A Retrospective Review of Chemo-Radiation in Anal Carcinoma

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Radiation Oncology

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DECLARATION

I, Yael Mark, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Radiation Oncology in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

……

Yael Mark

Signed at Johannesburg on the 06 day of November 2017.

Dedication

Dedicated to my husband Lior Schwartz,

for his tremendous support, wisdom and love.

You have been my strength through both the best and the worst of times.

1 ABSTRACT

Introduction

In South Africa, in 2007 there were 139 new cases of anal cancer. This malignancy shows a female predominance and is associated with several risk factors including smoking and infection with Human Immunodeficiency Virus and Human Papilloma Virus. The standard of care for the treatment of localised anal cancer is concurrent chemo-radiation.

The purpose of this retrospective study was to describe the patient characteristics and the treatment toxicity of chemo-radiation in patients with localized squamous cell anal cancer. A further aim was to describe the treatment outcomes.

Materials and Methods

A total of 64 patients with anal carcinoma, who presented to the department of radiation oncology at Charlotte Maxeke Johannesburg Academic Hospital between 2006 and 2012, were included in the study.

Only squamous cell carcinoma histological subtypes of anal carcinoma qualified for inclusion in the study. Patients with metastatic anal carcinoma were excluded from the study. Data about patient and tumour characteristics, treatment toxicities and treatment response were captured in a proforma sheet.

Once data collection was complete, statistical analysis using the SAS software package was carried out.

Results

The median age at first consultation was 48 years. Sixty-seven per cent of the study group was female. Sixty-eight per cent of patients presented with advanced tumours (T3/T4) and 60% of the patients had node positive disease. Fifty per cent of patients were Human Immunodeficiency Virus positive with a median cluster of differentiation 4 (CD4) cell count of 250 cells/mm^3.

The predominant adverse effects were skin toxicity in 81% of patients and pain in 75% of patients.

Thirty-eight per cent of patients who followed-up after treatment completion experienced a tumour recurrence at a median duration of 303 days after treatment. The progression free survival estimates at 12 months were 85% and at 24 months were 46%.

Conclusion

The patient population presenting to Charlotte Maxeke Johannesburg Academic Hospital radiation oncology department was predominantly comprised of middle aged females with advanced stages of anal carcinoma. Approximately half of these patients were Human Immunodeficiency Virus positive.

Skin toxicity and pain were the commonest adverse effects observed.

There was a high recurrence rate noted, likely due to the fact that most patients presented with advanced disease.

2 ACKNOWLEDGEMENTS

I would like to thank all the people who assisted me in completing my research report.

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4 ABBREVIATIONS

AIDS- acquired immune deficiency syndrome

CD4- cluster of differentiation 4

CMJAH- Charlotte Maxeke Johannesburg Academic Hospital

ECOG- eastern cooperative oncology group

GIT- gastro-intestinal tract

Gy- Gray

HAART- highly active antiretroviral therapy

HIV- human immunodeficiency virus

HPV- human papilloma virus

RECIST- response evaluation criteria in solid tumours

RTOG-radiation therapy oncology group

TNM- tumour nodes metastases

5FU- 5 fluorouracil

SEER- Surveillance, Epidemiology, and End Results

ARV- antiretroviral

CALGB- Cancer and Leukaemia Group B

AJCC- American Joint Committee on Cancer

CT scan- computed tomography scan

L5/S1- lumbar vertebral body 5/sacral vertebral body 1 interspace

WITS- Witwatersrand

USA- United States of America

CEO- Chief Executive Officer

GIT- Gastro-intestinal tract

5 INTRODUCTION

5.1 BURDEN OF DISEASE

In South-Africa in 2007, there were 62 new cases of anal cancer in men, constituting a lifetime risk of 1/2479 people and there were 77 new cases of anal cancer in women, constituting a lifetime risk of 1/2389 people.[1]

The majority of anal cancers are squamous cell carcinomas (85-90%), while the remainder are adenocarcinomas or other rare variants.[2]

5.2 RISK FACTORS

Risk factors associated with anal cancer are infection with HPV -particularly subtypes 16 and 18, female gender, sexual promiscuity, cigarette smoking, sexually transmitted infections, genital warts, receptive anal intercourse and infection with HIV- especially if the CD4 count is <200 cells/mm^3. The risk of developing anal cancer in men with HIV is reported to be 37.9 times higher than in non-HIV infected males, and 6.8 times higher in HIV infected women, versus HIV negative females.[3,4]

5.3 NATURAL HISTORY

Anal cancer is a slowly progressing disease that begins as a superficial mass. It is predominantly a loco-regional disease, although distant metastasis occurs in 20% of cases.[5]

Although anal cancer causes early symptoms and is easily accessible to clinical examination, patients often present with advanced disease.[6]

5.4 STAGING

Anal cancer is staged according to the AJCC 7th edition TNM staging criteria (appendix 1).

5.5 Prognosis

Factors that have been identified to portend for a poor prognosis in anal cancer are a tumour diameter >5cm, node positive disease and male gender. The response of the tumour to chemo-radiotherapy has also been shown to have prognostic significance.[7,8]

Despite the frequent late presentation of anal cancer, after treatment with combined concomitant chemo-radiation the progression free and overall survival rates are high. The progression free survival rate at three years, for advanced anal cancers is 40-68%.[17] The five year overall survival is 84% and the 8 year overall survival is 77%. The colostomy free survival at 5 and 8 years is 71% and 67% respectively.[9]

5.6 Management

The management of anal cancer has evolved greatly over the years. Treatment has changed from abdomino-perineal resection, which was considered the standard of care before 1980, to conservative therapy with concurrent chemo-radiation.[13] In 1973 Nigro et al. introduced a schedule of 5-fluorouracil (5FU) and mitomycin c chemotherapy, combined with radiotherapy to treat anal cancer. The use of chemo-radiotherapy has since been adopted as the standard of care and is considered “a model for organ conservative treatment”.[8]

There is concern over giving concurrent chemo-radiotherapy in HIV positive patients as there have been reports of worse toxicities and poorer clinical

outcomes. The severe toxicity reactions may necessitate treatment breaks and chemotherapy or radiotherapy dose adjustments.[3,10]

Studies have shown conflicting results of treatment of anal carcinoma in HIV positive patients with some showing equivalent outcomes to non-HIV infected patients and others showing worse toxicity and outcomes.[3]

The work-flow pertaining to anal carcinoma patients at CMJAH is as follows-

On the initial visit, a history and physical examination are carried out. All relevant investigations are performed, such as blood tests, staging tests and a metastatic work-up. Following this, the patient is booked for a planning CT scan. After the CT scan has been done, fields are placed and treatment is prescribed, based on the results of the history, examination and investigations documented in the patients file.

Although the departmental protocols (see below) are to prescribe concurrent chemo-radiotherapy with mitomycin c and 5FU, modifications are required in certain cases. For example, patients with HIV and a low white cell count, or a low CD4 count may be prescribed cisplatin instead of mitomycin c, or may be prescribed radiotherapy only.

Once field placement and the prescription are complete, the patient is then contacted with a date for verification and treatment initiation.

At CMJAH the population of patients with anal cancer consists of both HIV negative and HIV infected patients. The CMJAH protocol for treating anal carcinoma with concurrent chemo-radiation is as follows-

Chemotherapy consists of 5FU at 400mg/m2 intravenously as a bolus on days 1-4 and 22-25 of radiation, as well as mitomycin c 10mg/m2 intravenous bolus injection on day 1 of radiation.

Radiation therapy consists of three phases. The phase 1 dose is 30Gy in 15 fractions, at 2Gy per fraction. This encompasses the primary tumour, the anus and the regional lymph nodes. The superior field border is the interspace between L5/S1 vertebrae, the inferior field border is the tumour and a 3cm margin, and laterally the field borders are placed on the outer acetabulum, so as to include the pelvic and inguinal lymph nodes.

Phase 2 involves treating the tumour, the anus and any remaining clinically involved lymph nodes with an additional 20Gy in 10 fractions to a total of 50Gy, at 2Gy per fraction. This field may have the same field borders as Phase 1 if there were clinically positive lymph nodes. If the inguinal lymph nodes were negative for metastatic disease, the lateral field borders may be moved medially, to give a 2cm margin on the pelvic brim.

This is then followed by phase 3, a tumour boost of 6-10Gy, which treats only the residual tumour with a 3cm margin. If there is no residual disease after 50Gy (phases 1 and 2), then the boost may be omitted.

There is no scheduled gap in the treatment. If severe toxicity occurs, splits in treatment are introduced at the discretion of the treating oncologist. Thus from start to finish, treatment should take between 5 to 6 weeks, or 35 to 42 days in total, provided no split in treatment is required.

A gap, or a split, increases the overall treatment time and thus may predispose to worse outcomes, as seen in a trial by Graf R, et al.[11] They observed that an overall treatment time in excess of 41 days predisposed to reduced local control in anal cancer. Thus the length of the treatment gap is significant. Oehler C et al noted impaired cancer specific survival with a split of seven days or longer.[12]

5.7 Aim

The aim of the study was to describe the patient characteristics, the acute treatment toxicities and the progression free and overall survival outcomes of the population of patients with squamous cell anal cancer who were accepted for radical treatment with concurrent chemo-radiotherapy at CMJAH from 2006-2012.

6 LITERATURE REVIEW

6.1 PATIENTS CHARACTERISTICS

6.1.1 DEMOGRAPHICS

Age and Gender- in a review of the SEER programme data collected between 1973-2000, Johnson et al found that between 1973-1979 the incidence of anal carcinoma in women was higher, but between 1994-2000, men had a higher incidence. In both genders, the rate of anal carcinoma was highest in patients 65 years and older. The authors attributed the change in the disease gender distribution to the fact that in the USA, HIV rates had increased predominantly in men during that same time period.[4]

Ajani et al analysed the prospective database of the intergroup 98-11 trial, looking for prognostic variables in anal carcinoma. In addition to other prognostic variables, they found male gender to be a poor prognostic factor. Anal cancer was commoner in females, and females comprised 69% of the sample group, but they had better outcomes than their male counterparts.[7]

Gerard et al did a prospective trial to evaluate the long term outcomes of high dose radiotherapy and concomitant fluorouracil. They included 95 HIV negative patients in their evaluation. The median age of patients was 63 year of age. Ninety-one per cent of their study population was female.[9]

A trial looking at concurrent chemo-radiation for anal carcinoma, in HIV positive patients on HAART, found that the median age of patients at diagnosis was 45 years.[3] In another trial which included HIV infected patients with anal carcinoma, the median age of patients at presentation was 38 years.[14]

Thus the literature review of anal carcinoma showed a female predominance, with a younger median age of presentation in HIV positive patients. HIV infected individuals presented with the disease approximately two decades earlier.

