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PATTERN OF PRACTICE IN CARCINOMA OF THE CERVIX:

A RETROSPECTIVE ANALYSIS OF HIV POSITIVE PATIENTS TREATED WITH RADIATION AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPTAL 2008-2009

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Thesis submitted to the University of the Witwatersrand
in partial fulfillment of the requirements for the degree

Master of Medicine (MMed) in Radiation Oncology

Faculty of Health Sciences
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Declaration

I, Dr. Sibahle Nozuko Portia Ndamase hereby declare that the work on which this dissertation/ thesis is based on my original work, except where acknowledgements indicated otherwise and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Date 30 October 2017

PRESENTATIONS:

The Abstract has been accepted for presentation as a poster at the following forums:

- University of Witwatersrand, Faculty of Health Sciences Research Day- August 2015.

- South African Society of Clinical and Radiation Oncology (SASCRO) and South African Society of Medical Oncology (SASMO) congress April 2015.

Acknowledgments

I would like to thank God for helping me complete this work. I could not have done it without Him.

I would like to thank my family and friends for their unending support during this challenging process.

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ABSTRACT

INTRODUCTION: Carcinoma of the cervix is frequently diagnosed in the department of Radiation Oncology in Charlotte Maxeke Johannesburg Academic Hospital(CMJAH). It is therefore is a condition of priority and there is scarce literature in the management of HIV positive patients.

OBJECTIVES: The primary objective of the research is to determine the overall survival of 2yrs and more, as well as to determine acute and late toxicity for patients completing prescribed radiation treatment. The secondary objective was to determine the impact of highly active antiretroviral therapy on survival and toxicity. The study is limited to HIV positive women presenting with cervical cancer.

DESIGN & METHOD: The study is a retrospective study of patients treated at Charlotte Maxeke Johannesburg Academic Hospital between 2008-2009.
Inclusion criteria: Females between the ages of 18 and 70, Stages IB2 – Stage IIIB carcinoma of the cervix who have completed planned radiation therapy with or without chemotherapy. The sample size was 151 patients.

RESULTS: The mean age was 42.7yrs. The median CD4 count was 309 and 26.2% had CD4 counts below 200.The majority of patients had either Stage IIB (55.0%) or IIIB (31.8%). The total dose to Point A was a median dose of 74Gy. The majority of patients had either Grade II (38.4%) or III (31.1%) toxicity. Significant association between these adverse events and HAART status was rated as p=0.0008. The most common late complication was cystitis (15.9%). Overall survival at 2 years was 100% for Stage I, 92.8% for Stage II and 96% for Stage III.

CONCLUSION: The median age was lower than in the HIV negative patients. The acute complications for those not on HAART, were higher in comparison to patients on HAART. The overall survival at 2 yrs. was above 90% for all stages in this study cohort.

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LIST OF ABBREVIATIONS

GOG:	Gynecology Oncology Group
SWOG:	South West Oncology Group
RTOG:	Radiation Therapy Oncology Group
RT:	Radiation Therapy
HIV:	Human Immunodeficiency virus
AIDS:	Acquired Immunodeficiency Syndrome
HAART:	Highly active antiretroviral therapy
AP/PA:	Anterior-posterior/posterior-anterior
SD:	Standard deviation
OR:	Odds ratio
GIT:	Gastrointestinal
GUT:	Genitourinary
RVF:	Rectovaginal fistula
VVF:	Vesicovaginal fistula
HB:	Haemoglobin
BRACHY:	Brachytherapy
CANSA:	Cancer Association of South Africa
CI:	Confidence Interval
CMJAH:	Charlotte Maxeke Johannesburg Academic Hospital
CT:	Computed Tomography
EBRT:	External Beam Radiotherapy
FIGO:	International Federation of Gynaecology and Obstetrics
HR:	Hazard Ratio
IQR:	Inter quartile range
MRI:	Magnetic Resonance Imaging
NCR:	National Cancer registry

Definition of terms used in this study:

Term	Definition
Alive	All patients who are alive two years after treatment (living with nor without the disease)
Dead	All patients who had died or we were unable to follow up on before 31 December 2008.
Age	Date of birth to date of registration.
Treatment duration days	Treatment Start Date – Treatment End Date
Waiting period	Date of Diagnosis – Treatment Start Date
Last follow up date	Date last seen alive at the clinic post treatment.
Local failure	Generally as a lack of response or clinical deterioration in the area that was treated with radiation.
Point A	The major critical point for dose specification of intracavitary brachytherapy, is measured 2cm above cervical os and 2cm lateral to central tandem.
Acute toxicity	Adverse events occurring from the treatment within 90 days. In this study GIT, GUT and skin reactions graded according to RTOG(Appendix 1)
Late toxicity	Adverse events from treatment 90 days and after. These include for this study: cystitis, proctitis, RVF VVF.
Cystitis	Inflammation of the urinary bladder. It is often caused by infection and is usually accompanied by frequent, painful urination.
Overall survival	The length of time from either the date of diagnosis or the start of treatment for a disease, that patients diagnosed with the disease are still alive.

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Abbreviations:;CANSA, Cancer Association of South Africa; CMJAH, Charlotte Maxeke Johannesburg Academic Hospital; RT, Radiation Therapy; EBRT, External Beam Radiotherapy ;Brachy, Brachytherapy; AP/PA, Anterior-posterior/posterior-anterior; HIV, Human Immunodeficiency Virus; AIDS, Acquired Immunodeficiency Syndrome ;HAART, Highly active antiretroviral therapy; GIT, Gastrointestinal; GUT, Genitourinary; RVF, Rectovaginal fistula; VVF, Vesicovaginal fistula; HB, Haemoglobin SD, Standard deviation; OR ,Odds ratio; ; CI,. Confidence Interval; HR, Hazard Ratio; IQR, Inter quartile range

ABSTRACT

Carcinoma of the cervix is an important cancer in our department and there is scarce literature on the management of HIV positive patients. The primary objectives of the research is to determine the overall survival of HIV positive patients at 2 yrs. and more, as well as acute and late toxicity for patients completing prescribed radiation treatment in the department of Radiation Oncology.

