who commenced radical treatment for vulva carcinoma at Tygerberg Hospital's Division of Radiation and Clinical Oncology between 1st January 2007 and 31st December 2012. It examines the demographic and disease characteristics of these patients and also the percentage who completed the planned treatment and as far as possible the outcomes thereof. The study notes the HIV status of the patients in relation to the abovementioned characteristics. Descriptive statistics are used in view of the relatively low numbers of eligible patients and comparisons are drawn with similar publications from other centers.

Carcinomas of the vulva are rare, accounting only for about 2-4% of gynecologic malignancies and 0.6% of all cancers in women; consequently, published institutional reviews are relatively rare even though these are needed to assess efficacy of treatment and to make comparisons [(1)] . Thus, more work is needed to understand the disease better and to contribute to the body of knowledge regarding treatment and control strategies.

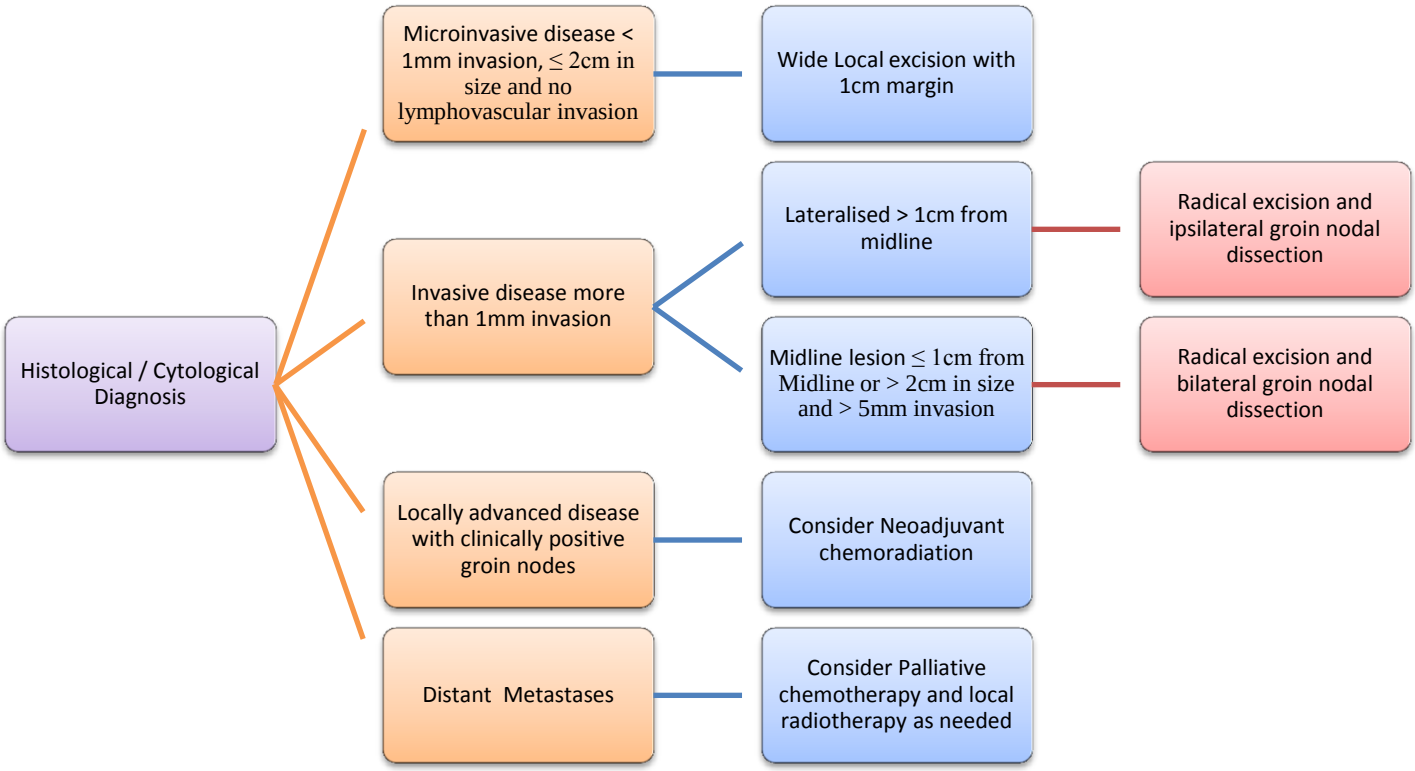
All the patients in this study were treated with radiation with or without chemotherapy concurrently or sequentially; all treatment was in line with departmental protocol unless otherwise stated.