6.1.2 HIV STATUS

A trial conducted by Place et al at the University of Texas, looked at the outcomes of a cohort of 23 HIV positive patients with anal carcinoma treated with chemo-radiation. Fourteen of the patients in the group had invasive anal squamous carcinoma, and the remainder had in situ disease. The data was collected retrospectively from records of patients treated between 1980 and 1999.

Those patients treated from 1998 and onwards were all commenced on antiretroviral therapy prior to initiating treatment. Thus the majority of the patients in this study cohort were not on antiretroviral therapy when they were treated. The average CD4 count of patients was 222 cells/mm^3 for those patients with invasive disease, and 200 cells/mm^3 for those with in situ disease.

The authors found that a low CD4 count at diagnosis, without the use of antiretroviral therapy, predicated for a poor prognosis. The one and five year mortality rates were 40% and 80% respectively. They also reported that the patients with AIDS succumbed to complications related to AIDS before succumbing to anal cancer, experienced worse toxicity from treatment and had poorer outcomes. Of the 10 patients who demised, 8 still had persistent local disease but they did not have distant metastases. The authors hypothesised that if antiretroviral therapy had been initiated in all patients prior to starting treatment,

there may have been reduced treatment toxicity and improved therapeutic outcomes.[10]

Cleator et al reported that in their group of 12 HIV positive patients, the median CD4 count was 209 cells/mm^3 at diagnosis and 9/12 patients were on ARV therapy at presentation. The 9 of 12 patients had early disease (T1 and T2) and only one patient had node positive disease. Eleven patients were available for follow-up. At the end of treatment, 9 patients had a complete remission, 1 patient had a partial response but was salvaged with abdomino-perineal resection and 1 patient had disease progression on treatment and died of anal cancer. After a median follow-up at 4.8 years, 4 patients had demised. Two died from the anal cancer, 1 from opportunistic infection and 1 died from treatment complications.[15]

In summary, the literature showed that HIV positive patients who were on antiretroviral therapy had less treatment toxicity and better outcomes than those not on ARVs. In addition, although patients had comorbid HIV, those who presented with early disease had favourable outcomes.

6.1.3 Tumour Characteristics

The presenting tumour stage for the 682 patients in the RTOG-98-11 trial included 27% advanced stage tumours, 5cm or more in size (T3/T4), and 26% had clinically involved lymph nodes.[7]

In the trial by Gerard et al, which included 95 patients, 63% of the study population had tumours that were 4cm or larger in maximal diameter, and only 19% had tumours smaller than 4cm with no metastatic nodal involvement.[9]

Thus it appears that patients presented with a predominance of advanced stage anal carcinoma lesions.

6.2 Toxicities

In a trial looking at outcomes of combined modality treatment for HIV infected patients with squamous cell anal carcinoma, by Edelman et al, the main toxicities experienced during treatment were skin and haematological toxicity, in 8 and 9 out of 17 patients respectively. Their treatment protocol did not include a planned split, and the authors did not report on the frequency of unplanned splits due to toxicity, that may have occurred throughout the treatment course.[14]

A similar trial by Cleator et al, showed skin toxicity to be the most common (92%), followed by GIT toxicity –diarrhoea (83%) and haematological toxicity (50%).[15]

A trial by Tanum et al evaluated toxicity and outcomes of treatment in anal carcinoma treated with chemo-radiotherapy. One hundred and seventeen patients were included in this trial. All patients experienced toxicity but there were no treatment related deaths. The commonest toxicities were dermatitis/mucositis, fatigue and diarrhoea. Forty nine per cent of patients required a split course of treatment due to side effects of treatment.[16]

Thus, the commonest treatment toxicities reported in the literature were dermatitis, diarrhoea and haematological toxicity.

6.3 Outcomes

Ajani et al found that patients with a tumour diameter >5cm, and those with node positive disease had adverse prognostic outcomes, with poorer five year disease

free and overall survival outcomes. The combination of a tumour more than 5cm in size and node positivity had the worst disease free survival- only 30% were disease free at 3 years, compared with 74% of the best group, that is, those with tumours<5cm and node negative disease. Four year overall survival in the node positive and tumour>5cm group was 48%, compared with 81% for the best prognostic factor group.[7]

A systematic review of multiple trials of chemo-radiation in anal carcinoma, by Lim et al showed a 3 year disease free survival of 40-68% in T3 and T4 cancers. The 5 year overall survival rates in the non-randomised studies included in this trial ranged between 67-91%.[17]

In a CALGB trial by Meropol et al, using initial induction chemotherapy with 5-FU and cisplatin, followed by concurrent chemo-radiation with mitomycin c and 5-FU, the 48 month disease free survival rates were 61%. The 48 month overall survival rates were 68%. Patients included in the trial had anal cancer stage T3/T4 and or bulky N2/N3 disease.[19]

Thus TNM stage is an important prognostic factor, with advanced stages being associated with inferior outcomes.

7 METHODS

This was a retrospective study, which included data collected from the files of 64 patients with anal carcinoma, who were accepted for radical chemo-radiation at CMJAH radiation oncology department between 2006 and 2012.

After obtaining ethics clearance from the WITS Human Research Ethics Committee (appendix 6 and 7), the hospital CEO (appendix 8), and the post-graduate committee (appendix 9) data was collected from patient files. The data was collected using a proforma (appendix 2).

Inclusion criteria were as follows, patients were required to have localized disease of the squamous carcinoma histological subtype only.

Data collection centred around gathering information about patient characteristics such as age, gender, HIV status, performance status and risk factors for anal carcinoma. Tumour characteristics relating to the TNM stage were also captured. Treatment related toxicities were graded where possible, grouped into categories and captured for analysis. In cases where patients had presented for post-treatment follow up visits, information relating to outcomes was also collected. Statistical analysis of gathered data was conducted.

The aim of the study was to describe the local South African patient population with anal carcinoma, the treatment they had received, the toxicities they experienced whilst on chemo-radiation and to describe the treatment outcomes. A further aim was to then compare the local data with international data on anal carcinoma in order to assess comparability of the presenting population, tumour

stage at presentation, therapeutic regimens and tolerability as well as treatment outcomes.

7.1 Statistical Methods

Data analysis was carried out using the software package SAS (version 9.3).

The chi-squared test was used to assess the relationships between categorical variables. Fisher's exact test was used for 2 x 2 tables or where the requirements for the chi-squared test could not be met. The strength of the associations was measured by Cramer's V and the phi coefficient respectively.

The relationship between continuous and categorical variables was assessed by the t-test (or ANOVA for more than two categories). Where the data did not meet the assumptions of these tests, a non-parametric alternative, the Wilcoxon rank sum test (or the Kruskal-Wallis test for more than two categories) was used. The strength of the associations was measured by the Cohen's d for parametric tests and the r-value for the non-parametric tests.

8 RESULTS

8.1 PATIENT CHARACTERISTICS

Patients with histological subtypes other than squamous cell carcinoma were excluded from the trial. Patients" who presented with metastatic disease or had disease progression requiring a change to a palliative regimen while awaiting treatment, were also excluded from the trial.

8.1.1 DEMOGRAPHICS

The mean age at first consultation was 48 years, with no significant difference between the mean ages of men (48) and women (49). The distribution of age is shown below.

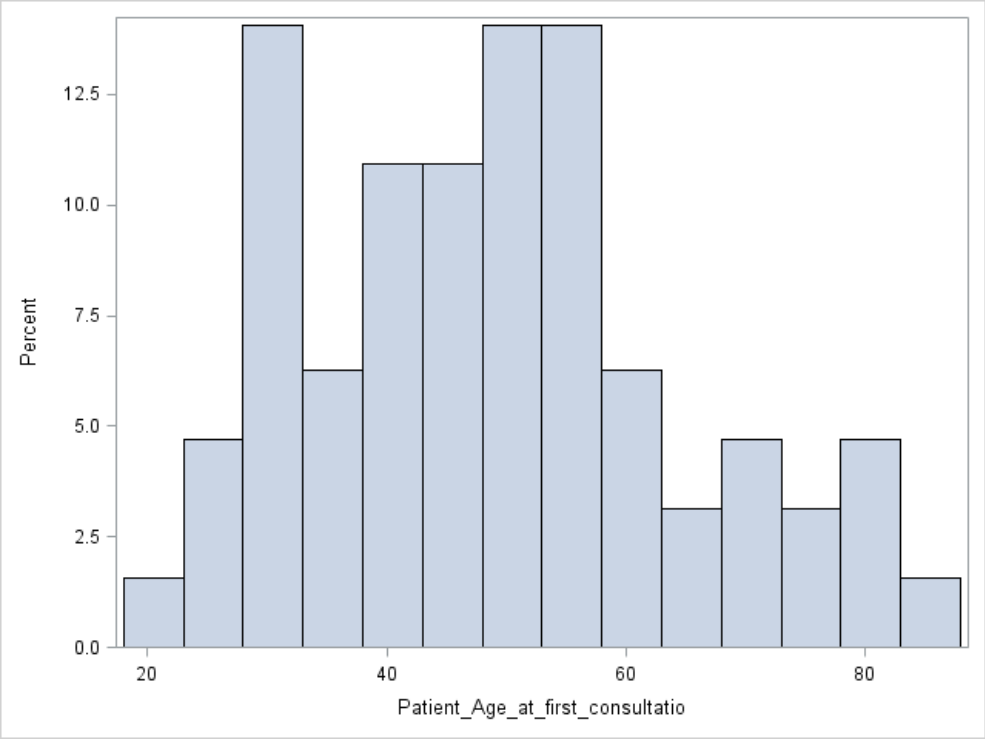

Figure 1: Age at first consultation

Gender: Sixty-seven per cent of the study group was female.

8.1.2 General Characteristics

Performance status:

This was measured using the ECOG scale (appendix 3). Fifty per cent of patients were ECOG1 at presentation, 27% were ECOG2, 9% ECOG3, 8% ECOG0, and the remainder did not have a recorded performance status.

The distribution of the performance status is shown in the graph below.