The secondary objective was to determine the impact of HAART on survival and toxicity. The study is limited to HIV positive women presenting with cervical cancer. This was a retrospective study of patients treated at CMJAH over a 2 year period. This included patients between the ages of 18 and 70, with Stages IB2 – Stage IIIB carcinoma of the cervix. Completion of planned radiation therapy with or without chemotherapy.

The sample size was 151 patients with age was 42.7yrs. The median CD4 count was 309, 26.2% had CD4 counts below 200.The majority of patients had either Stage IIB (55.0%) or IIIB (31.8%). Majority of patients had either Grade II (38.4%) or III (31.1%) toxicity. Significant association between these adverse events and HAART status (p=0.0008).
The most common late complication was cystitis (15.9%).

CONCLUSION: The age seen in this study cohort is lower than that seen in HIV negative patients. The acute complications for those not on HAART, were higher in comparison to patients on HAART. The overall survival at 2 yrs. was above 90% for all stages in this study cohort. HAART also impacted on toxicity in this study cohort.

INTRODUCTION:

At present, there are approximately 5.7 million people living with HIV/AIDS in South Africa, of which 60% are women. Cervical cancer is the commonest cancer in African (black) women who reside in South Africa with a prevalence of 22 per 100 000. It forms 17.76% of all female cancers(1). Since 1997, more than 33 000 women have died of cervical cancer in South Africa (approximately 3000 per year). In addition, approximately 7000 women will develop the disease every year (2).

Carcinoma of the cervix has been classified as an acquired immunodeficiency syndrome (AIDS) defining disease in patients who are HIV positive (3). With the HIV pandemic in Africa, there has been a change in the pattern of presentation. The patients are presenting at a younger age with locally advanced and metastatic disease. They also have shorter duration of symptoms and poor differentiation of tumor(4).

A study done in Johannesburg showed that HIV positive patients presented with cervical cancer almost 10 years earlier than the HIV negative patients. The mean age was 44 yrs. vs. 53 yrs(5). The researchers also showed that patients with CD4 counts less than 200/mm3 had significantly more advanced stage disease when compared to HIV negative patients. However, it has been shown that radical chemo radiation in conventional doses can be given safely to patients who are HIV positive (6). A study done in Cape Town showed that HIV positive patients do far worse than HIV negative patients because of later presentation and a decreased likelihood of completing treatment (7). This conveys the importance of completing radiation treatment for better outcomes.

The use of HAART is associated with improved outcome in HIV infected females with cervical neoplasia (8). This has also been shown in other studies looking at the role of HAART and impact in lymphoma patients(9). The study showed that viral load decreased as soon as HAART was initiated.

The standard of treatment for carcinoma of the cervix depends on the stage of the cancer (Appendix 1). The treatment for Stage 0-stage IB1 is surgical. From stage IB2 to Stage IV the standard of care is concurrent chemo-radiotherapy in the pre- HIV era (10). This was using cisplatin as the chemotherapeutic radiosensitizing agent. Multiple randomized trials have shown efficacy of chemotherapy when added to radiation, however the addition of cisplatin increases the risk of hematological, renal, and gastrointestinal toxicities (Appendix 2).
A systematic review found that there are no standard guidelines for HIV positive patients, therefore these patients were managed like their HIV negative counterparts (11). There is a bias in using chemotherapy in patients who have a CD4 count more than 200. This is based on a trial done in patients with anal cancer(12). This trial showed that patients with a CD4 count more than 200 had excellent disease control and acceptable morbidity as compared to patients with a CD4 count <200.cells/mm3.

The most commonly reported problem in faced by researchers was that HIV positive patients who could not receive the recommended dose of chemotherapy.
Hammad et al. found that only 45 % of HIV positive patients completed chemotherapy as compared to 89% of HIV negative patients with anal cancer(13).

The recommended dose of Cisplatin chemotherapy is 40mg/m2 weekly concurrently with radiation. In a Phase 1 study done in Johannesburg, the authors reported that a weekly dose

of 25mg/m2 of Cisplatin was the maximum tolerable dose(14) . This was significantly lower than the recommended dose. The following factors were found to be a reason for the lowered dose: inherent renal dysfunction, advanced stage cancer, chronic infections, dehydration and volume depletion, drug related factors, limited medical facilities. It was noted that in this study, the HIV status of the patients was not evaluated separately.

Chemoradiation reduces the CD4 and T-cell count drastically, which decreases the chances of survival if the patient is HIV positive, because AIDS is induced with a dramatic fall in CD4 and T-cell count(15).

The total treatment of more than 6 weeks also has a significant adverse effect on survival especially for Stage III patients(16). Prolongation of treatment time in patients with Stage IB, IIA, IIB, and III carcinoma of the uterine cervix has a significant impact on pelvic tumor control (17).
Fowler et al. have reviewed 12 retrospective studies and found a 3-25% decrease in local control by lengthening the treatment time by one week in head and neck cancers.(18). This is because the potential doubling time for head and neck cancers are similar to cervical cancers and therefore a comparison might be drawn from these studies(19).

Hemoglobin level has also been found to be a significant prognostic indicator. Several large retrospective reviews have found correlations between anaemia during radiation and local failure (20)(21). A study done in Johannesburg by Majeed et al showed that patients with mid treatment HB of >=12g/dl had significantly lower pelvic failures and higher 5yr overall survival(22). Girinski et al found that even brief periods of severe anaemia(<10g/mL) during radiation therapy were associated with increased risk of local failure (23). Serkies et al found that median overall survival in patients with initial Hb >or=12 g/dl was 66 months compared to 22 months in those with lower baseline Hb levels (p = 0.0001). Baseline Hb >or=12 g/dl was also associated with longer disease-free survival and improved local control. Declining Hb level during radiotherapy predicted for improved 5-year disease-free survival and local control probability (24).

The use of HAART simultaneous with chemotherapy drugs has high potential for drug-drug interactions. These may result in chemotherapy or HAART drug concentrations in the blood that are higher or lower than expected, leading to more side effects or reduced efficacy. However, there has not been much data published with regards to interactions with Cisplatin and HAART. However what has been seen in this study is that the patients may have immunosuppressive effects such at leukopenia, cutaneous side effects complicated by fungal infections and diarrhea (25).