Chemo-radiation for vulva cancer produces significant acute morbidity, which has been well documented [(2)] , but far less is known about the effects of HIV positivity in patients and if this could influence treatment related morbidity, quality of life and overall outcomes in HIV positive patients.

Treatment

At Tygerberg Hospital the patients are managed as per the Western Cape protocol for Gynecological malignancies [(3)] .

On evaluation of a confirmed malignant vulval lesion, the treatment algorithm is as shown below.



Treatment Flow Chart, Figure 1

Post-operatively, If all nodes are histologically negative, the patient is then followed up with clinical examinations three monthly for the first two years then six monthly until five years. If there are positive ipsilateral lymph nodes, then the patient is offered contralateral groin dissection.

If the patient still has positive nodes or close margins the patient is then offered adjuvant therapy with further excision either with or without chemo-radiation

If the patient presents with clinically positive locally advanced disease, neoadjuvant chemo-radiation is administered to downsize the tumour and make it amenable for less debilitating surgery.

Patients who present with metastatic disease may be considered for palliative chemotherapy and local radiotherapy as appropriate.

Approach to Radiotherapy:

Radiotherapy specifically involves individualizing target volume but includes in most cases the vulva, groin and pelvic nodes.

Typically, a pair of anterior posterior parallel-opposed portals are used. A dosage of 2.5 Gray daily, five times per week for two weeks is administered (25 Gray mid plane dose).

A re-assessment is made two weeks later, having allowed for settling of any perineal skin reaction and regression of tumour. If nodal disease is not present, and sufficient regression of the primary tumour has occurred, wide local excision is performed.

If regression of the primary tumour is insufficient, a repeat course of chemo-radiation may be given at an additional dosage of 20 Gray in ten fractions. A reassessment is made two to three weeks later.

Every attempt is made to excise residual tumour. If regression is complete, a biopsy of the tumour bed is done to confirm eradication of the tumour.

If surgery is not possible, or extensive residual nodal disease is present, small volume booster doses of 15-20 Gray are applied to any residual tumour.

An alternative approach to fractionation is to treat to 45 Gray in 25 fractions to the larger volume and a booster dose up to 20 Gray in 1.8 – 2 Gray fractions as appropriate over a 6-week period with or without weekly chemo-sensitization with cisplatin.

Literature Review

A systematic search was performed using the databases of PubMed, Ovid, Embase, Google Scholar and the Cochrane Library to identify relevant publications produced between 1960 and the current time of writing. Publications deemed relevant were those reporting on studies of patients with Human Immune-Deficiency Virus (HIV) infection and vulva cancer who were treated with radiotherapy and chemotherapy concurrently or sequentially.

Acquired Immune-Deficiency Syndrome (AIDS) was found to be caused by Human Immune-Deficiency Virus (HIV) Infection and has been an epidemic in sub-Saharan Africa for the past two decades [(4)] .

Highly Active Antiretroviral Therapy (HAART) is now generally available in public health institutions and this treatment has had a major impact in controlling HIV infection, delaying the progression to AIDS and death [(5)] . Infection with HIV has now been transformed into a manageable, chronic disease.

Donahue et al. (1989) argue that HIV infection in malignant disease can be managed as a chronic disease while on HAART or a more virulent disease without treatment [(6)]. In consequence, infected individuals on HAART could potentially have improved outcomes when treated for their cancers as morbidity from competing opportunistic infections declines.

The management of patients with locally advanced vulvar cancer in itself is a therapeutic challenge to both the patient and the radiation oncologist due to the location of the tumour and organs involved [(7)].
In the background of HIV infection, patients could be confronted with multiple competing conditions and sequels making it necessary to pursue the most effective therapy with a minimal toxicity profile [(8)] .
According to Cottrill et al. (1997), a multidisciplinary approach is essential in treatment and management [(2)] .
Primary exenterative surgery was the traditional approach for locally advanced disease, which necessitated colostomy and/or urinary diversion with debilitating morbidity and mortality and a poor quality of life for patients.