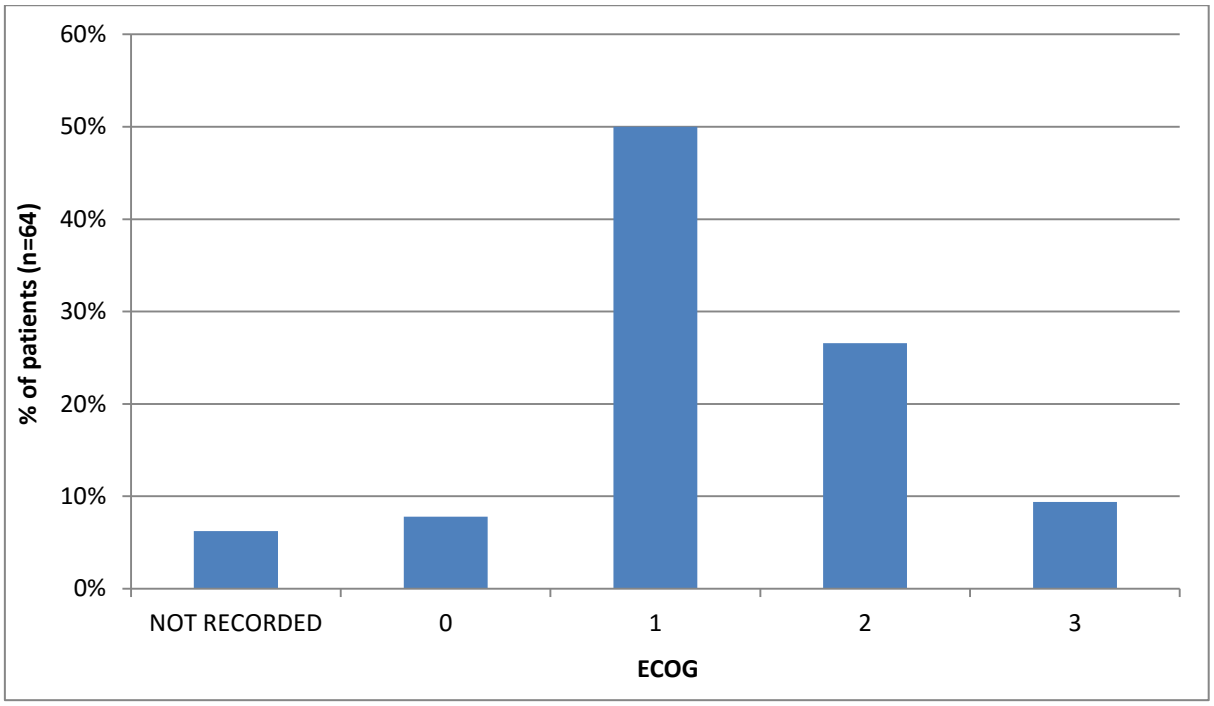

Figure 2: Performance status pre-treatment

Weight and Height at Presentation:

It was not possible to do an analysis of these variables as they were frequently not recorded.

Colostomy Insertion:

Sixty-eight per cent of patients had a colostomy inserted. The majority (95%) were inserted prior to starting treatment. It was not possible to draw a conclusion

regarding anal sphincter preservation rates following treatment completion. This was due to insufficient data recorded on follow-up detailing whether the colostomies had been reversed and what the anal sphincter tone was on per rectal examination following completion of chemo-radiation treatment.

8.1.3 HIV STATUS

Fifty per cent of the patients were HIV-positive, while 28% were HIV-negative. Data regarding HIV status was missing in the remaining 22% of patients.

In the HIV-positive patients:

The median CD4 count was 250 cells/mm^3. Thirty-eight per cent of the patients had CD4 counts <=200 cells/mm^3, while 56% had CD4 counts above 200 cells/mm^3. The distribution of CD4 counts is shown in the graph below.

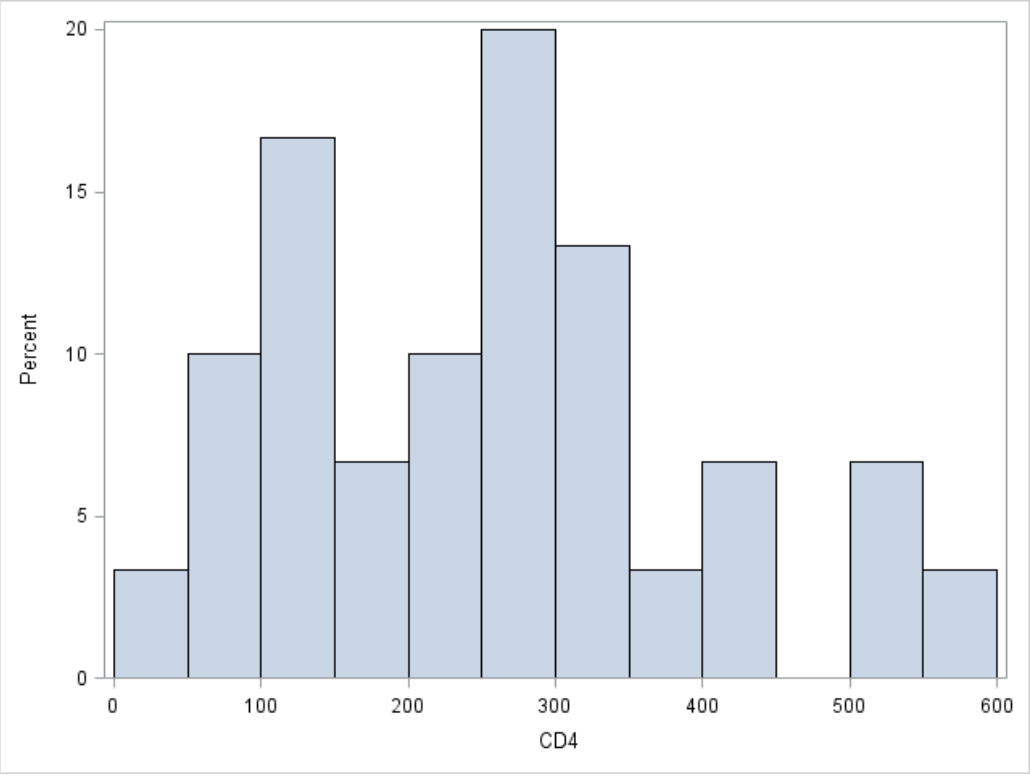

Figure 3: CD4 count pre-treatment

ARV usage:

Seventy-eight per cent of the patients were on ARV's at their first consultation in the department.

Of the 7 patients not on ARV's initially, 4 were sent for ARV initiation after the first consultation, 1 was sent after treatment, and the status of the remaining 2 patients is unknown.

Risk factors for Anal Carcinoma:

The following risk factors were included in the data collection proforma; HIV status, HPV presence on the histology specimen, female gender, history of sexually transmitted infections and genital warts, sexual promiscuity (>10 partners), receptive anal intercourse and cigarette smoking.

It was not possible to do an analysis of the risk factors for anal carcinoma, other than HIV status and gender, due to missing data.

8.1.4 Tumour Characteristics

The TNM staging system was used to stage the tumours (appendix 1).

Prior to starting treatment the median tumour size was 6 cm (range 1-20 cm). The distribution is shown below.

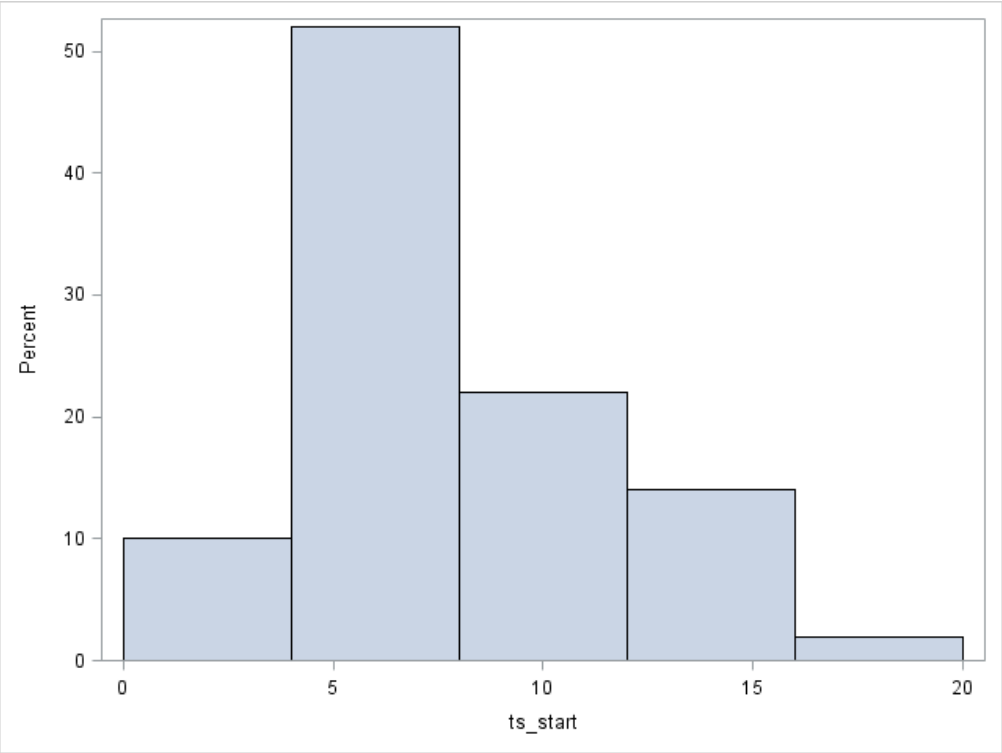

Figure 4: Initial tumour size

In this study, 68% of patients presented with advanced tumours (T3/T4) and 60% presented with node positive disease. Fifty-two per cent of the study group had both node positive and advanced T-stage disease.

There was no significant association noted between age and presenting stage, or between gender and stage at presentation.

There was, however a significant association noted between HIV status and presenting T-stage. The HIV positive group had a higher proportion of T3 tumours, and a lower proportion of T2 tumours, than the HIV negative group. See the graph below for the distribution of HIV status and stage at presentation.