Perez et al looked at the dose to point A and the effect of treatment outcome (17). Lanciano et al showed that the dose with the highest rate of complications was one exceeding 85Gy (15). That study also showed that the use of intracavitory radiation is the single most important treatment factor with respect to survival and pelvic control for Stages, II, III. In our study all the patients completed the recommended treatment. The American Brachytherapy Society recommends that dose to point A should be equal or more than 85Gy(26).

Another interesting component in patients with HIV is whether HIV increases the sensitivity of cells with radiation. A cellular basis for radiosensitivity is supported by findings that fibroblasts from the skin of HIV patients with Kaposi's sarcoma are more sensitive to ionizing radiation when compared to those of healthy controls(27). One proposed explanation

for this is that HIV induces a systemic glutathione deficiency leading to a depletion of radio protective thiols and increased oxidative stress(28). However, it remains to be seen whether these in vitro effects in fact contribute to increased radiation sensitivity in HIV-infected patients.

A study done at the Tata Memorial Hospital in India, found that in HIV positive patients, 50% of patients receiving radiation therapy achieved a complete response. Palliative fractionated radiation therapy was also effective for patients in poor performance status and locally advanced carcinomas in relieving the symptoms associated with carcinoma of the cervix. However, there was a high rate of toxicity seen, especially acute gastrointestinal and acute skin toxicity(29).

Five year overall survival for the present study done by Logar et al was 47.2%(30). They found that the Point A dose and histology influenced the outcome. Shrivastava et al described a study group of 42 HIV positive patients and 50% had complete response at 6 weeks follow up, although with high toxicity rates (29). For all stages of cervical cancer, the five-year survival rate is 68%. When detected at an early stage, the five-year survival rate for women with invasive cervical cancer is 91%(31).

CMJAH sees about 700 new patients of cervical cancer yearly. About 30% of patients are HIV positive. There is a scarcity of data looking at HIV positive patients and their outcomes available. The primary objective of this analysis was to look at this cohort of patients to determine the overall survival at 2 years after completion of radiation and also to determine early and late toxicity. The secondary objective was to determine if patients who started on HAART will have better outcomes in terms of survival than those patients who did not get initiated.

The study looked at the epidemiology, variables such as total treatment time, haemoglobin level, dose to point A, the effect of chemotherapy and highly active anti-retroviral therapy (HAART) added to radiation and the toxicities relating to radiation therapy. The study was limited to HIV positive women presenting with cervical cancer. South Africa is unique because it has one of the highest HIV prevalence in the world.

MATERIALS AND METHODS

This is a retrospective study looking at patients treated at CMJAH between 2008-2009. The data came from files of the patients treated in that period.

Inclusion criteria:

1) Females between the ages of 18 and 70

2) Stages IB2 – Stage IIIB carcinoma of the cervix

3) HIV positive patients

4) The patients must have completed the planned radiation therapy (external beam with or without brachytherapy) with or without chemotherapy

Exclusion criteria:

1) Patients treated at Johannesburg Hospital from other African countries as these patients will not have follow up in South African hospitals

2) HIV negative females with carcinoma of the cervix

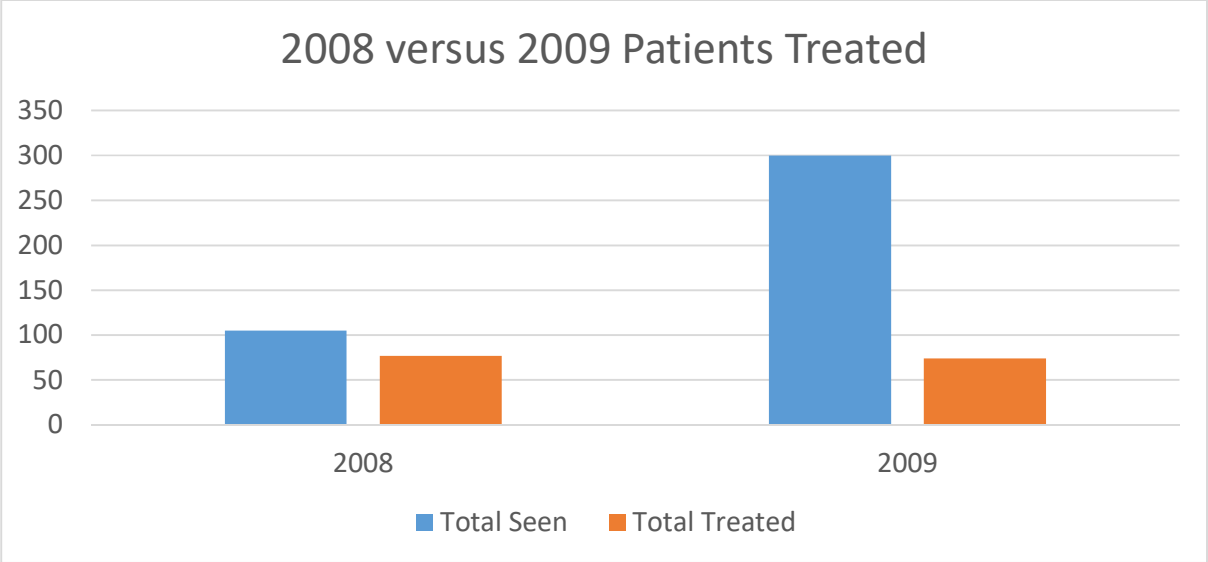

FIGURE 1

Sample size calculation using Strat software:
This is measured as a proportion. Since we do not know what this proportion might be (from a pilot study or from literature), we make a worst case assumption that the proportion is 50%. To estimate this proportion with a 5% precision requires a sample size of 385, given by the sample size calculation for the estimation of proportions.

The sample size of 153 used in this study is considerably lower than what was calculated and would lead to the estimation of a 50% proportion with only ~8%, rather than 5% precision.

Radiation therapy technique:

External beam radiation therapy
Patients included in the study received whole pelvic radiation therapy at mid pelvic
dose per fraction of 2 Gy to a total dose of 46 Gy-50Gy in 23 -25 fractions respectively for 5 days /week.

The field size was determined at 2 Dimensional(2D) simulation.