Initial studies by Boronow et al. (1987) explored the efficacy of a combined radiation-surgical approach with encouraging results obtained from a sample of 48 treated cases (37 primary cases and 11 cases of recurrent disease). This suggested that a combined therapeutic approach of radiotherapy and surgery as opposed to exenterative surgery alone, could lead to a high probability of bladder and/or rectal preservation, low primary mortality, low treatment morbidity with very good cancer control[(11)].

Other authors such as Hruby et al. (2000) in Australia advocated for concurrent neo-adjuvant chemo-radiation with planned surgery if any residual disease should become resectable. This was proposed as a way to achieve maximum benefit in unresectable disease as opposed to surgery alone [(7)].

Based on these trials and other independent studies extrapolated from cervical cancer the Gynecological Oncology Group (GOG) protocol 101 studied cisplatin plus 5-fluorouracil chemo-radiation for the preoperative treatment of 71 patients with locally-advanced squamous cell carcinoma of the vulva which was not amenable to standard surgical resection. The intention was to evaluate prospectively the efficacy of chemo-radiotherapy in reducing the extent of surgical morbidity with acceptable toxicities of treatment. [(12)] Of these patients, 46.5% had no visible vulvar cancer at the time of planned surgery and 53.5% had gross residual cancer at the time of operation.

Thirteen percent of the latter patients with gross residual cancer had positive resection margins and underwent further radiation therapy to the vulva.

Using this strategy of preoperative, split-course, twice-daily radiation combined with cisplatin plus 5-fluorouracil chemotherapy, only two of the 71 patients had residual unresectable disease.

In only three patients was it not possible to preserve urinary and/or gastrointestinal continence.

The toxicity profile was acceptable, with acute cutaneous reactions to chemo-radiotherapy and surgical wound complications being the most common adverse effects.

A follow-up Phase Two trial Gynecological Oncology Group (GOG) 205 was initiated which specified cisplatin 40 mg/m^2 (to max dose 70 mg) weekly and concurrent to radiation therapy; this approach was borrowed from cervical cancer studies[(13)].

Phase Two evaluated 58 patients of whom 40 (69%) completed the study treatment. There were 37 patients with a complete clinical response (37/58; 64%). Among these women there were 34 who underwent surgical biopsy and 29 (78%) who also had a complete pathological response.

The common adverse effects included leukopenia, pain, radiation dermatitis and metabolic changes.

This Phase Two study eliminated a planned treatment break. It delivered a higher total dose of radiation (20% escalation in dose over GOG protocol 101) to the primary tumour with an impressive outcome: the findings suggest that neo-adjuvant chemo-radiation for unresectable locally advanced vulva carcinoma should be the standard of care followed by surgical excision of residual disease if possible [13].

Studies by Watkins et al. (1987) focused on reactions presenting in the head and neck and the findings suggested that HIV positive patients may have an enhanced oral mucosal radiosensitivity and may develop severe oral mucosal reactions at a lower dose than HIV negative patients. This could influence the completion of treatment by patients judged capable of tolerating a radical course of radiotherapy: this has however not been reported in literature on vulva cancer as far as our literature search can establish [14].

A clinico-pathological review of five cases of HIV infected patients with vulva cancer is reported by Sekowski et al. (2008). Their review covers cases from Polokwane, South Africa and describes responses to radiotherapy alone and one case of concomitant chemo-radiation with good responses and acceptable toxicity [15].

Rogers et al. (2009) reported on a retrospective study of 50 women treated with chemo-radiation for advanced vulva cancer during the period 1982 to 2001. Fourteen (28%) of the women had a complete response while 29 (58%) had a partial response. Of these, seven women underwent post-radiation surgery with a significantly better survival outcome. HIV sero-positivity and response to therapy in these patients were not discussed in this study [16] .

To the best of the writer's knowledge, it appears that except for a few isolated case reports, there have been few studies of the management of locally advanced vulva cancer in a background setting of HIV infection, using radiotherapy with or without sequential or concomitant chemotherapy. Certainly, this issue has never been studied sufficiently to provide a specific treatment model tailored for Sub-Saharan Africa and parts of the developing world with similar challenges.

At best, studies done on the treatment of HIV infected patients with primary cervical and anal cancers have been extrapolated to establish guidelines for the treatment of vulva carcinomas regardless of the patients' HIV status.