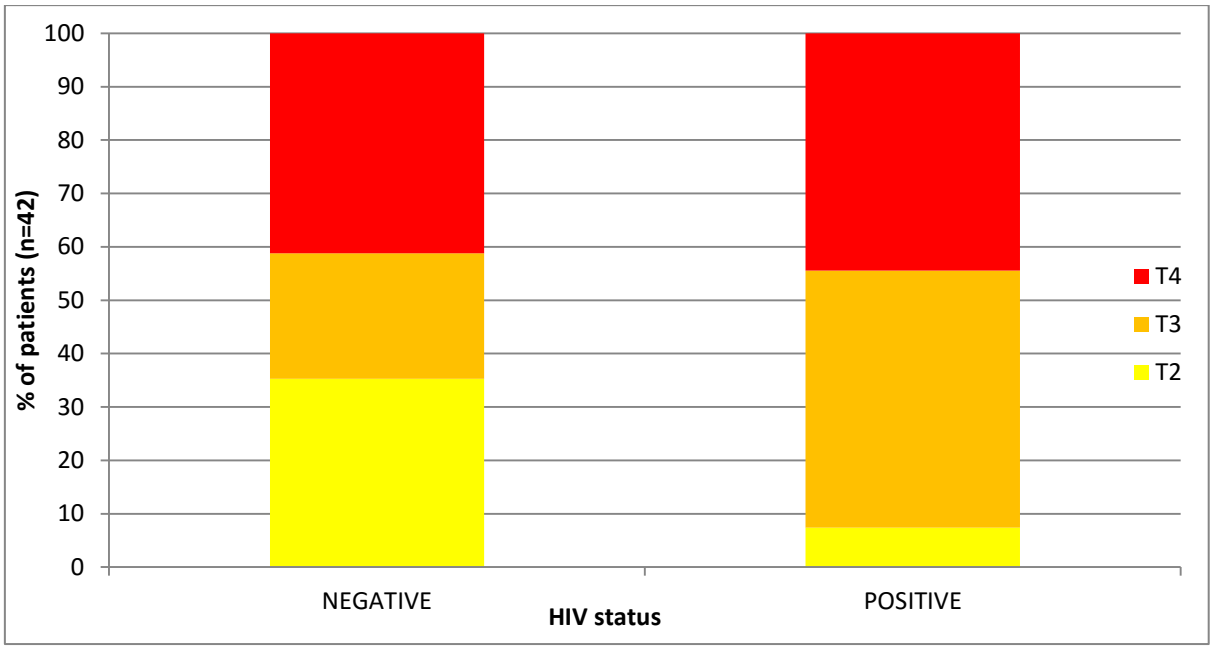

Figure 5: HIV status

There was no significant association noted between HIV status and N-stage.

8.2 Toxicity

Toxicity was graded according to the RTOG acute radiation morbidity scoring criteria (appendix 4). In this study, the commonest toxicity experienced was skin toxicity, in 81% of patients, followed by pain and fatigue in 75% of patients. GIT toxicity was experienced by 32% of patients, urinary toxicity in 26% of patients and haematological toxicity was noted in 12% of patients.

Grade 3 skin toxicity was recorded in 19% of patients and grade 4 skin toxicity occurred in 42% of patients. In cases where it was noted in patient files that there was skin toxicity present, but there was no recorded grade, 'yes' was captured during data collection. See figure 6 below for the distribution of grades of skin toxicity experienced on treatment.

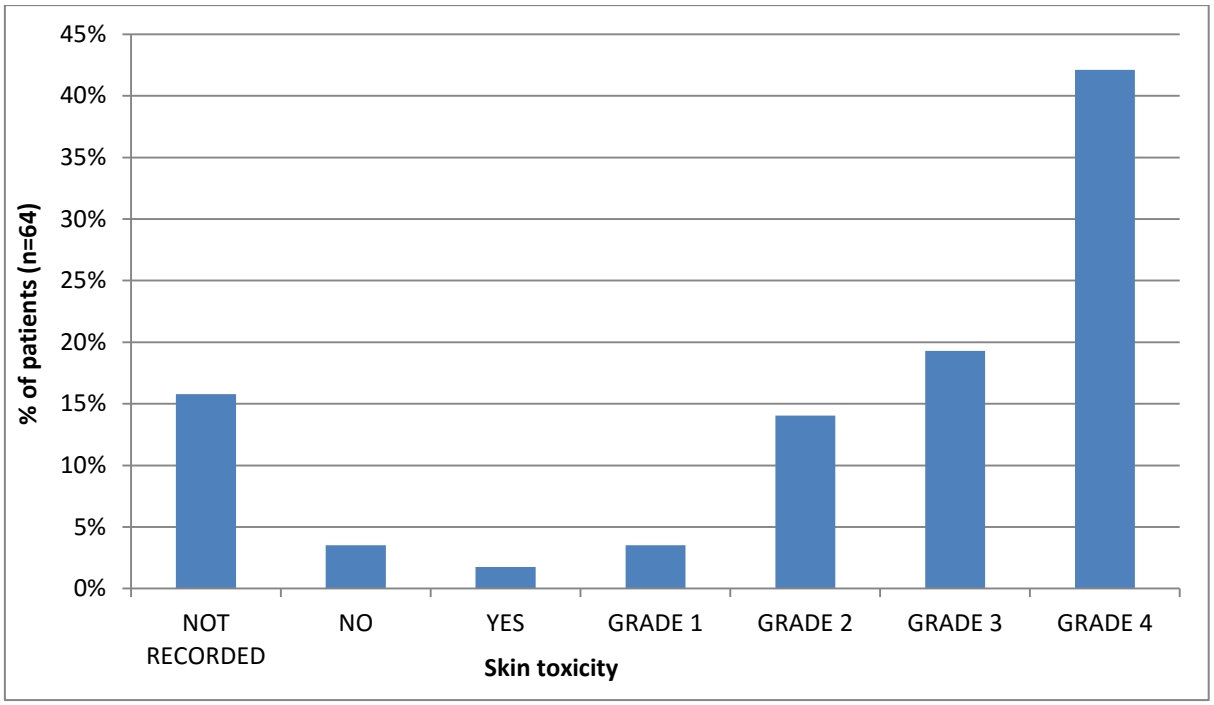

Figure 6: Skin toxicity

There was no significant association noted between HIV status and skin toxicity. Skin toxicity was the predominant cause for the 33% prevalence of treatment splits that occurred.

Most patients (68%) who required a treatment split, had a split of 5 days or less. Forty-seven per cent of the split patients were hospitalised when treatment was split, and 32% were not. The remaining 21% had missing data. The predominant cause for the splitting of treatment was skin toxicity.

8.3 Outcomes

Data regarding treatment related factors which may impact the outcomes, is presented below.

8.3.1 Treatment related factors

8.3.1.1 Delay between first visit and starting treatment:

The median delay was 47 days (range 4-432 days). The distribution of the data is shown below:

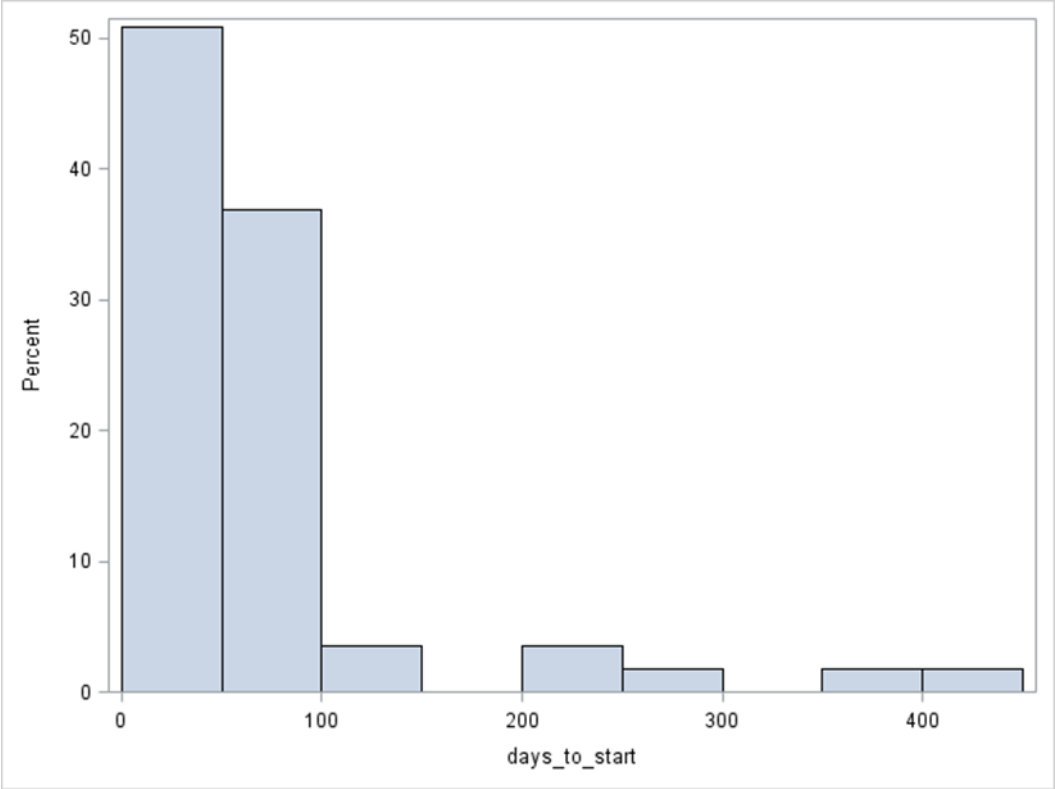

Figure 7: Treatment initiation delay

After the planning CT scan and field placement were performed, the treatment prescriptions were filled out. Six per cent of patients (4 patients) had their prescriptions altered from the normal protocol to receive radiation only, due to electrolyte and other blood test abnormalities such as a low haemoglobin result.

The remaining 94% of patients (60 patients) were prescribed both chemotherapy and radiotherapy. Of those, 54 were to receive concurrent 5FU days 1-4 and 22-25, as well as mitomycin c day 1. Four patients were to receive 5FU and cisplatin and 1 patient was to be given 5FU only on days1-4 and 22-25 and not mitomycin c on day 1. The chemotherapy regimen to be given in 1 patient was not documented. The reasons for adjustments made to the standard chemotherapy

regimen were low white cell counts, low CD4 counts and in one instance, mitomycin c was out of stock.

Out of the 64 patient's initially accepted and prescribed for radical treatment, 11% (7 patients) did not ultimately begin treatment. The reason for this was not recorded in 2 patients. One patient had a low haemoglobin and electrolyte abnormalities, was referred back to their local hospital to correct these abnormalities, and was not seen again. The remaining four patients demised while awaiting treatment initiation.

Thus 57 patients of the initial 64 went on to start treatment.

8.3.1.2 TREATMENT

The median total radiation dose delivered was 56Gy. See the graph below for the distribution of total treatment radiation dose.