<u>AP/PA fields</u>
Superior border – Mid L5 vertebra
Inferior border -No vaginal involvement - Bottom of obturator foramen

- Vaginal involvement less than two thirds - Bottom of ischial tuberosity flower half of vagina involved, this was marked and the lower border of the field placed 2 cm below the mark.

Lateral borders

1.5-2cm beyond the pelvic rim, unless the lower 1/3 of the vagina involved, the inguinal nodes were treated to beyond the acetabular margin.

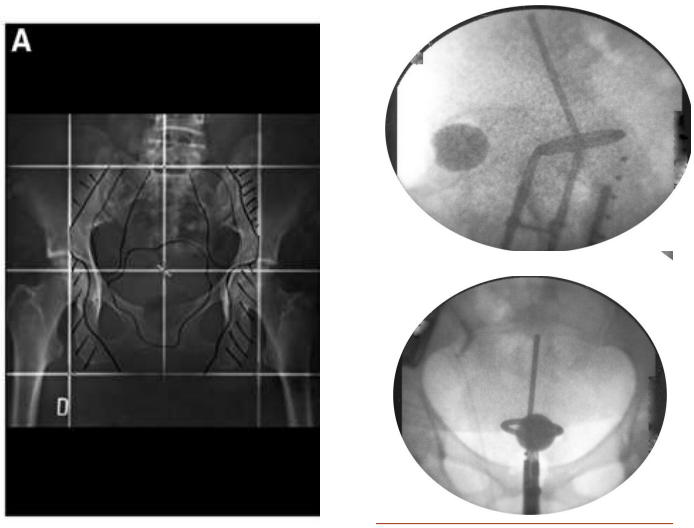

FIGURE 2: AP/PA simulation film, Lateral brachytherapy insertion radiograph, Anterior-posterior brachytherapy insertion radiograph

Brachytherapy
Three intracavitary applications with High Dose Rate Brachytherapy, with the Dose prescribed to point 'A', were given. In most of the patients a rigid intrauterine tandem (Nucleotron (trademark) 6cm, 4cmor 2cm in length) and a ring applicator (Nucleotron 3.4cm, 3cm or 2.6cm in diameter) were used with a rectal shield. If the tumour involved more than 3 cm of vagina, a Joss Flynn applicator was used to treat up to 4 cm of the vagina. If the tumour infiltrated further down the vagina, the treatment was individualized.

Evaluation of Toxicity
Patients were evaluated for toxicity weekly during treatment using the RTOG/WHO common toxicity criteria (Appendix C). Acute side effects were those occurring during treatment and within 90 days' post treatment.

Criteria for response
All responses were measured clinically. Response to treatment was classified as complete or incomplete. A complete response was defined as the complete Disappearance of all gross disease at 3 months post completion of treatment. Incomplete response was defined as the presence of disease based on physical examination findings.

METHODOLOGY

The sample comprised one hundred and fifty-one (151) adult female HIV positive patients with cervical cancer who were registered to start radiotherapy at CMJAH in the period 2008-2009

The analysis was done using STATA version 13. To fulfill the objective of the description of demographic characteristics, frequency tables were compiled for the category variable and appropriate central tendency measures were computed for the continuous variable. The results for the description of demographic characteristics are presented in tables 3 and 4.

The effect of HAART on acute skin reaction was fitted with an ordinal logistic regression univariate and multivariate model, after running a proportional odds assumption test. The ordinal logistic regression model was used because the outcomes were ordered.

RESULTS

The Shapiro Wilk test for normality was used to assess the distribution of age. Age was found to be nominally distributed and hence were reported.

TABLE 1

PATIENT CHARACTERISTIC	FREQUENCY	%
AGE	MEAN: 42.67YRS	SD=8.48
HISTOLOGY	**TOTAL =149**	
SCC	139	92.7%
ADENOCARCINOMA	10	2.60%
STAGE	**TOTAL N = 151**	
IB2	11	7.28
IIA	8	5.30
IIB	83	54.97
IIIA	1	0.66
IIIB	48	31.79
HAART INITIATED	**TOTAL N = 146**	
YES	34	22.52
NO	112	73.20
CHEMOTHERAPY GIVEN		
YES	4	2.60
NO	147	85.60
CD4 COUNT		
<200	34	22.52
>=200	112	77.48
HAEMOGLOBIN BEFORE DXT		
<10	146	96.69
>=10	5	3.31

The mean age reported was 42.67 years. This was in keeping with other studies seen in HIV positive patients. The Histology most commonly seen was squamous cell carcinoma (92.7%) compared to adenocarcinoma (2.60%). The commonest stage seen was stage IIB(54.97%) followed by stage IIIB (31.79%).

Of the 34 patients who were known to have been initiated on HAART, 38.20% (n=13) were initiated before the start of radiation therapy, and 61.80% (n=21) after the start of radiation therapy. No statistical evaluation could be done due to the small numbers in subgroup.

Chemotherapy status: The chemotherapy status of 10.6% of the patients were unknown. Only 4 patients (2.6%) were known to have undergone chemotherapy, while the rest (n=147) did not receive chemotherapy. The reasons for not receiving chemotherapy Stage IIIB disease (n=48) CD 4 count < 200 (n=34), and abnormal renal function.

Radiation technique. All the patients (n =151) had AP/PA simulation.
Brachytherapy was given with a ring applicator in 143(95.97%) of patients. Joslin application was given to 6(4.03%) patients

CD4 count was divided into 2 groups. The majority of patients had a \CD4 count above 200 (77.48%).
The majority of patients had a Haemoglobin level less than 10g/dl prior to radiation(96%).