A review of trends in completion of pelvic radiotherapy in HIV positive patients

As Highly Active Antiretroviral Therapy (HAART) became widely available there have been dramatic decreases in HIV mortality. Concurrently, the incidence of Non-Aids Defining Cancers (NADCs) has increased as people with chronic HIV infection survive longer and become older [4,6,17] . Thus, the spectrum of NADCs has expanded as the size of the HIV positive population has increased. HIV positive patients with pelvic cancer have generally been reported to have a poorer outcome than HIV negative patients and typically have more advanced cancers at presentation, relapses, and worse therapeutic response. This finding was initially reported by Agarwal et al. in the case of patients who were not on antiretroviral therapy to control the infection [17] .

In studies of cervical cancer, Gichangi et al. (2005) reported a positive association between HIV infection and an increased risk radiation-related toxicity; this would lead to unplanned treatment interruptions and a higher probability of pelvic treatment failure with residual disease. It should be noted that this study did not indicate whether these patients were on antiretroviral therapy [19].

Lomalisa et al. (2000) conducted a retrospective review of 60 HIV positive and 776 HIV negative patients with invasive cervical cancer, with the finding that on average, HIV positive patients presented with invasive cervical cancer almost ten years earlier than HIV negative patients. This did not affect the extent of disease at presentation nor was there an associated increased incidence of cervical cancer [20]

These findings were consistent with Moodley et al. (2005) who conducted studies in Kwa-Zulu Natal on the prevalence and outcomes of treatment, arguing that the increased morbidity and mortality in HIV positive patients was due to other competing conditions associated with HIV infection [8] .

A similar study was conducted by Simonds et al. (2012) on HIV positive patients with cervical cancer receiving chemo-radiotherapy. It found that good medical care of HIV positive patients with antiretroviral medication can enable those patients to complete treatment for locally advanced cervical cancer as well as the immune-competent patients [21]. The study stressed that it was important for those patients to complete radiotherapy.

It can be therefore concluded that there is insufficient data on vulva cancer in the presence of HIV co-infection: this is primarily due to the rarity of the disease and changing trends with the introduction of anti-retroviral therapy, partly as a consequence of this, there is no evidence to suggest that the management of vulva cancer in sero-positive and sero-negative patients should not be managed in the same way.

Chapter 2: Research Design and Methodology

Introduction

Study Aims and Objectives

This study gives a retrospective review of patients who commenced radical treatment for local vulva carcinoma using radiotherapy with or without chemotherapy, either concomitant or sequentially as per the FIGO definitions (Stage I-III). It describes the various complications in each group of patients and specifically examines how each group appears to relate to possible aggravating factors such as HIV sero-positivity.

The study also aims to explore any need for adjustments in future protocols and if necessary it suggests areas for more detailed examination in any subsequent prospective study.

It reviews patient folders and records sourced from the Division of Radiation Oncology, Tygerberg Academic Hospital, Cape Town, South Africa after approval by the Human Research Ethics Committee of the University of Stellenbosch and the Western Cape provincial department of Health through the Tygerberg Hospital administration.

Eligibility criteria are:

- Cytologically and/or histologically confirmed primary cancer of the vulva.
- Locally advanced vulva cancer (Stages I-III).
- Treatment with radical intent.
- Patients treated between 1st January 2007 and 31st December 2012.

One exclusion criterion:

- Previous therapeutic irradiation to the pelvis.

The study reviews patients who met the above-mentioned criteria and who were treated between January 1, 2007 and December 31, 2012. Patients are grouped according to: HIV status; clinical, demographic and disease characteristics; types of chemotherapy and surgery when utilized; treatment time to completion; and, total dose of radiotherapy in two Gray equivalents. The study also records the reasons why patients either failed to complete their treatment as prescribed or had it delayed.

Responses are assessed by the clinical examination notes as per the new response evaluation criteria in solid tumours: Revised (RECIST) guideline (version 1.1) [22].

HIV positivity was defined as positivity of ELISA laboratory testing of blood samples during the routine pre-intervention work-up. The presentation of the data is followed by a detailed discussion of the findings and where possible, comparison to the results derived from similar data collected elsewhere.

Data Capturing and safety

All data were captured in Excel, rendered anonymous on chart abstraction, and were handled and stored in a password secure computer.