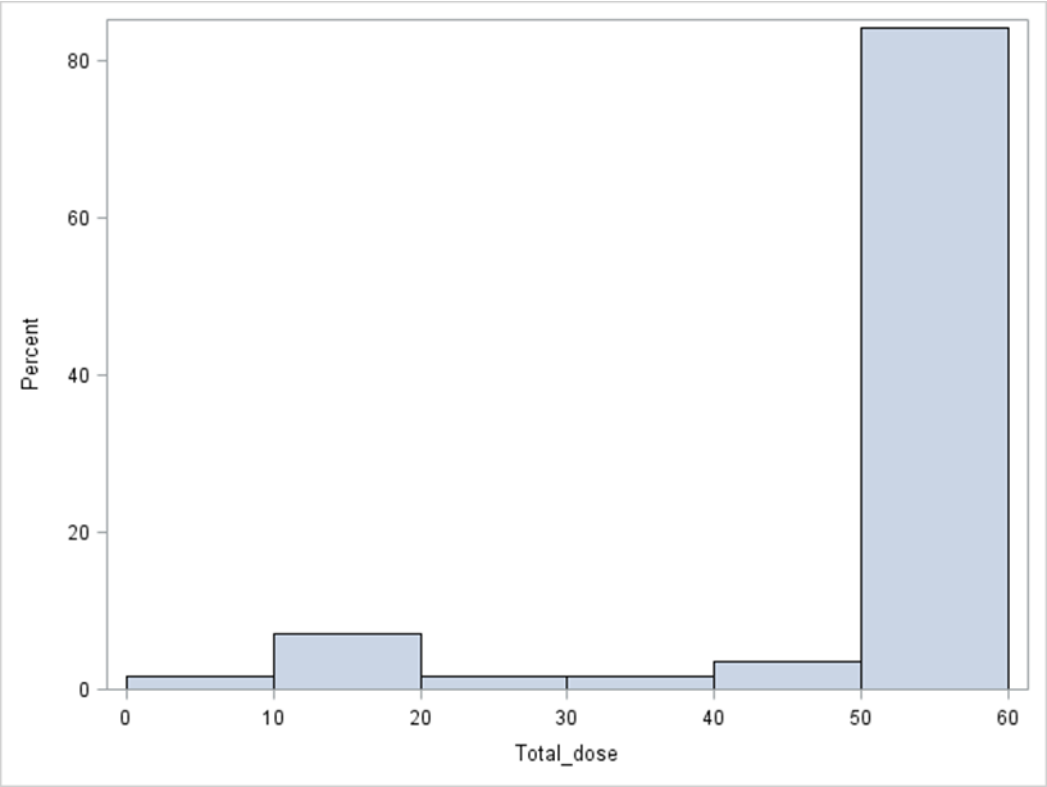

Figure 8: Total dose

8.3.1.3 BOOST

Fifty six per cent of patients received a boost. The commonest boost dose was 6Gy.

Seventy-four per cent of patients completed their full course of treatment.

The reason for not completing the full prescribed course of treatment was not documented in 11 out of 15 patients.

As for the other 4 patients: one patient developed metastases on radical treatment and the script was thus altered to a palliative dose. Two patients who were initially prescribed a boost were found to have no residual tumour after completion of the first two phases of treatment and thus the boost was not given. The remaining patient developed an infected perianal ulcer and thus treatment was stopped.

8.3.1.4 Duration of treatment:

The median duration of treatment was 44 days (range 0-216 days). The distribution of the data is shown in figure 9 below:

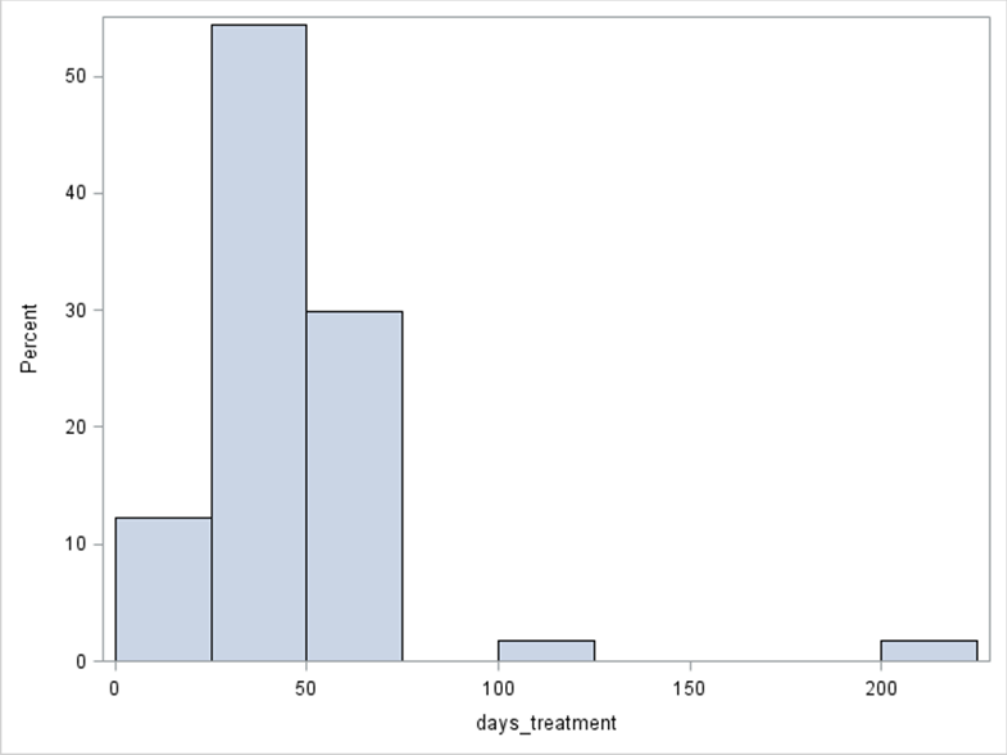

Figure 9: Treatment duration

8.3.1.5 Missed Days of Treatment:

During data collection it was noted that there was a high prevalence of patients who missed treatment for several days during their scheduled course of radiation. The missed days were seldom consecutive. These gaps did not affect the total dose of radiation delivered, as the originally prescribed dose and number of fractions was completed, but the overall treatment time was affected. These gaps were not doctor initiated treatment splits related to toxicity of treatment, as there is no documentation in the notes accounting for the gaps. Rather one may assume that for some reason, patients were unable to attend treatment on these days.

Eighty-one percent of the patients had missing days in treatment. Within these 46 patients:

The median number of missed treatment days was 4 (range 1-49 days). The distribution of the data is shown below in figure 10:

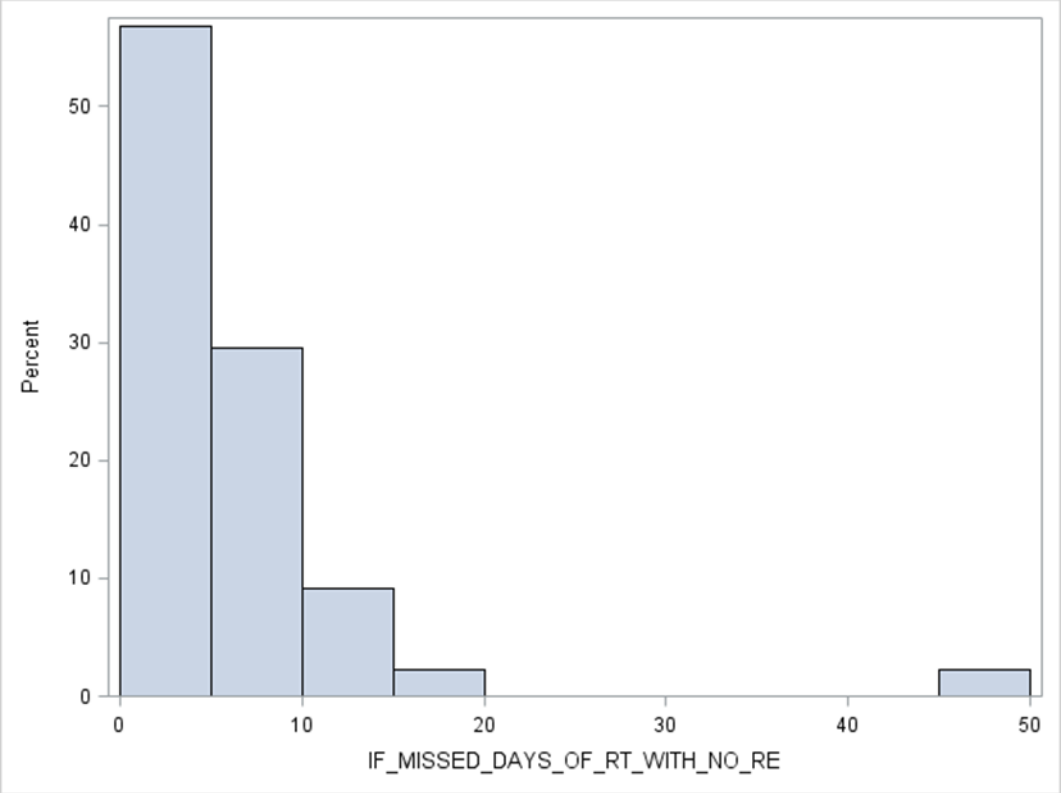

Figure 10: Missed treatment days

There was a significant association between whether or not days of treatment were missed and tumour response at follow up. All seven patients who had no missed days had a complete response. However, the 33 patients who had missed treatment days, included patients with stable and progressive disease. See figure 11 below:

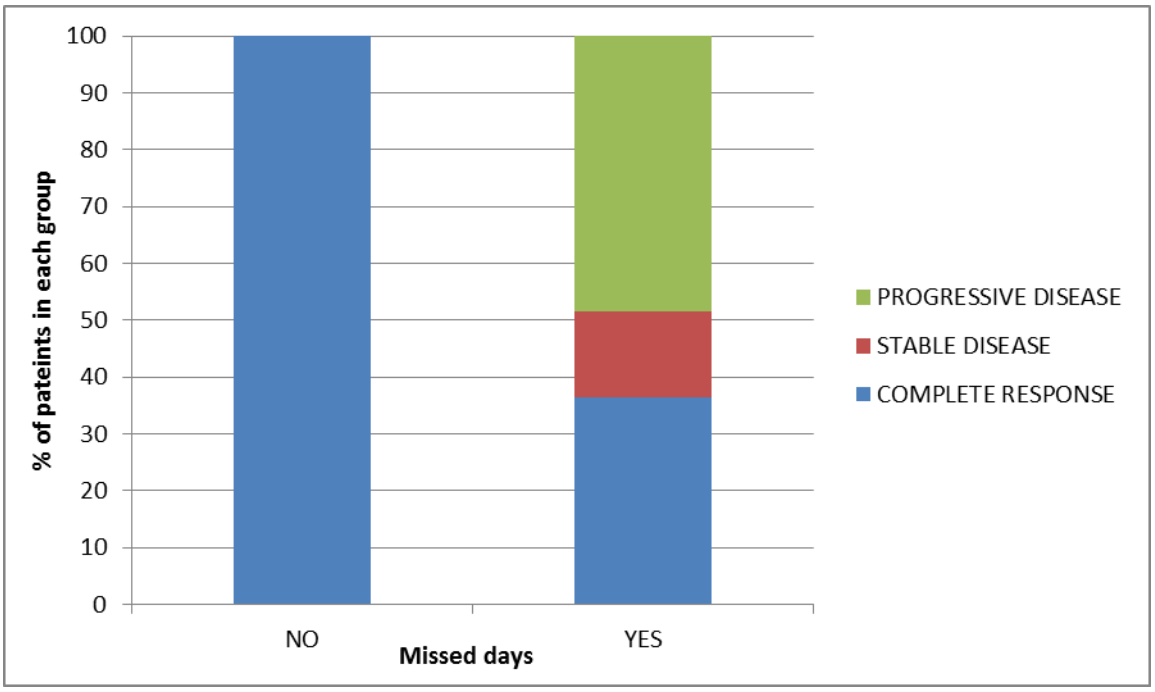

Figure 11: Tumour response versus missed treatment days

8.3.2 Treatment Response

Response was measured using the RECIST criteria (appendix 5).