TABLE 2 (Appendix 3 reference)

TREATEMENT CHARACTERISTICS	FREQUENCY	%
ACUTE SKIN REACTION		
NONE	34	22.67
GRADE 1	10	6.67
GRADE 2	58	38.67
GRADE 3	47	31.33
GRADE4	1	0.67
ACUTE GUT REACTION		
NONE	84	56.00
GRADE 1	29	19.33
GRADE 2	37	24.67
ACUTE GIT REACTION		
NONE	93	62.00
GRADE 1	24	16.00
GRADE 2	32	21.33
LATE TOXICITY		
PROCTITIS	14	9.46

CYSTITIS	24	16.22
VVF	5	3.38
RVF	4	2.70
NONE	101	68,24
TREATMENT DELAY		
<6 WEEKS	12	7.94
>=6 WEEKS	139	92.05
TREATMENT TIME		
<6 WEEKS	80	52.98
>=6 WEEKS	71	47.02
FAILURE SITE		
LOCAL	9	5.96
BRAIN	1	0.66
LUNG	0	0.00
BONE	4	2.65
TOTAL DOSE: POINT-A	MEAN = 73.76GY	SD = 7.60

The most commonly seen acute skin reaction was grade 2 (38.67%). Acute toxicity: there was no difference for acute skin reaction (p=0.635), GUT (p=0.073) and GIT (p= 0.223)
The most common late complication was cystitis (16.22%) However these results must be interpreted with caution as most of the patients (68.24%) were lost to follow up and therefore were not able to be included. There was a treatment delay of more than 6 weeks in 92.05% of patients and this contributes to the outcomes. The most common failure site was local in 5.96% in those patients that did follow up.

TABLE 3

UNIVARIATE				**MULTIVARATE**		
CHARACTERISTIC	**OR**	**P-VALUE**	**CI**	**OR**	**P-VALUE**	**CI**
ACUTE SKIN REACTION : BASE=ON HAART						
NOT ON HAART	0.84	0.635	0.41-1.73	0.92	0.645	0.64 - 1.32
ACUTE GUT REACTION						
NOT ON HAART	1.98	0.073	0.94 -4.17	1.65	0.088	0.93 - 2.93

ACUTE GIT REACTION						
NOT ON HAART	1.63	0.223	0.74 -3.59	1.33	0.313	0.76 – 2.
LATE TOXICITY						
NOT ON HAART	3.27	0.002	1.53 -7.01	1.46	0.003	

This above figure showed that patients who were not initiated on HAART had a 1.98 chance of having acute GUT reactions while on radiation treatment. The most significant (p value 0.002) variable seen was that patients not on HAART who were 3 times more likely to have a late toxicity than those patients who had started HAART treatment.

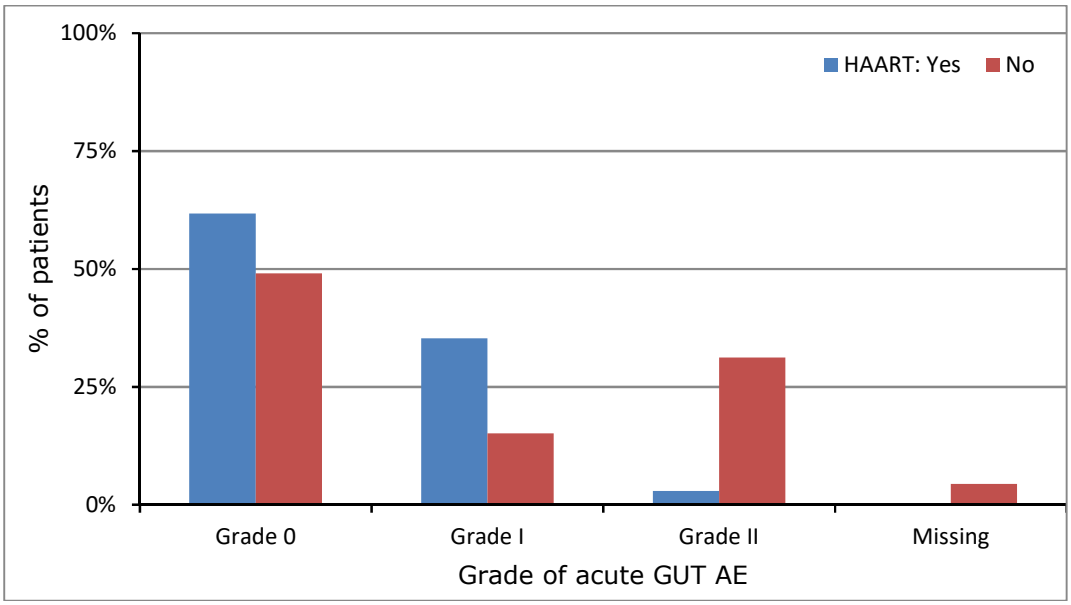

FIGURE 3

Survival analysis: This was done taking the last day they were seen as alive, dead and treatment failure which were negative events. When treatment failure came before the date last seen, the number of months to treatment failure was used.
The Kaplan Meyer graph was used to assess the overall cancer related deaths. This was then analyzed to look at patients who initiated HAART, and by Stage

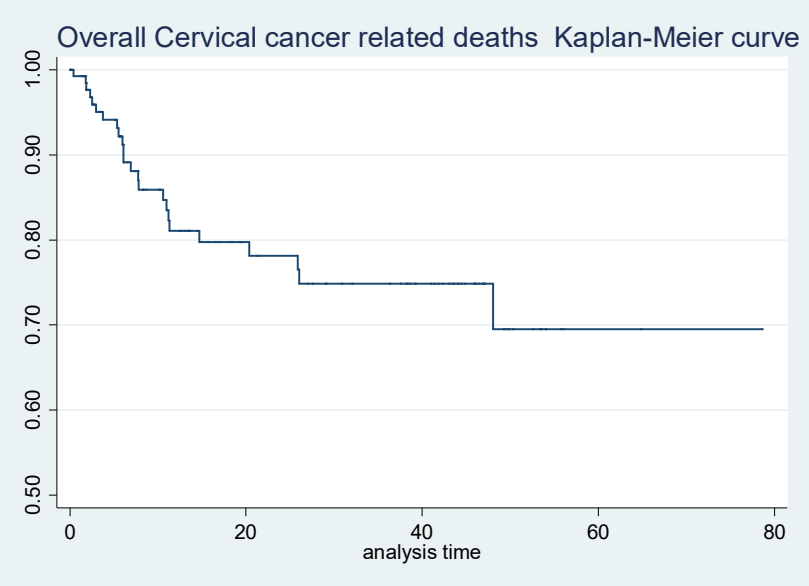

FIGURE 4 (Analysis time in months)

This graph shows that overall survival seen in this study cohort was 47 months in 70 % of patients.