Data were analysed in Statistica version 10 (2012) with the help of J. Harvey at the Centre for Statistical Consultation, University of Stellenbosch.

The potential risk of loss of confidentiality was dealt with by using a study number for each patient, with grouped patient reporting and password protection. Only the principal investigator has the recourse to link the patient records to the study numbers.

This was a minimal risk study and justified the use of retrospective data without informed consent. Therefore, a waiver of informed consent was requested and was duly granted by the University of Stellenbosch Health Research and Ethics Committee.

Descriptive data analysis was utilized.

Chapter 3: RESULTS

In total, records of 68 patients with vulva cancer were identified. Of these, 25 patients met the inclusion criteria, notably the criterion of having locally advanced vulva cancer (Stage I-III) and the criterion of deemed to have a potential benefit from radiotherapy with or without chemotherapy.

Amongst ineligible patients, one had rhabdomyosarcoma with lung metastases and the remainder were treated palliatively for advanced disease.

Of the 25 patients treated radically, seven (28%) were HIV positive and 18 (72%) were HIV negative.

The median age at presentation was 58 years for the sero-negative women and 39 years for sero-positive women, with a range of 36 to 89 years. Most women were of mixed race, representing 56% of the total patients, 32% were black and 12% were white. This is representative of the local population demographics.

List of Tables

Table 1

HIV- status	Positive n = 7	%	Negative n = 18	%
Median age				
At Diagnosis (years)	39		58	
Range (90th centiles)	30-46		38-89	
Ethnic group				
Mixed race	2	29	12	66
Black	5	71	3	17
White	0	0	3	17
ECOG Performance Status				
0	0	0	3	17
1	2	29	11	61
2	5	72	4	22
3	0	0	0	0
4	0	0	0	0
FIGO Stage Grouping				
0 Tis N0 M0	0	0	0	0
I: T1 N0 M0	0	0	0	0
IA: T1a N0 M0	0	0	0	0
IB: T1b N0 M0	0	0	7	39
II: T2 N0 M0	1	14	5	28
IIIA: T1, T2 N1a, N1b M0	3	43	1	6
IIIB: T1, T2 N2a, N2b M0	1	14	1	6
IIIC: T1, T2 N2c M0	2	29	4	22
IVA: T1, T2 N3 M0	0	0	0	0
T3 Any N M0	0	0	0	0

Table 2

HIV- status	Positive		Negative	
	n = 7	%	n = 18	%
Smoking				
Current	0	0	8	44
Never	3	43	1	6
Former	3	43	2	11
Unknown	1	14	7	39
Upfront Tumour Surgery				
Yes	7	100	16	89
No	0	0	2	11

Table 3

HIV- status	Positive n =7	%	Negative n = 18	%
Treatment Given				
Adjuvant RT	4	57	10	55
Adjuvant CRT	3	43	6	33
Definitive RT	0	0	1	6
Definitive CRT	0	0	1	6
Treatment interruptions				
Yes	2	29	2	11
No	5	71	16	89
Mean Treatment Time				
OTT (Weeks)	7		6	
Gaps (Days)	2		0.06	
Total Radiotherapy Dose				
EQD2 (Grays)	52		49	

HIV- status	Positive n =7	%	Negative n = 18	%
Tumour Failure				
Yes	1	14	4	22
No	6	86	14	78

Table 1: Acute adverse effects in HIV Positive patients

	Acute adverse effect				
Acute adverse effect Grading	0	1	2	3	4
Neutropenia	6	0	1	0	0
Thrombocytopenia	6	1	0	0	0
Anemia	5	0	2	0	0
Gastrointestinal Nausea and Vomiting	0	5	2		
Urinary Bladder	0	5	2	0	0
Nephrotoxicity	6	1	0	0	0
Neurotoxicity	6	1	0	0	0
Rectum	0	3	4	0	0
Cutaneous/ Skin	0	3	1	3	0

Table 2: Acute adverse effects in HIV Negative patients

	Acute adverse effect				
Acute adverse effect Grading	0	1	2	3	4
Neutropenia	17	1	0	0	0
Thrombocytopenia	18	0	0	0	0
Anemia	14	4	0	0	0
Gastrointestinal Nausea and Vomiting	0	11	7	0	0
Urinary Bladder	1	12	5	0	0
Nephrotoxicity	15	3	0	0	0
Neurotoxicity	18	0	0	0	0
Rectum	1	12	5	0	0
Cutaneous/ Skin	0	8	9	1	

Data analysis

Of the HIV positive group, 71% were black and 29% were of mixed race. In the HIV negative group 16% were black, 67% of the patients were of mixed race and 16 % were white.

On the issue of performance status using the Eastern Cooperative Oncology Group (ECOG) grading, 28% of HIV positive patients had a performance status of 1 and 71% had a performance status of 2. In the case of sero-negative patients, 16 % had a performance status of 0; 61% a status of 1 and 22% a performance status of 2.

In the sero-positive subgroup, 86% of patients presented with at least stage 3 disease while only 34% of sero-negative patients presented with stage 3 disease

All sero-positive (100%) patients had upfront surgery. Of these, 57% had adjuvant radiotherapy alone and 43% had adjuvant concurrent chemo-radiation. Two patients (29%) had treatment interruptions due to severe acute skin reactions with continuous vulva chemo-radiation and a treatment break was permitted to allow for healing which increased the mean treatment time to 7.29 weeks.

The mean total radiotherapy dose in equivalent 2 Gray per fraction (EQD2) was 51.78 Gy (range 44.25 Gy to 61.95 Gy).

Following chemo-radiotherapy, six (86%) sero-positive patients had no visible cancer twelve weeks after treatment. One HIV positive 36 year-old patient with stage 3c cancer had residual disease confirmed histologically and was referred for further salvage surgery with complete excision of the tumour and negative nodal disease.

A total of 88% of the sero-negative patients received upfront surgery. Two patients (11%) did not have upfront surgery; one was a 58 year-old patient who presented with stage 3c locally advanced vulva cancer. She received 45 Grays in 25 fractions with a boost dose of 12.6Gy/7 fractions and four cycles of weekly concurrent chemo-radiation; she showed poor response to treatment and persistent disease twelve weeks after completing treatment. She was later palliated with a urinary diversion and a colostomy.
A second sero-negative patient with a performance status of 2 who had been on PTB therapy and had significant weight loss also presenting with stage 3c disease, received 40Gy in 15 fractions. She was found to have lung metastases upon work-up for surgical resection of the primary tumour. It is possible that the patient had metastatic disease from the outset.

A third sero-negative 63 year-old patient presented with locally advanced vulva carcinoma with a previous history of a cerebro-vascular accident two years previously; she was diabetic, hypertensive with a right big toe amputation secondary to vascular disease. She also had a 30 pack-year smoking history. The patient was treated with external beam therapy 45Gy in 25 fractions and a boost dose of 21.6 Gy/12 fractions without concurrent chemotherapy with residual disease which was later surgically excised.

The mean treatment time for the sero-negative patients was 6.11 weeks (Range: 3 to 7 weeks) and the total treatment dose in 2 gray equivalent (EQD2) was 49.29 Gy.

Severe myelo-suppression during treatment was absent. Three patients developed moist desquamation during chemo-radiation therapy and had their treatments delayed. Overall, 25 patients completed the prescribed treatment plan and were evaluable for response (see Tables). Toxicity was acceptable for stage and location of disease.

Co-morbid chronic conditions and opportunistic infections were also noted. In the HIV positive group, one patient was on treatment for Type 2 Diabetes Mellitus, another for pulmonary tuberculosis while another one was being treated for hypertension.

In the HIV negative subgroup, a total of eleven patients had been on treatment for hypertension including one who had suffered a cerebro-vascular accident two years earlier; all had their blood pressure well controlled.

Three patients had been previously treated for pulmonary tuberculosis and another was on Type 2 Diabetes Mellitus treatment.

One should note that these patients were medically stabilized before and during treatment to optimize the treatment outcome.

Chapter 4:

Discussion

Accelerating the increase of cancer in developing countries has been the HIV/AIDS pandemic the epicenter of which is Sub-Saharan Africa, where close to 70% of the world's HIV positive population lives only exacerbating this situation.

It is critical to evaluate current treatment options for vulva cancer and to develop future options appropriate to the diseases seen in the background of HIV infection and competing comorbidities.

Vulva cancer is a rare gynecological malignancy which carries a heavy burden of morbidity. Its treatment is challenging, especially given the frequent background of HIV infection which often presents with competing comorbidities and conditions.

A critical concern in a resource limited environment is that excess toxicity does not just translate to morbidity as it does in resource-replete care settings, but can easily lead to mortality.

In our study, patients were offered the same treatments for their disease regardless of their HIV status and good treatment compliance was achieved.

One notable issue was that most of the sero-positive patients were black (71%) and presented at a significantly younger age than the sero-negative patients. This latter observation is consistent with the findings of Moodley et al. (2005) who found that these sero-positive patients presented, on average, at least ten years younger than sero-negative ones. This suggests that the sero-positive patients were infected at a younger age which is consistent with the South African HIV/AIDS prevalence and demographic data. This suggestion may need to be investigated further to introduce interventions that could mitigate against this burden [(8)].

Chemotherapy was well tolerated in both the sero-positive and sero-negative subgroups; this was mostly due to the prudent selection process whereby patients only received concurrent chemo-radiation if they had a good performance status and organ function and were already on antiretroviral therapy with CD4 counts of over 200 cells per cubic millimeter as per the Western Cape guidelines.

Cutaneous toxicity was more apparent in the HIV positive subgroup but the mechanisms which resulted in these reactions are not clear.

As per the findings of the Gynecologic Oncology Group (GOG) trials and related anal cancer studies, chemo-radiation was observed to have better outcomes than radiation therapy alone [12,13].

Concurrent chemotherapy could possibly achieve the same local control rate at a lower toxicity than a treatment plan employing higher total doses of radiation; this has been extrapolated from Ca cervix studies [16].

When used in the treatment of squamous cell carcinoma of the anus, cisplatin plus 5-fluorouracil chemo-radiation yielded results superior to radiation therapy alone, and local control rates were comparable to 5-fluorouracil and mitomycin-C, suggesting that chemo-radiation is superior to radiotherapy alone [23,24] .

There is evidence that the prolongation of overall treatment time may be counterproductive to overall outcome; this is based on the radiobiology studies of head and neck squamous cell carcinoma. Thus, any extending, interruption or postponement of treatment should only be allowed following the development of severe acute skin reactions, and such delay should be for the shortest duration possible as described by Bese et al [25].

In the Tygerberg Hospital, the practice was to administer weekly cisplatin at 40mg/m^2 , to a maximum dose of 70mg weekly, to patients who were carefully judged to be capable of tolerating therapy. There were no significant differences between the two groups treated with chemo-radiation, concerning increased toxicity such as neutropenic sepsis, acute renal failure and severe gastroenteritis.

Treatment gaps were minimized and planned breaks were avoided.

The data reported on, in this thesis, were collected as part of routine clinical management. The current medical literature on vulva cancer still leaves unresolved the issues of whether concurrent chemotherapy improves treatment results and if so, whether there are any significant differences in the outcomes for sero-positive and sero-negative patients.

These findings call for the need to create a research and care infrastructure sufficient to meet this challenge of providing effective treatment in resource-constrained settings where vulva cancer remains an under-recognized and under-resourced cause of morbidity and mortality. There is also a need for a prudent goal-directed management strategy.

Strengths and Limitations

This is a retrospective study with a limitation of non-uniform reporting of treatment side effects and in some cases there are missing data such as follow-up CD4 Counts.

The boost dose and response of the vulva epithelial carcinoma to radiation therapy are not clearly identified as patients received various boost doses to the tumour.

New radiotherapy techniques such as Intensity Modulated Radiation Therapy (IMRT) and Image Guided Radiation Therapy (IGRT) have evolved and if these techniques are accessible then they could change the toxicity profile of treatment of locally advanced vulva cancer in both subsets of patients.

In 2009, the International Federation of Gynecology and Obstetrics (FIGO)[26] reviewed the staging system for carcinoma of the vulva; this did not affect our study to any great extent as it focused on locally advanced disease.

The quality of life of patients was not evaluated in this retrospective study.

The follow-up time was too brief and the number of patients was too small to allow for an in-depth analysis of survival or patterns of failure and to make a comparison between HIV positive and negative patients.

Recommendations

Future prospective trials should attempt to identify the optimum sequence of chemo-radiotherapy and surgery for the treatment of locally-advanced carcinoma of the vulva in patients presenting with HIV. The objective would be define, better, the optimal combination of radiation and chemotherapy doses that could lead to optimal local control and function preservation for that specific group of patients.

The rarity of vulva cancer calls for prospective randomized clinical trials to be conducted in the setting of multi-centre, institutional and even international collaboration to study the disease further.

Chapter 5

Conclusion

The number of patients in this study was relatively small. Also, there is relative dearth in literature addressing the treatment outcomes for HIV positive patients with vulva cancer. However, the results of the study provide no reason to suggest that the approach towards treatment of HIV positive patients stabilized on HAART should differ from their HIV negative counterparts.

Treatment options in the resource-constrained setting of the Tygerberg Hospital are limited, both by financial constraints as well as by the need to avoid toxicity, which is associated with high morbidity.

In the developed world, vulva carcinoma is generally encountered in older patients and at an earlier stage than the patients reported on in this study. The findings of this study have demonstrated acceptable and comparable treatment outcomes for the disease stages observed, with both objective responses and clinical benefit observed in a resource-limited care setting.

This conclusion could be used as the basis for a reasonable baseline model in the development of policies when setting up new radiotherapy services in resource-constrained settings. It could incentivize the further refinement of local policies and possibly clinical care protocols to improve outcomes in the developing world, which faces the challenges of scarce resources, with younger patients typically presenting at a more advanced stage of the disease. Also, as the study has shown, many patients with vulva cancer in the developing world also present with HIV infection which could now be considered to be a chronic long-term disease when treated with anti-retroviral therapy; as a result, this type of patient typically has a longer life-expectancy than in the past and this needs to be taken into account when prescribing treatment.

Radiotherapy remains central to the treatment of vulva cancer and in view of its importance, further prospective randomized clinical trials are needed to identify the optimal radiation techniques and dosing. Those trials could examine possible novel chemotherapy agents, doses, newer anti-retrovirals and their optimization in terms of a concomitant or sequential approach in combating vulva cancer.

Radiotherapy should be avoided in those instances of early vulva cancer which can be surgically managed.

The data obtained during this study should promote a better understanding of the disease processes in HIV and Cancer at biological and clinical level , including treatment processes, objective quality of life assessments that will contribute to the design of future prospective clinical trials in this patient population.

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Approved with Stipulations
New Application

08-Mar-2013
OPAKAS, Jesse Elungat

Ethics Refernce #: S13/02/024

Title: **Radiotherapy in the management of carcinoma of the Vulva in HIV positive and negative patients and factors influencing the completion of treatment : An institutional experience.**

Dear Dr Jesse OPAKAS,

The **New Application** received on **13-Feb-2013**, was reviewed by members of **Health Research Ethics Committee 2** via Expedited review procedures on **26-Feb-2013**.

Please note the following information about your approved research protocol:

Protocol Approval Period: **08-Mar-2013 -08-Mar-2014**

The Stipulations of your ethics approval are as follows:
1. Synopsis/Protocol:
The research question is not phrased as a question but an aim; rephrase or change to "aim".

2. General: If the intention is to obtain a waiver of individual informed consent, it should be requested and motivated either in the protocol or the covering letter.

3. No names or other identifiers tshould appear on data capture forms; use study numbers.

Please remember to use your **protocol number** (**S13/02/024**) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:
Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired.
The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.
Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.
For standard HREC forms and documents please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at 0219389207.

Included Documents:
Supervisors declaration

Supervisors declaration
Synopsis
cv jesse
Application form
Investigators declaration
cv Hannah
Protocol
CV Gerald
Checklist

Sincerely,

Mertrude Davids
HREC Coordinator
Health Research Ethics Committee 2

Western Cape Government
Health

Tygerberg Hospital and
Mitchells Plain & Tygerberg Oral Health Centres
ENQUIRIES : Dr M Mukosi
TELEPHONE: 021 938-5966

ETHICS NO: S12/02/024

Radiotherapy in the management of carcinoma of the Vulva in HIV positive and negative patients and factors influencing the completion of treatment: An institutional experience.

Dear Dr Jesse Elungat Opakas

PERMISSION TO ACCESS TYGERBERG HOSPITAL PATIENT FOLDERS

Permission is hereby granted to access patient folders for the above-mentioned research here at Tygerberg Hospital.

Kind regards.

DR M MUKOSI
MANAGER: MEDICAL SERVICES

Date: 11th April 2013

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