In the 45 evaluable patients who attended follow-up after completing their treatment, 42% had a complete response and 36% had a tumour recurrence. Partial response was noted in 2% and stable disease in 11%. The response was not recorded in the remaining 9% of patients. The median duration to recurrence was 303 days.

The distribution of the outcomes on follow-up is shown in the figure 12 below.

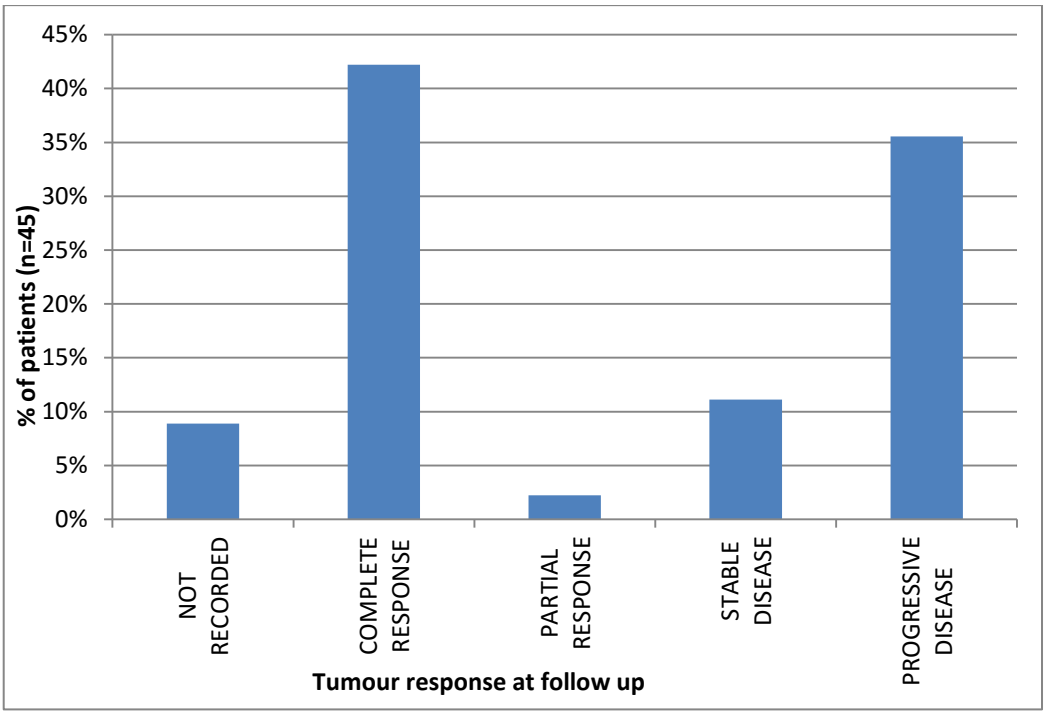

Figure 12: Tumour response at follow-up

8.3.3 Follow-up duration:

The median follow-up duration was 392 days (91-597 days IQR). This distribution is shown below in figure 13.

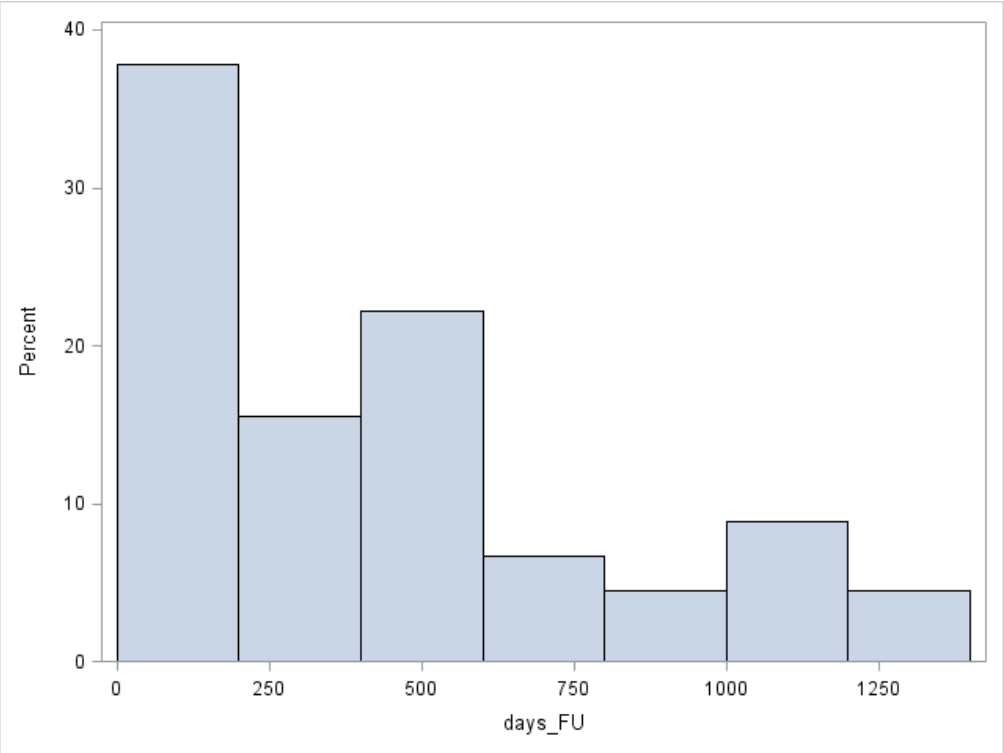

Figure 13: Follow-up durations

8.3.4 Progression Free Survival

The Kaplan-Meier estimate of progression-free survival is shown below:

The progression-free survival estimates at 12 and 24 months were 85% and 46%.

The median progression-free survival time was 19 months.

See figure 14 below.

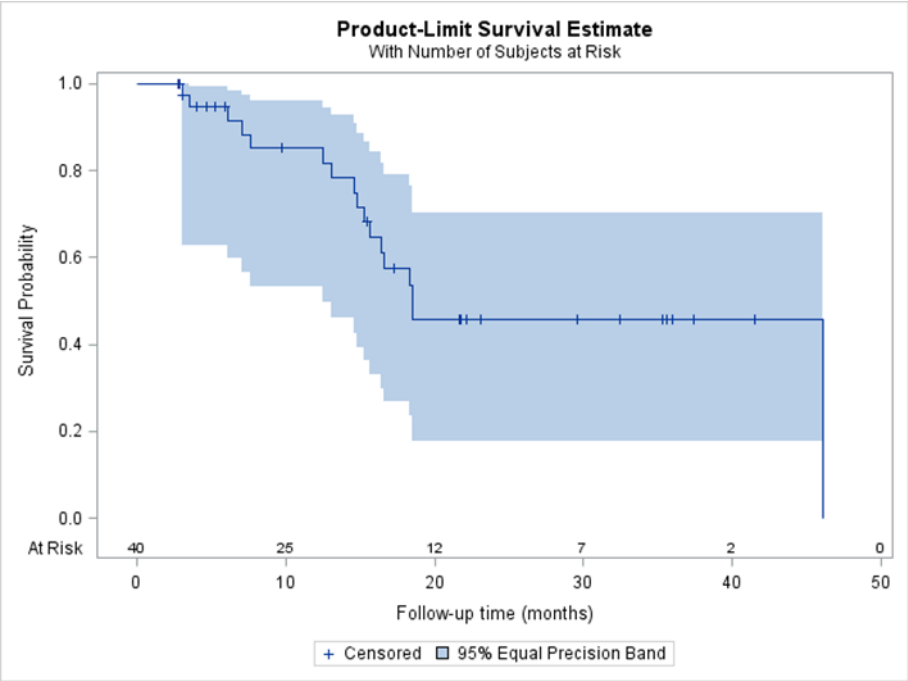

Figure 14: Progression free survival

8.3.5 Overall Survival

No deaths were recorded in those patients that stopped attending follow-up, so it was not possible to do an analysis of the overall survival rates.

9 DISCUSSION

This study was a descriptive analysis which aimed to report on various aspects relating to chemo-radiotherapy of localised anal cancer. Included were the patient and tumour characteristics, treatment toxicities and the treatment outcomes.

Treatment outcomes are affected by a variety of factors, including patient related factors such as performance status and HIV status, tumour related factors such as presenting tumour stage and tumour grade, as well as treatment related factors such as dose, delays in starting treatment and overall treatment time. These are discussed below.

9.1 PATIENT CHARACTERISTICS

9.1.1 DEMOGRAPHICS

This study included data from 64 patients of which 67% were female and 50% were HIV positive. The median age of the patients in the study was 48 years.

The female predominance as well as the age at presentation was consistent with the data recorded in the literature.[7,14]

9.1.2 HIV STATUS

A review of the literature with regards to age at presentation with anal cancer, showed that this variable is affected by HIV status. HIV negative patients presented with the disease about two decades later than HIV positive patients. In addition, most of the literature showed a female predominance, with the exception of regions and eras where HIV was commoner in males, usually related to homosexual behaviour patterns.[4,9,14]

The average age at presentation of the HIV positive patients in this study was 43 years old, compared to 59 years old for the HIV negative patients.

Thus the epidemiological findings of this review are consistent with those trials in the literature which included HIV positive patients with regards to the female predominance and the age at presentation.

Information regarding other risk factors for anal cancer, including sexual history, smoking history and a history of sexually transmitted infections, was lacking in the patient files. Thus a conclusion could not be drawn regarding these variables. On the other hand, documentation regarding HIV status, CD4 counts and ARV use was more comprehensive and this thus enabled an analysis.

Most of the patients (78%) who were HIV positive were on ARV therapy prior to starting treatment, with a median CD4 count of 250 cells/mm^3. Those patients who were not on ARVs before starting treatment were referred to initiate HAART therapy. The fact that the majority of the HIV positive patients included in the study were on ARV therapy and had a median CD4 count >200 cells/mm^3, may account for the reason that the treatment toxicities experienced did not differ from those in studies which included HIV negative patients.