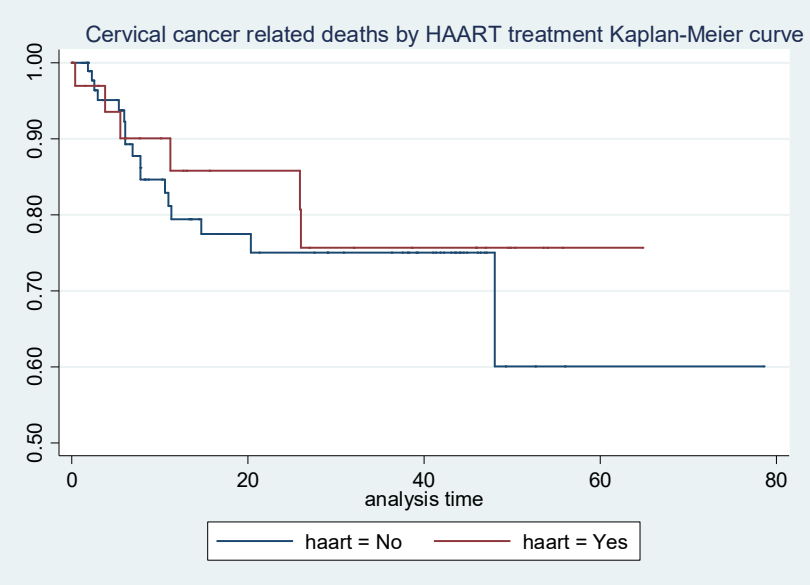

FIGURE 5 (Analysis time in months)

The above graph shows that there was not much difference seen in survival in patients who had initiated HAART treatment to those who did not start HAART especially in the first 15 months following therapy. Between 15 and 20 months following therapy, the trend showed better survival in patients who had initiated HAART. This levelled out for patients on HAART, but the survival dropped for patients not on HAART at 45 months.

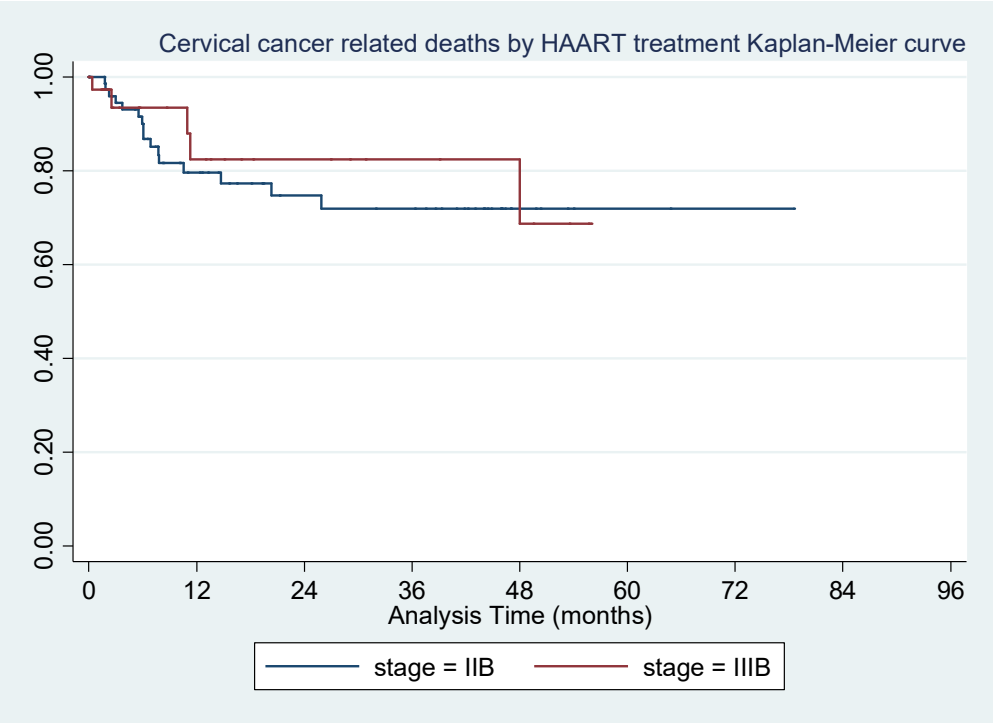

FIGURE 6
The graph above shows that Stage was also important in terms of survival. Those patients who were stage IIIB had a trend for poor survival than patients who were Stage IIB when looking at 12 to 48 months after treatment. These Stages were the most common stages seen in this study cohort.

DISCUSSION

This study had important questions to be answered when managing a special cohort of patients with HIV. Review of patients while on treatment is important, and ideally should be consistent either by using one doctor or by having a standard form. There were limitations to the study that limited these vital answers. The most important was follow up. The use of patient files, with numerous doctors seeing the patients, meant that there was no uniformity in assessing the acute reactions. The patients lost to follow up was why the results for overall survival could not be used with any accuracy.

The standard of care for the treatment of cancer of the cervix is concurrent chemo-radiotherapy for the best outcomes. In our study, the majority of patients (85.6%)did not receive chemotherapy, with only 4 patients (2.6%) receiving chemotherapy. Therefore a comparison between patients receiving chemo-radiotherapy and radiotherapy alone could not be made. Reasons for not giving chemotherapy were mainly based on the fact that the renal function was not suitable for chemotherapy.

There is a bias in the use of chemotherapy in patients who have a CD4 count more than 200. This is based on a trial done in patients with anal cancer (16). This trial showed that patients with a CD4 count >than 200 had excellent disease control and acceptable morbidity as compared to patients with a CD4 count <200. In our study the median CD4 count was 309, and 26.2% of patients had a CD4 <200. The departmental protocol is that chemotherapy is excluded for patients with Stage IIIB cervical cancer, due to the lack of benefit seen in these patients(32).

The most commonly found problem was that HIV positive patients did not complete the recommended dose of chemotherapy(13).
In this study, the inclusion criteria were that patients must complete their treatment.

The demographic information was found to be similar between this study group and other studies done in developing countries. The median age at registration in this study was 41yrs (Range 26-67yrs). This was also found by Lomalisa et al, their study showed that HIV positive patients presented 10 yrs. earlier than their HIV negative counterparts (44yrs vs 53yrs) (5). A study by Gighangi et al from Kenya showed that their patients presented 5yrs younger as compared to HIV negative patients (19).

The stage of the cancer is also an important variable when predicting outcomes for HIV positive patients. In our study the majority of patients had either stage IIB (55%) or stage IIIB (31.8%). This is in line with other studies which have found that HIV positive patients present at advanced stages of the disease. Mainman et al found that 71% of patients had clinical stage II or more when compared to 37% of HIV negative patients in a study of 115 patients. There was no HIV patient who presented with early stage disease (stage 1A or IB) (20). The advanced stage of disease can also be correlated with CD 4 count. Lomalisa et al found that patients with CD 4 count <200 were significantly more likely to have advanced stage disease at diagnosis (5). In our study there was no correlation between the CD4 and advanced stage.

Haemoglobin is also a prognostic factor for patients with cancer of the cervix. This is because tumour hypoxia is a potential mechanism of resistance to radiation in bulky cervical tissues. In our study the hemoglobin levels at the start of treatment was >11g/dl for the majority of patients (45%) and <10g.dl was 15%. The haemoglobin levels at 3 weeks during radiotherapy had 56.3% of missing data and therefore could not be analyzed. In the department we accept haemoglobin levels above 10g/dl prior to treatment of cervical cancer with radiation. Those patients who have haemoglobin levels < 10g/dl are transfused.

In our study only 22.2% of patients were initiated on HAART at some point during their treatment. Of the 34 patients who had started HAART, 13(38.2%) were initiated prior to radiation therapy and 21(61.8%) started after radiation therapy was commenced. Due to the small group size obtained this did not translate to any meaning correlation on the impact of initiating HAART and outcomes.

There was a delay between registration and the start of treatment. The median time to delay was 3 months. The median treatment duration was 5 weeks for the majority of patients (75%) The reasons for prolonging treatment were treatment breaks due to toxicity. The longest total treatment time was 10 weeks. An extended treatment time of more than 6 weeks has been shown to have a 14 % decrease in local control over 4 years especially in stage IIIB which was seen in 31.8% of patients in our study (10).
For this study, it was difficult to look at the effect of treatment time and local failure, due to the lack of proper follow up in the study cohort.

It is important to note that while the cell kinetics in head and neck cancers and cervical cancer may be similar, there is a component of using brachytherapy in addition to external beam radiation in the treatment of cervical cancer. This means that an increased radiation dose can be given to the tumour to compensate for the accelerated repopulation that can happen when treatment is prolonged. It has been shown that completing brachytherapy is essential in getting better outcomes (7). This is important then when looking at the total dose received by point A. The average dose given to Point A was 74Gy in our study which was below what is recommended by the American Brachytherapy association (26). Therefore we need to look at this closely to see the impact of a decreased total dose and on outcomes especially in HIV positive patients with cervical cancer.

The improvement of total dose can be done by optimizing the brachytherapy technique. In a study done by Niel et al, they found that by adapting the existing high dose rate applicator, they could get higher dosimetric accuracy and more adequate irradiation(27).

In terms of the acute and late complications, Gichanji et al looked at the HIV impact on acute toxicity and pelvic tumour control. He found that HIV infection was associated with a 7-fold higher risk of multisystem toxicity: skin, gastrointestinal tract (GIT) and genitourinary tract (GUT) systems. It was also an independent risk factor for treatment interruptions(30). However, in this study, the patients did not receive any brachytherapy due to constraints, and only received external beam radiation. In our study most patients had Grade II acute reactions to skin, GUT, GIT.

Long term side effects were difficult to access due to the lack of follow up in our patients. In studies done by Kapp et al, they found that all severe bowel complications occurred within 1.5 years whereas urinary tract sequelae continued to develop throughout the follow-up period. FIGO stage was associated with a significant increase in late sequelae (29). The

probability of late toxicities of any grade found in a study by Logar et al were 16.6% for gastrointestinal, 15.7% for genitourinary and 22.3% for the vagina in the first 5 yrs. of treatment. The mean interval before developing the late complications was 27.6 months(31). It is worth noting that in this study they used 2D (2 dimensional) treatments as we do in our unit, and their mean dose to point A was 66.5Gy which is lower than the dose used by our department. It may be possible that we would perhaps anticipate similar results should we do a prospective study in our patients.

The effect of these long term side effects on the quality of life has been looked at by Kuku et al (32). They found that women with cervical cancer were younger and appeared to suffer more severe symptoms of late bowel toxicity, which impacted negatively on their quality of life.

In terms of overall survival, in our study, this was difficult to ascertain with certainty due to the lack of follow up in the study group, therefore there was a lot of missing data. When looking at the results where all patients are alive, overall survival is above 90%. The follow up in our department is done by taking 2 telephone numbers from the patient. They are given dates and contacted should they not arrive for the treatment itself. During follow up after completion of treatment, patients are not called if they do not arrive on their expected date. This would have to be changed for data to be collected.

LIMITATIONS AND SUGGESTIONS TO IMPROVE:

Limitations included

- Incomplete data in the files.
- Inability to compare certain aspects of the study.
- No information regarding the type of HAART initiated.
- Patients were lost in follow up. This made it difficult to know the overall survival with any accuracy.

Suggestions include:

- A standard form for clerking and review while on treatment.
- A way to contact patients when they do not arrive for follow up.
- A booking system might be useful.
- A prospective study to further evaluate this group of patients with accuracy and for a study in outcomes with radiation.

CONCLUSION:

The study showed that HIV positive patients do tolerate the radiation treatment well. The acute side effects of radiation were easily treatable, and no prolonged treatment breaks took place. They are able to complete the prescribed radiation treatment that is recommended. They are, however, have 3 times more chance of developing late radiation toxicities without the addition of HAART. The overall survival with available information was above 90% for the study cohort. Further prospective studies are needed.