As discussed previously, an outcomes analysis of HIV positive patients with anal squamous cell carcinoma by Place et al. reviewed treatment toxicities and outcomes in a group of 73 patients between 1980 and 1999. Only those patients who presented in 1998- the last year of the trail- were on ARV therapy. The authors concluded that patients with anal cancer who were HIV positive and who were not on ARVs, obtained little benefit and had significant toxicity from chemo-radiotherapy. [10]

In contrast to this, a paper by Fraunholz et al reported that in their series of 21 HIV positive patients, all of whom were on ARV therapy, there was acceptable treatment related toxicity and favourable treatment outcomes. Chemotherapy and radiotherapy could be completed in all 21 patients, with a reduction in chemotherapy dose and/or interruption in radiotherapy in 24% of the group (5 patients). The five year local control rate was 59%.[3]

Down modifications of the radiation and chemotherapy doses were not traditionally mandated for HIV positive patients at CMJAH, and they tolerated the same treatment protocols as immune competent patients. The exception was in cases where patients had a CD4 count of less than 200 cells/mm^3. In these cases, chemotherapy was either omitted or altered. The alteration made was either to omit mitomycin c and use only 5FU, or to use cisplatin as a substitute for the mitomycin c.

In this study the HIV positive patients presented with later T stage tumours then the HIV negative patients.

There was however no significant association between HIV status and a requirement to split treatment, missed days of treatment or completion of the course of chemo-radiation in this study.

There was also no significant association between HIV status and tumour recurrence.

9.2 Toxicity

The commonest adverse effect noted was skin toxicity. This occurred in 81% of patients and the majority had severe grade 3 and 4 reactions. The next

commonest toxicities were fatigue and pain, which occurred in 75% of patients. GIT toxicity occurred in 32% of patients, and urinary and haematological toxicity were less common, occurring in 26% and 12% of patients respectively.

The distribution of toxicities noted in this study differs somewhat from that in the literature. Skin toxicity or dermatitis was also the commonest adverse event noted in the literature review[14,15], but in this study the next most prevalent adverse events noted were fatigue and pain, with GIT toxicity and haematological toxicity being less common.

The reason for the difference may be variations in field borders used in different centres, as some may use a higher superior field border and include more bowel in the high dose region.

A possible reason for the 'lesser occurrence' of haematological toxicity in this study compared to the literature may be differing institutional practices for monitoring of full bloods counts while patients are on treatment. At CMJAH, blood results are checked prior to administering of chemotherapy, but not always on a weekly basis thereafter. This may result in lower detection rates of haematological toxicity.

HIV positive patients did not experience significantly worse treatment toxicities than HIV negative patients, nor did they require an increased number of treatment splits. They had equal rates of treatment completion when compared to HIV negative patients.

Thus in conclusion the distribution of treatment toxicities noted in this study differed somewhat from the that reported in the literature with similar prevalence of

skin toxicity but less common haematological and GIT toxicity rates, possibly due to variations in field borders and blood count monitoring rates. HIV positive patients had similar toxicity profiles and treatment tolerability to HIV negative patients.

9.3 Outcomes

The group of patients who completed their treatment and attended follow-up comprised 45 evaluable patients.

9.3.1 Treatment Outcomes

The median duration of follow-up was 392 days.

Follow-up of patients was done by clinical assessment with a history and an examination. It was not the departmental policy to follow-up patients by performing routine biopsy. Thus recurrence was diagnosed clinically, and once assessed as such- patients were then worked up and referred for biopsy.

At the last recorded follow-up visit, of the 45 evaluable patients 38% had recurrent disease and 51% did not have a recurrence. There was missing data regarding the outcome in the remaining 11% of patients. The Kaplan-Meier progression free survival rates were 85% at 12 months and 46% at 24 months. The median progression free survival time was 19 months.

Lim et al did a systematic review of chemotherapy/radiotherapy trials in anal cancer. Some of the trials included in their review were ACT I and II, ACCORD-03, EORTC 22861, RTOG-8704 and RTOG-9811. The authors concluded that patients with T3/T4 lesions had poor outcomes, with a 3 year disease free survival of 40-68%.[17]

A trial by Gerard et al conducted in France, examined the long term results in a group of 95 patients with anal carcinoma, treated with radiation and concurrent fluorouracil and cisplatin. Sixty-three per cent of the patients had advanced disease with tumours of >4cm in diameter. Only 19% of their patient group with tumours <4cm in size had no metastatic lymph node involvement. None of the study participants was HIV positive.[9]

With regards to the outcomes, in the trial by Gerard et al, local recurrence was noted in 14 patients (15 % of the study population), 11 recurrences were in the anal canal, 1 was in the perirectal wall above the anus and 2 were in the lateral pelvis. The median time to recurrence was 12 months after completion of treatment. The loco-regional control rate was initially 80% but with successful salvage surgery of 13 patients after relapse, the ultimate loco-regional control rate was 93%.[9]

In contrast to the trial by Gerard et al, the outcomes of this study more closely reflect those noted in the paper by Lim et al.[17] Of course the outcomes and local control rates would need to be compared over a similar time frame, as the current outcome data from this study are based on an average follow-up of approximately 13 months. Unfortunately the patient population in our setting differs from those in a first world environment and access to health care is a challenge.

9.3.2 Treatment related factors

In addition to the stage at presentation, other factors that affect the outcomes include radiotherapy fields and doses, chemotherapy use, splits in treatment and delays in starting and completing treatment.

In a review of the literature regarding radio-chemotherapy in anal cancer, the treatment protocol at CMJAH is comparable to other centres. One notable difference is that 5-fluorouracil is administered as a bolus over 4 days at CMJAH, instead of being given as an infusion, as in the trials by Chapet et al, and Gerard et al. [8,9]

In this paper it was noted that there was a median delay of 47 days to initiation of treatment and a median treatment duration of 44 days. Eighty-one per cent of patients had unplanned gaps in the course of their treatment. In addition 33% of patients needed a split in treatment due to toxicity. These factors contribute to a delay in starting radiotherapy as well as an increase in the overall treatment time.

There is literature to suggest that the potential doubling time (Tpot) of anal cancer is 4 days.[2] The potential doubling time is defined as the time necessary to double the number of proliferating tumour cells in the absence of spontaneous cell loss. Thus a delay in initiating therapy, as well as prolonged overall treatment times would lead to upstaging of the tumour and worse treatment outcomes.

A systematic review entitled “does delay in starting treatment affect outcome of radiotherapy” by Huang et al reviewed 47 studies which included 15 782 patients with a variety of malignancy types, the commonest being breast and head and neck cancer. The authors found that there was an association between an increased local recurrence rate in these cancers and a delay in initiating radiotherapy. One may extrapolate from this data that a delay in starting treatment in anal cancer is also associated with reduced local control rates.[18]

On statistical analysis of the data from this trial, there was no significant association between the delay in starting treatment, or a planned split in treatment

and adverse outcomes. There was also no increase in local recurrence in those patients who did not receive a boost, compared to those who did.

There was no significant association noted between T and N stage and outcomes. There was also no significant association noted between recurrence and HIV status, age and gender.

There was however a significant association between adverse outcomes and missed treatment days. There was a complete response in all patients who did not miss days of treatment. However, the patients who did have unscheduled gaps in treatment included those with stable disease and disease progression and had a complete response rate of less than 40%.

Thus the most significant factor related to recurrence in this study, was unscheduled gaps during treatment.

9.4 Strengths and Limitations

A strength of this study is that multiple data variables and outcomes were collected and analysed. Although not complete, the data in the patient files provided a strong base for a hypothesis for further research questions related to anal cancer treatment at CMJAH.

Another positive aspect of the study, is that the research was inexpensive to conduct as it relied upon data already present in departmental files.

One of the limitations of this study lies in the fact that it was conducted retrospectively. This led to a limitation of the available data in the files, most notably the lack of charting of risk factors for anal carcinoma and paucity of information about the grade of treatment related toxicities experienced.

A further limitation of the study was the poor follow-up of patients during and after radiotherapy. This led to an inability to measure overall survival outcomes. It may also have resulted in an over-estimation of the progression free survival rates as progression may have occurred quite some time before it was documented.

10 Conclusion

Anal carcinoma causes significant morbidity to patients and is one of the few cancer types that relies on treatment from oncologic services primarily, rather than surgical services. Anal carcinoma is a tumour in which it is comparatively easy to assess treatment response and outcome in, as it is accessible to clinical examination. Measuring local response does not require imaging or blood tests. Thus, in our resource constrained environment, there are fewer barriers to ensuring sound follow-up, compared to other carcinomas, such as lung or stomach cancer.

The demographics, treatment toxicities and outcomes in this study largely paralleled those in the literature for centres with a similar patient HIV burden and presenting tumour stage.

Better documentation and patient follow-up is needed to get a clearer picture of the acute tumour response to therapy and the long term treatment outcomes.

Better monitoring of patient attendance during treatment is also imperative as unplanned gaps in chemo-radiation were correlated with recurrence in this study.

Further studies may look at the quality of life of these patients with regards to sphincter preservation rate, sexual function, and long term urinary and bowel function post pelvic radiotherapy.

Another area of future interest is the effect on the incidence of anal carcinoma in women, related to the national rollout of the HPV vaccination. The programme was initiated in 2014, with girls from age 9 and onwards being vaccinated. The main aim was to reduce the incidence of cervical cancer, but since HPV is also a risk

factor for anal cancer, reduced numbers of this type of malignancy may be a spin-off benefit of wide-spread HPV vaccination.

11 APPENDICES

11.1 APPENDIX 1: AJCC 7TH EDITION TMN STAGING OF ANAL CARCINOMA

T-Staging

TX Primary tumour cannot be assessed.

T0 No evidence of primary tumour.

Tis Carcinoma in situ (i.e., Bowen disease, high-grade squamous intraepithelial lesion, and anal intraepithelial neoplasia II–III.)

T1 Tumour ≤2 cm in greatest dimension.

T2 Tumour >2 cm but ≤5 cm in greatest dimension.

T3 Tumour >5 cm in greatest dimension.

T4 Tumour of any size invades adjacent organ(s), e.g. vagina, urethra, and bladder.

N-staging

NX Regional lymph nodes cannot be assessed.

N0 No regional lymph node metastasis.

N1 Metastases in perirectal lymph node(s).

N2 Metastases in unilateral internal iliac and/or inguinal lymph node(s).

N3 Metastases in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes.

M-staging

M0 No distant metastasis.

M1 Distant metastasis.

11.2 Appendix 2: Proforma for data collection

Category 1: Patient Demographics

1. Patient assigned study number:

2. Date of first consultation at radiation:

3. Patient date of birth:

4. Patient gender:

Male	Female

5. TNM stage:

6. Degree of differentiation on histology:

Well	Moderate	Poor	Unknown

7. Patient assigned study number:

8. HPV on histology:

Present	Absent	Unknown

9. Initial weight in kg:

10. Initial height in cm:

11. Initial performance status:

EGOC0	ECOG1	ECOG2	ECOG3	ECOG4

12. HIV status:

Positive	Negative	Unknown

13. If HIV positive, what is CD4 count on presentation:

	Unknown

14. If patient is HIV positive, are they on ARV's prior to starting radiation:

Yes (Date Initiated)	No	Unknown

15. If not on ARVs at presentation, was the patient sent to initiate ARV treatment:

Yes	No	Unknown

16. Other risk factors for anal carcinoma (Check all which apply):

☐ History of STI

Syphilis	Herpes	Gonorrhoea	Chlamydia

☐ History of Anal Warts

☐ Sexual Promiscuity (>10 sexual partners)

☐ Receptive Anal Intercourse

☐ Smoking

Current	Previous	Unknown

17. If positive smoking history, Number of pack years:

< 0	=>10	Unknown

Category 2: Treatment

18. Prescribed Treatment:

Chemo-Radiation	Radiotherapy Only

19. If chemotherapy given, which drugs given:

5FU D1-4 and 22-25 and MMC D1	5FU D1-4 and 22-25, and Cisplatin D1

20. If chemotherapy omitted/altered, cause for this:

Low CD4 count	Poor Performance Status	Age	Unknown

21. Date of Starting Treatment: (DD/MM/YY)

22. Date of Completing Treatment: (DD/MM/YY)

23. If the patient did not get treatment although it was planned, cause for this:

Demised	Defaulted	Disease progression	Severe comorbidities (specify :)	Unknown

24. Was there a colostomy inserted:

Yes	No	Unknown

25. If a colostomy was inserted, when was this done:

Prior to starting treatment	During treatment	After treatment	Unknown

26. Was a boost administered:

Yes	No

27. If there was a boost, dose in Gray:

28. Was the full course of prescribed RT completed:

Yes	No

29. If full course of prescribed RT was not completed, what dose was

completed in GY:

30. Reason for not completing radiation:

Treatment Toxicity	Disease Progression	Patient Demised	Patient Defaulted	Unknown

31. Was treatment split:

Yes	No

32. If treatment was split, length of split (days) :

33. If treatment was split, was patient admitted to hospital during the split:

Yes	No	Unknown

34. Cause for the split (“YES” = Present but grade unknown):

Skin toxicity	□ Grade 1	□ Grade 2	□ Grade 3	□ Grade 4	□ YES
GIT toxicity	□ Grade 1	□ Grade 2	□ Grade 3	□ Grade 4	□ YES
Urinary toxicity	□ Grade 1	□ Grade 2	□ Grade 3	□ Grade 4	□ YES
Haematological toxicity	□ Grade 1	□ Grade 2	□ Grade 3	□ Grade 4	□ YES
Neutropaenic sepsis	□ Grade 1	□ Grade 2	□ Grade 3	□ Grade 4	□ YES

35. Did patient follow-up after treatment completion:

Yes	No

Category 3: Tumour Response

36. Tumour size in CM:

Prior to starting treatment:	On completion of 50Gy:	If boosted, size of tumour on completion of boost:
(,Unknown)	(,Unknown)	(,Unknown)

37. Response at Completion of all Planned Treatment:

Complete response	Partial response	Stable disease	Progression of disease	Unknown

38. Response 6 weeks after completion of all planned treatment:

Complete response	Partial response	Stable disease	Progression of disease	Unknown

Category 4: Treatment Toxicities

39. On treatment complications:

Skin toxicity	☐ Grade 1	☐ Grade 2	☐ Grade 3	☐ Grade 4	☐ YES
GIT toxicity	☐ Grade 1	☐ Grade 2	☐ Grade 3	☐ Grade 4	☐ YES
Urinary toxicity	☐ Grade 1	☐ Grade 2	☐ Grade 3	☐ Grade 4	☐ YES
Haematological toxicity	☐ Grade 1	☐ Grade 2	☐ Grade 3	☐ Grade 4	☐ YES

Fatigue	Yes	No	Unknown
Pain	Yes	No	Unknown
Other			

Category 5: Outcomes

40. If patient did follow-up after treatment completion, and there was recurrence, what date was it diagnosed:

41. If a recurrence is present, is it:

A local recurrence (at anus)	Loco-regional (inguinal nodes/perirectal nodes/internal iliac nodes)	Distant metastasis (lung/liver/bone/brain)	Unknown

42. Date last seen:

43. On last date seen, what was the tumour response:

Complete response	Partial response	Stable disease	Progression of disease	Unknown

44. If there was persistent disease/progression/recurrence, what was done for the patient:

Referral for palliative care/Hospice	Referral for surgery	Palliative radiation	Other	Unknown

11.3 Appendix 3: Eastern Cooperative Oncology Group performance status

Grade 0: Fully active, able to carry on all pre-disease performance without restriction

Grade 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

Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

Grade 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

Grade 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

Grade 5: Dead

11.4 Appendix 4: RTOG Acute Radiation Morbidity Scoring Criteria

GRADE	[0]	[1]	[2]	[3]	[4]
SKIN	No change over baseline	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/ moderate oedema	Confluent, moist desquamation other than skin folds, pitting oedema	Ulceration, haemorrhage, necrosis
GENITOURINARY	No change	Frequency of urination or nocturia twice pretreatment habit/ dysuria, urgency not requiring medication	Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anaesthetic (e.g., Pyridium)	Frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross haematuria with/ without clot passage	Haematuria requiring transfusion/ acute bladder obstruction not secondary to clot passage, ulceration or necrosis
LOWER G.I. INCLUDING PELVIS	No change	Increased frequency or change in quality of	Diarrhoea requiring parasympatholytic drugs (e.g., Lomotil)/ mucous	Diarrhoea requiring parenteral support/ severe mucous or blood	Acute or subacute obstruction, fistula or perforation; GI

		bowel habits not requiring medication/ rectal discomfort not requiring analgesics	discharge not necessitating sanitary pads/ rectal or abdominal pain requiring analgesics	discharge necessitating sanitary pads/abdominal distension (flat plate radiograph demonstrates distended bowel loops)	bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
HEMATOLOGIC WBC (X 1000)	>=4.0	3.0 - <4.0	2.0 - <3.0	1.0 - <2.0	<1.0
PLATELETS (X 1000)	>=100	75 - <100	50 - <75	25 - <50	<25 or spontaneous bleeding
NEUTROPHILS	>=1.9	1.5 - <1.9	1.0 - <1.5	0.5 - <1.0	<0.5 or sepsis
HEMOGLOBIN (GM %)	>11	11-9.5	<9.5 - 7.5	<7.5 - 5.0	-------
HEMATOCRIT (%)	>=32	28 - <32	<28	Packed cell transfusion required	-------
GUIDELINES: The acute morbidity criteria are used to score/grade toxicity from radiation therapy. The criteria are relevant from day 1, the commencement of therapy, through day 90. There-after, the EORTC/RTOG Criteria of Late Effects are to be utilized.					

The evaluator must attempt to discriminate between disease- and treatment-related signs and symptoms.

An accurate baseline evaluation prior to commencement of therapy is necessary.

All toxicities Grade 3, 4 or 5* must be verified by the Principal Investigator.

*Any toxicity which caused death is graded 5.

11.5 Appendix 5: Revised RECIST guidelines (version 1.1)

Evaluation of target lesions

1) Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in the short axis to <10mm.

2) Partial Response (PR): At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

3) Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on the study.

4) Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm (note the appearance of one or more new lesions is also considered progression of disease).

11.6 Appendix 6: Ethics Clearance Certificate

R14/49 Dr Yael Mark

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150424

NAME: (Principal Investigator)	Dr Yael Mark
DEPARTMENT:	Radiation Oncology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A Retrospective Review of Chemo-Radiation in Anal Carcinoma
DATE CONSIDERED:	24/04/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr NB Singh
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	06/05/2015

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

11.7 Appendix 7: Ethics Change of Supervisor

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10004, 10th floor.
Medical School Secretariat: PV Tobias Building, 2nd Floor.
Private Bag 3, Wits 2050, www.wits.ac.za

Tel +27 (0)11-717-1252
Tel +27 (0)11-717-2700
Fax +27 (0)11-717-1265

10 December 2015

Dr Yael Mark
PO Box 1208
Highlands North
Johannesburg
2037

Sent by email to: y.mark.schwartz@gmail.com

Dear Dr Mark

Re: **Protocol Ref no: M150424**
Protocol Title: A Retrospective Review of Chemo-Radiation in Anal Carcinoma
Principal Investigator: Dr Yael Mark
Change of Supervisor: Dr NB Singh to Prof Sharma

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) has noted the change of supervisor for the abovementioned protocol from Dr NB Singh to Prof Sharma, as detailed in your letter dated 23 May 2015.

Thank you for keeping us informed and updated.

Yours Sincerely,

Mr Rhulani Mkansi
Administrative Officer
Human Research Ethics Committee (Medical)

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH
10 DEC 2015
RESEARCH OFFICE HREC (Medical)
JOHANNESBURG

11.8 Appendix 8: CEO Permission

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Mr. J. Maepa
Office of the Clinical Director
Tell: (011): 488-3365
Fax: (011): 488-3753
23 June 2015

Dr. Y. Mark
CMJAH

Dear: Dr. Y. Mark
STUDY TITLE: A Retrospective Review of Chemo-Radiation in Anal Carcinoma.

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not anyway incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported/~~not supported~~

Dr. M.I. Mofokeng
Clinical Director
DATE: 23/6/2015

~~Approved~~/not approved

Ms. G. Bogoshi
Chief Executive Officer
DATE: 24.06.2015

11.9 Appendix 9: Approval of Title

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Ms Thokozile Nhlapo
E-mail: thokozile.nhlapo@wits.ac.za

01 June 2015
Person No: 0101737P
PAG

Dr Y Mark
P O Box 1208
Highlands North
2037
South Africa

Dear Dr Mark

Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *A retrospective review of chemo-radiation in anal carcinoma* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

11.10 Appendix 10: Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I YAEL MARK (Student number: 0101737P) am a student registered for the degree of FC RAD ONC (SA) in the academic year fourth / final.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: MARK-Y Date: 22/11/2016

1

11.11 Appendix 11: Turnitin Report

Document Viewer

Turnitin *ORIGINALITY REPORT*

- Processed on: 29-Nov-2016 3:33 PM SAST
- ID: 744117275
- Word Count: 9869
- Submitted: 1

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