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Appendix 1:

Table 2. Stage-Based Management of Localized Cervical Cancer

Stage	Treatment	
Early disease	Stage IA1	Surgery, total hysterectomy, radical hysterectomy, and conization
	Stage IA2, IB, or IIA	Combined external beam radiation with brachytherapy and radical hysterectomy with bilateral pelvic lymphadenectomy for patients with stage IB or IIA disease Radical vaginal trachelectomy with pelvic lymph node dissection is appropriate for fertility preservation in women with stage IA2 disease and those with stage IB1 disease whose lesions are ≤2 cm Cisplatin-based chemotherapy with radiation for stage IA-IIA patients who have specific high-risk features (positive lymph nodes, surgical margins, and/or parametria)
Advanced disease	Stage IIB, III, or IVA	Cisplatin-based chemotherapy with radiation
Metastatic disease	Stage IVB and recurrent cancer	Cisplatin on a palliative basis, radiation therapy for control of bleeding and pain, and systemic chemotherapy for disseminated disease including cisplatin, paclitaxel, carboplatin, docetaxel, topotecan, and bevacizumab

Source: References 5, 20.

Appendix 2

Table 1: Study protocols of the randomized controlled trials evaluating chemo-radiation in cancer cervix.

Study protocol	Author and year	Study arm	Control arm	Stage
GOG 123	Keys[3] 1999	Cisplatin (40 mg/m^2) weekly for 6 weeks and RT followed by extra-fascial hysterectomy	RT followed by extra-fascial hysterectomy	IB2
SWOG 8797	Peters[4] 2000	Cisplatin (70 mg/m^2) and 5-FU (4000 mg/m^2 infused over 4 days) every three weeks for 4 courses and RT	RT alone	IA2, IB, IIA
GOG 85	Whitney[5] 1999	Cisplatin (50 mg/m^2) on days 1, 29 and 5-FU 1000 mg/m^2 per day on days 2-5 and 30-33 during EBRT and RT	RT and Hydroxyurea (80 mg/Kg twice a week	IIB, III, IVA
GOG 120	Rose[6] 1999	Cisplatin (40 mg/m^2) weekly for 6 weeks and RTCisplatin (50 mg/m^2) and 5-FU (4000 mg/m^2 infused over 4 days) every three weeks for 2 courses and Hydroxyurea (2 mg/m^2) twice a week for 6 weeks and RT	RT and Hydroxyurea (3 mg/m^2) twice a week for 6 weeks	IIB, III, IVA
RTOG 90-01	Morris[7] 1999	Cisplatin (75 mg/m^2) and 5-FU (4000 mg/m^2 infused over 4 days) on days 1 and 22 and RT	RT alone	IB, IIA IIB - IVA

Appendix 3:

Appendix – 1

Acute RTOG scale	Grade 1	Grade 2	Grade 3	Grade 4
GU	Frequency of urination or nocturia twice pretreatment habit/dysuria or urgency not requiring medication.	Frequency of urination is less frequent than every hour (day: 12-16 times; nocturia 5-8 times)/dysuria, urgency, bladder spasm requiring local anesthetic.	Frequency of urination is more frequent than every hour (day>16 times; nocturia>8 times)/ dysuria, bladders spasm, urgency requiring frequent regular narcotic/ gross hematuria.	Hematuria requiring transfusion/ obstruction not due to clots/ ulceration/ necrosis.
GI	Increased frequency or change in quality of bowel habits not requiring medication/ rectal discomfort not requiring analgesics.	Diarrhea requiring parasympatholytic drugs/ mucous discharge not necessitating sanitary pads/ rectal or abdominal pain requiring analgesics.	Diarrhea requiring parenteral support/ severe mucous or blood discharge necessitating sanitary pads/ abdominal distension.	Obstruction, fistula, or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion.
Late RTOG/ EORTC scale	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
GU	Frequency during day 0,5-1h; nocturia 2-3; slight dysuria or microscopic hematuria requiring no medication, bladder capacity > 300 cc.	Frequency during day 1-2h; nocturia 4-6; moderate dysuria or intermittent hematuria requiring medication, bladder capacity 150-300 cc.	Frequency during day >2h; nocturia >6; severe dysuria, frequent hematuria, bladder capacity 100-150 cc.	Necrosis, severe hemorrhagic cystitis, bladder capacity < 100 cc.
GI	Mild diarrhea, mild cramping, bowel movements 2-5/day, slight rectal discharge or bleeding.	Moderate diarrhea, intermittent severe cramping, bowel movements >5/day, rectal discharge, intermittent bleeding.	watery diarrhea, obstruction requiring surgery, bleeding requiring surgery.	Necrosis, perforation.

Grade 0 = no morbidity; Grade 5 = death; GU = genitourinary; GI = gastrointestinal.

APPENDIX 4:

R14/49 Dr Sibahle Ndamase

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M131114

NAME: (Principal Investigator)	Dr Sibahle Ndamase
DEPARTMENT:	Radiation Oncology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Patterns of Practice in Carcinoma of the Cervix: A Retrospective Analysis of HIV Patients Treated Radiation at Charlotte Maxeke Johannesburg Academic Hospital 2008-2009
DATE CONSIDERED:	29/11/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Vinay Sharma
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	02/12/2013

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

APPENDIX 5: clinical research form
CODE NO:

AGE AT PRESENTATION:

IS HAART INITIATED? 1: YES, 2: NO DATE STARTED:

CD4 COUNT BEFORE TX:

CD4 COUNT AT F/U:

STAGE:

REGISTRATION DATE: (YYYY/MM/DD)

DATE 1ST TREATED (YYYY/MM/DD)

DATE LAST TREATED (YYYY/MM/DD)

HB AT START OF TREATMENT: HB AT 3/52:

RADIATION GIVEN:

TOTAL DOSE: EXT DOSE:
BRACHY:

RECTAL DOSE 1: RECTAL DOSE 2:

BLADDER DOSE1: BLADDER DOSE 2:

RADIATION TECHNIQUE:

RING APPLICATION:

JOSLIN APPLICATION:

ACUTE TOXICITY:

ACUTE SKIN REACTION DATE: ACUTE GUT DATE:
ACUTE GIT DATE:

RADIATION RELATED LATE TOXICITY:

PROCTITIS:
CYSTITIS:
VVF:
RVF:

FOLLOW UP:
ALIVE WELL:

TX FAILURE DATE: (YYYY/MM/DD)
FAILURE SITE:

DEMISE: IF YES, DATE: