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A RANDOMISED STUDY TO COMPARE RADICAL CONCURRENT CHEMORADIATION AGAINST RADICAL RADIOTHERAPY, AS TREATMENT OF CANCER OF THE CERVIX IN HIV INFECTED PATIENTS

A Research Report Submitted to the Faculty of Health sciences, University of the Witwatersrand, in Partial Fulfillment of the Requirements for the Degree of Master of Medicine in the Branch of Radiation Oncology

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ABSTRACT

Title

A RANDOMISED STUDY TO COMPARE RADICAL CONCURRENT CHEMORADIATION AGAINST RADICAL RADIOTHERAPY, AS TREATMENT OF CANCER OF THE CERVIX IN HIV INFECTED PATIENTS

Objectives

Cancer of the cervix is one of the commonest cancers in South African females. Up to 30% of patients are HIV positive. The addition of chemotherapy to radiotherapy has been shown to significantly improve local control and survival and concurrent chemoradiation is the standard treatment for locally advanced cancer of the cervix. There is very limited literature available concerning the tolerance and efficacy of this treatment in HIV positive patients. This study aims to assess the acute toxicity of combined modality treatment in these patients. This study is part of a multicenter International Atomic Energy Agency sponsored study.

Materials and methods

Patients with FIGO stage IB2 to IIIB (without hydronephrosis) cervical cancer and who are HIV positive, were randomized to receive radiotherapy alone or chemo-radiation. All patients received 46 Gy in 23 fractions external beam radiation and high-dose-rate-

brachytherapy 8 Gy x 3 fractions. Chemotherapy consisted of bolus Cisplatin 30mg/m^2 weekly given concurrently with the radiotherapy. Acute treatment toxicity was documented weekly during treatment.

Results

64 patients were recruited to the study. 31 patients were randomized to the chemoradiation arm and 33 patients to the radiation alone arm. Of the 64 patients recruited to the study, 6 in the chemoradiation arm and 5 in the radiation only arm did not receive any treatment and were therefore not evaluated. Stage IIB was the most common stage. The mean CD4 count was 410 in the chemoradiation arm vs. 358.4 in the radiation only arm at randomization. Only 6 patients were on antiretroviral therapy at start of treatment, 3 in each arm. The number of chemotherapy cycles received by patients in the chemoradiation arm ranged between 0 and 5 cycles. A total of 96 chemotherapy cycles were administered, with a median of 4 cycles per patient. Overall, at least 76% of patients received at least 4 cycles of chemotherapy. The full five intended courses of cisplatin were administered in 10 (40%) patients. Chemotherapy was not administered most commonly due to toxicity (renal, leucopaenia), other reasons being logistical and non compliance. The principle major adverse effects observed were leucopaenia and cutaneous reactions.

The incidences of Grades 3 and 4 leucopaenia were significantly higher in the chemoradiation arm. 41 of the 51 evaluable patients at 3 months had complete responses to treatment, 20 (80%) in the chemoradiation arm and 21 (80.7%) in the radiation alone arm.

Conclusion

The treatment was well tolerated. This study has shown that radical chemoradiation in conventional doses can be given safely in HIV positive patients with invasive cervical cancer. Many patients did not receive the planned cisplatin dose due to various factors not related to toxicity. Chemoradiotherapy is a resource intensive treatment, involving considerable input from doctors, nurses, radiographers and pharmacists and a high degree of coordination is necessary for treatment to be delivered effectively. In general the same principles that guide the oncologic management of immunocompetent patients should be applied to HIV patients. Further follow up is required to assess survival functions. Larger studies assessing toxicity and efficacy of concurrent chemoradiation in cervical cancer patients who are also HIV positive need to be done.

DECLARATION

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

Signed at: Lusaka, Zambia on the 7th of May 2009

Signed: 

DEDICATION

To the Source and Sustainer of all Potential, my personal savior, the Lord Jesus Christ.

To my precious husband, Kateshi and my parents, Steven and Elizabeth.

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PRESENTATIONS

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

- University of Witwatersrand, Faculty of Health Sciences Research Day- August 2006.
- South African Society of Clinical and Radiation Oncology (SASCRO) and South African Society of Medical Oncology (SASMO) congress April 2007.

TABLE OF CONTENTS **Page**

ABSTRACT……..……...ii

DECLARATION…….....v

DEDICATION ……vi

ACKNOWLEDGEMENTS…….....vii

PRESENTATIONS …….....viii

TABLE OF CONTENTS ……..ix

LIST OF TABLES……..xii

LIST OF FIGURES…….....xiii

LIST OF ABBREVIATIONS…….....xiv

1.0 INTRODUCTION…….....1

1.1 Management of cervical cancer…….....2

1.1.1 Concurrent Chemotherapy and Radiation Therapy…….....3

1.1.1.1 Rational for combining chemotherapy with radiotherapy……....3

1.1.1.2 Clinical evidence …….....3

1.1.1.3 Prospective randomized trials of concurrent radiotherapy …….....4

1.2 HIV infection and invasive cervical cancer…….....17

1.2.1 Management of cervical cancer in HIV positive patients…….....19

1.3 Highly active antiretroviral therapy (HAART) and its …….....22

Impact on prognosis in HIV infected patients

1.4 Toxicity of chemoradiotherapy……23

1.4.1 Toxicity of chemotherapy…….....24

1.4.2 Acute toxicity of chemoradiotherapy…….....24

1.4.3 Studies reporting on acute toxicity and compliance……25

2.0 CURRENT STUDY

2.1 Background……27

2.2 Objectives……27

2.3 Materials and Methods…….....28

2.3.1 Inclusion criteria……...28

2.3.2 Exclusion criteria…….....29

2.3.3 Staging work up……...29

2.3.4 Treatment…….....30

2.3.4.1 External beam radiotherapy…….....30

2.3.4.2 Brachytherapy……..33

2.3.4.3 Concurrent chemotherapy……..……..34

2.3.5 Evaluation of toxicity……..……...35

2.3.6 Criteria for response……..……36

2.3.7 Data analysis…….……..36

3.0 RESULTS……..……37

3.1 Patient characteristics……..…37

3.2 Treatment delivery……..39

3.2.1 Radiotherapy delivery…….39

3.2.2 Cisplatin administration……..42

3.3 Toxicity……...44

3.4 Treatment efficacy……..49

4.0 DISCUSSION ……...50

5.0 STUDY LIMITATIONS……..58

6.0 CONCLUSION…….59

7.0 REFERENCES…….61

8.0 APPENDIX……69

LIST OF TABLES **Page**

TABLE 1.1.1.2.1	Prospective randomized trials of concurrent radiotherapy and chemotherapy for patients with local regionally advanced cervical cancer	4
Table 1.1.1.3.1	Major adverse effects – Rose et al	11
Table 1.1.1.3.2	Major adverse effects – Whitney et al	12
Table 1.1.1.3.3	Major adverse effects – Keys et al	13
Table 1.1.1.3.4	Major adverse effects – Peters et al	14
Table 1.1.1.3.5	Major adverse effects – Morris et al	15
Table 1.1.1.3.6	Major adverse effects - Pearcey et al	16
Table 1.2.1.1	Treatment recommendations for cervical carcinoma in Human Immunodefiency Virus infected women.	21
Table 3.1.1	Patient characteristics	37
Table 3.2.1.1	Treatment Delivery	40
Table 3.2.1.2	Treatment fields	41
Table 3.2.1.3	Treatment Duration	41
Table3.2.2.1	Cycles of chemotherapy received in the chemoradiation arm	43
Table 3.2.2.2	Reasons for omitting chemotherapy	43

Table 3.3.1	Adverse effects	46
Table 3.3.2	Grade 3 and 4 adverse effects	47
Table 3.4.1.	Response to treatment	49
Table 4.1	Grade 3 and 4 toxicity in comparison to other trials using weekly cisplatin	53
Table 4.2	Chemotherapy cycles in comparison to other studies with weekly cisplatin	56

LIST OF FIGURES

Page

Figure 2.3.4.1.1	Anterior-posterior simulation film	32
Figure 2.3.4.1.2	Lateral simulation film	32
Figure 2.3.4.2.1	Lateral brachytherapy insertion radiograph	33
Figure 2.3.4.2.2	Anterior-posterior brachytherapy insertion radiograph	34
Figure 3.1.1	Stage distribution by protocol	38
Figure 3.3.1	CD4 trends during and after treatment	48

LIST OF ABBREVIATIONS

FIGO…….International Federation of Gynaecologists and Obstetricians

5 FU……...5 Fluorouracil

GOG.....Gynaecology Oncology Group

CT.....Chemotherapy

SWOG.....South West Oncology Group

RTOG.....Radiation Therapy Oncology Group

NCIC.....National Cancer Institute of Canada

CDDP.....Cisplatin

RT.....Radiation Therapy

HIV.....Human Immunodeficiency virus

AIDS.....Acquired Immunodeficiency Syndrome

HAART.....Highly active antiretroviral therapy

$5HT_3$.....5-Hydroxytryptamine-3

AP/PA.....Anterior-posterior/posterior-anterior

1.0 INTRODUCTION

Cervical cancer is the second most common cancer in women worldwide (471,000 annual cases, 233,000 deaths). Almost 80% of cases occur in less developed countries, where cervical cancer accounts for 15% of cancer in women, with a life time risk of 2%. In more developed countries it accounts for only 4.2% of new cancers, with a life time risk of 1%. The highest incidence rates are observed in Latin America, the Caribbean, Sub-Saharan Africa, and South and Southeast Asia. In more developed countries, incidence rates are relatively low (1).

In South Africa, cancer of the cervix comprised 20% and 17% of all cancer cases in 1998 and 1999, respectively. It was the leading cancer in women in 1998 and the second leading cancer following breast cancer in 1999. South African women had a life time risk of developing cervical cancer of 1 in 26 in 1998 and 1 in 31 in 1999. It is the leading cancer in black women, with the second highest rates in the coloured population, with Asian women having the lowest cervical cancer incidence rates (2).
In Johannesburg Hospital, Radiation Oncology department, the number of patients with cancer of the cervix treated ranges between 662 and 721, annually (3).

Women represent an increasing proportion of the Human immunodeficiency virus (HIV) infected population. HIV infection is a common comorbid infection in patients with invasive cervical cancer in the African setting.

Women infected with HIV have a significantly higher risk of developing squamous intraepithelial lesions (SIL), the premalignant stage of cervical cancer (4, 5). Studies have also pointed to an association between HIV infection and both invasive carcinoma of the cervix and a faster progression to more advanced stages of cervical carcinoma, the latter with higher treatment failures and more recurrences (4, 5 and 6). HIV seropositive patients with invasive cervical cancers have not been evaluated in detail regarding the radiation response, its toxicities, patient compliance and patterns of survival. Standard treatments for this set of patients have not been defined (7).

1.1 Management of cervical cancer

The choice of treatment of cervical cancer depends on the stage of the tumour. For smaller tumours confined to the cervix (stages IA and IB1) the treatment consists of surgery or radiotherapy, with 5-year survival rates of 80-95 % (8-11). For more advanced disease (stage IB2-IVA) the 5-year survival is less favourable with radiotherapy as the sole modality. Therefore many attempts have been made over the last decades to improve the treatment outcome in this group. The tolerance of the normal tissues in the pelvis was a major barrier for radiotherapy and combinations of chemotherapy and radiotherapy were subsequently studied.

Concurrent Chemotherapy and Radiation Therapy

1.1.1.1 Rationale for combining chemotherapy with radiation therapy

Several phase II studies showed promising results of radiotherapy and concurrent chemotherapy with 3-year survival rates of 40% to 69% in stage III and IV tumours (12-19). Cisplatin is believed to augment the effects of radiotherapy by inhibiting the repair of radiation induced sublethal damage and by sensitising hypoxic cells to radiation. Because of its cytotoxic effect, the drug reduces the bulk of tumours, which leads to reoxygenation of the tumour and entry into a radiosensitive phase of the cell cycle (20).

1.1.1.2 Clinical evidence

Since 1999 five randomised trials (Table 1.1.1.2.1) have studied the addition of chemotherapy to radiotherapy and showed concomitant chemotherapy with radiotherapy improves overall survival, progression free survival and reduces local and distant recurrence (21-25).

TABLE 1.1.1.2.1 Prospective Randomised Trials of Concurrent Radiotherapy and Chemotherapy for Patients with Local Regionally Advanced Cervical Cancer

Trial	Eligibility	n	CT in investigational arm	CT in Control Arm
Rose et al (23) GOG 120	IIB-IVA	526	Cisplatin 40mg/m^2/wk Up to 6 cycles Cisplatin 50mg/m^2 5FU4g/ m^2/96hrs (3 cycles) HU 2g/m^2 (2x weekly) 2 cycles	HU 3g/m^2 (2xweekly) HU3g/m^2 (2xweekly)
Morris et al (22) RTOG 9001	IB-IIA>5cm, IIB-IVA	403	Cisplatin 75mg/m^2 5FU 4g/m^2/96h (3 cycles)	None
Keys et al (21) GOG 123	IB >4cm followed by hysterectomy	369	Cisplatin 40mg/m^2/wk (up to 6 cycles)	None
Whitney et al (24) GOG 85	IIB-IVA	368	Cisplatin 50mg/m^2 5FU 4g/m^2/96h (2 cycles)	HU3g/m^2 (2xweekly)
Peters et al (25) SWOG 8797	I-IIA after radical hysterectomy with nodes, margins or parametrium positive	268	Cisplatin 70mg/m^2 5FU 4g/ m^2 / 96h (2 concurrent + 2 adjuvant cycles)	None
Pearcy et al (26) NCIC	IB-IIA (5cm) IIB-IVA or Pelvic lymphnode involvement	268	Cisplatin 40mg/m^2/wk (up to 6 cycles)	None

HU- hydroxyurea, 5-FU- 5 Flourouracil, CT - chemotherapy

1.1.1.3 Prospective randomised trials of concurrent radiotherapy and chemotherapy for patients with local regionally advanced cervical cancer

Gynaecology Oncology Group (GOG) 120 (23)

Rose et al performed a trial of radiotherapy in combination with 3 concurrent chemotherapy regimens – cisplatin alone; cisplatin, 5-FU and hydroxyurea; and hydroxyurea alone. Women with cervical cancer stage IIB- IVA without para-aortic lymph node involvement were included. The analysis included 526 women. The median duration of follow up was 35 months. Both groups that received cisplatin had a higher rate of progression free survival than the group that received hydroxyurea alone. Haematologic toxicity was the principal adverse effect in this trial. The frequencies of grade 3 and 4 leucopaenia were significantly higher with the 3 drug combination than with the 2 single drug regimens (Table 1.1.1.3.1). There were no significant differences in the duration of radiotherapy between the 3 groups.

Gynaecology Oncology Group (GOG) 85 (24)

Whitney et al randomised 388 patients with FIGO stage IIB, III or IVA cervical cancer with negative cytologic washings and para-aortic lymph nodes to receive either standard whole pelvic radiotherapy with concurrent 5-FU infusion and bolus cisplatin or the radiation plus hydroxyurea.

Adverse effects (recorded and graded according to GOG adverse effects criteria) were predominantly haematologic and gastrointestinal in both regimens (Table 1.1.1.3.2). Severe life threatening leucopoenia was more common in the hydroxyurea group than the cisplatin-5-FU group. The difference in progression free survival was statistically significant in favour of the cisplatin and 5-FU group. The sites of progression in the 2 treatment groups were not substantially different. Survival was significantly better for the patients randomised to cisplatin and 5-FU group.

Gynaecology Oncology Group (GOG) 123 (21)

Keys et al randomised women with bulky stage I cervical cancers (tumours greater/equal to 4 cm in diameter) to receive radiotherapy alone or in combination with cisplatin (40 mg/m^2/weekly for 6 doses), followed in all patients by adjuvant hysterectomy. Women with evidence of lymphadenopathy on computed tomographic (CT) scanning or lymphangiography were ineligible. The cumulative dose of external pelvic and intracavitary radiation was 75 Gy to point A and 55 Gy to point B. Cisplatin was given during radiation and adjuvant hysterectomy was performed 6 weeks later. The rates of progression free survival and overall survival were significantly higher in the combined therapy group at 3 years. However, in the combined therapy group there were higher incidences of grade 3 and grade 4 adverse haematologic and gastrointestinal effects (Table 1.1.1.3.3).

South West Oncology Group (SWOG) 87-97 (25)

Peters et al reported results of an Intergroup SWOG and GOG study with clinical stage IA2, IB and IIA carcinoma of the cervix, initially treated with radical hysterectomy and pelvic lymphadenectomy, and who had positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametria. Patients received 49.3 Gy in 29 fractions to a standard pelvic field with/without bolus cisplatin 70 mg/m^2 and a 96-hour infusion of 5-FU 1000 mg/m^2/day 3 weekly for 4 cycles, with the first and second cycles given concurrent to the radiation. The progression free survival and overall survival was significantly better in the patients who received chemoradiation. The median follow up was 43 months. The 4-year survival rate for women on the concurrent Cisplatin and 5 Fluorouracil and the irradiation arm was 81%, versus 71% for women on the pelvic radiation arm. Grade 3 and 4 hematologic toxicity and gastrointestinal toxicity were more frequent in the chemoradiation arm (Table 1.1.1.3.4).

Radiation therapy Oncology Group (RTOG) 90-01 (22)

Morris et al compared the effect of radiotherapy to a pelvic and para-aortic field with that of pelvic radiation and concurrent chemotherapy with fluorouracil and cisplatin in women with advanced cervical cancer confined to the pelvis.

403 patients were randomised to receive either 45 Gy of radiation to the pelvis and para-aortic nodes or 45 Gy of radiation to the pelvis alone plus 2 cycles of fluorouracil and cisplatin. 5 year survival was 73% in the chemoradiation arm and 58% in the radiation alone arm. Disease free survival rates at 5 years were 67% in the combined therapy group and 40% among patients in the radiotherapy alone group. The rates of both distant metastasis and locoregional recurrences were significantly higher among patients treated with radiotherapy alone. The seriousness of side effects was similar in the 2 groups, with a higher rate of reversible haematologic effects in the combined-therapy group (Table1.1.1.3.5).

Negative trial

National Cancer Institute of Canada (NCIC) (26)

Pearcy et al randomised 259 patients with FIGO stage IB to IVA squamous cell cervical cancer to receive radiotherapy (external beam radiotherapy and brachytherapy) plus weekly cisplatin chemotherapy (40 mg/m^2) (arm 1) or the same radiotherapy without chemotherapy (arm 2). No significant difference was found in progression free survival or 3 and 5 year survival rates.

The results of this study conflicts with the results of previous trials. One possible explanation suggested for the lack of a demonstrable effect of cisplatin in this study is that the addition of cisplatin may only be effective when the radiation is protracted as in the studies reported by Rose et al (23) and Whitney et al (24). In these studies the median duration of each treatment course was 62 and 64 days, respectively, compared with 51 days in the Canadian study. Each extra day by which the treatment is protracted may lose as much as 1.2% in local control probability resulting in worse survival. This may exaggerate the benefit of adjuvant chemotherapy when the primary modality of treatment is suboptimal. Another possible explanation may be that there was a significantly greater decrease in haemoglobin (Hb) levels in the chemoradiotherapy arm than in the radiotherapy only arm.

This is the largest randomised controlled trial to directly test the hypothesis that cisplatin given concurrently with radical radiotherapy would improve pelvic control rates and survival. The results of the other trials addressed similar but different questions.

Despite the results of the study performed by the National Cancer Institute of Canada, (26), the positive results of the other studies were supported by a meta-analysis, which showed an overall survival benefit of 12 % (27).

A Cochrane review published in 2002 concluded that concomitant chemotherapy and radiotherapy appears to improve progression-free survival and overall survival in locally advanced disease (28).

To date, the optimal chemotherapy schedule (multidrug or single drug regimen and optimal cisplatin dose) in combination with radiation is still debatable. The study by Rose et al. (23) demonstrated the equivalence of cisplatin alone and cisplatin combined with 5-flourouracil (5-FU), with greater toxicity in the latter.

In 1999, the United States National Cancer Institute issued an alert that concomitant chemotherapy should be considered with radiotherapy for all patients with cervical cancer. Radiotherapy with chemotherapy is the current standard of care for cervical cancer (29).

TABLE 1.1.1.3.1 Major adverse effects – Rose et al

Adverse effect	Radiotherapy and Cisplatin (n=176) (%)		Radiotherapy and cisplatin, 5FU and Hydroxyurea (N=173) (%)		Radiotherapy and Hydroxyurea (N=177) (%)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Leucopaenia	21	2	41	5	20	1
Thrombocytopenia	2	0	3	1	1	0
Other Hematologic	10	5	23	10	16	2
Gastrointestinal	8	4	9	9	10	4
Genitourinary	3	2	1	1	2	1
Cutaneous	1	1	3	2	3	1
Neurologic	1	0	1	0	1	1
Pulmonary	0	0	0	0	0	0
Cardiovascular	0	0	2	0	0	0
Fever	0	0	0	0	0	1
Fatigue	0	0	1	0	1	0
Pain	0	0	1	0	0	0
Weight loss	1	0	2	0	0	0
Hypomagnesaemia	2	1	0	0	0	0
Other	1	2	2	1	1	0

TABLE 1.1.1.3.2 Major adverse effects – Whitney et al

	5 FU/Cisplatin(n =169)		Hydroxyurea(n=188)	
Adverse Effect	Grade 3 (%)	Grade 4(%)	Grade 3(%)	Grade 4(%)
WBCs	2.4	1.2	21.8	2.7
Platelets	0.0	0.0	0.0	0.5
Other haematologic	2.4	0.6	4.8	1.1
Gastrointestinal	5.3	2.4	3.2	1.1
Genitourinary	1.2	0.0	0.0	1.6
Neurologic	0.0	0.0	0.0	0.0
Pulmonary	0.6	0.0	0.0	0.5
Cutaneous	2.4	0.0	1.6	0.0
Cardiovascular	0.6	0.0	0.0	0.0
Fever	1.2	0.0	1.1	0.0
Other	0.0	0.0	0.5	0.0

TABLE 1.1.1.3.3 Major adverse effects – Keys et al

Adverse Effect	Radiotherapy alone (n=186) Number of patients		Radiotherapy and cisplatin (n=183) Number of patients	
	Grade 3	Grade 4	Grade 3	Grade 4
Haematologic	3	0	33	6
Gastrointestinal	4	5	17	9
Genitourinary	5	1	1	2
Cutaneous	3	1	0	0
Neurologic	1	0	2	0
Other	4	1	9	3

TABLE 1.1.1.3.4 Major adverse effects – Peters et al

Toxicity	Chemoradiation (No of patients) n=122		Radiation alone (No of patients) n=112	
	Grade 3	Grade 4	Grade 3	Grade 4
Anaemia	3	1	0	0
Diarrhoea	8	4	1	0
Hearing	1	0	0	0
Granulocytopaenia	24	11	1	0
Infection	1	0	1	0
Leucopoenia	40	3	0	0
Desquamation	3	0	0	0
Nausea	17	0	0	0
Renal Failure	0	0	0	0
Thrombocytopenia	1	0	0	0
Vomiting	12	3	0	0

TABLE 1.1.1.3.5 Major adverse effects – Morris et al

Toxicity	Chemoradiation (n=195) Number of patients		Radiation alone (n=193) Number of patients	
	Grade 3	Grade 4	Grade 3	Grade 4
Haematologic	57	16	2	0
Cutaneous	4	1	0	1
Upper Gastrointestinal	14	3	2	0
Lower Gastrointestinal	12	5	1	0
Bladder	57	16	2	0

TABLE 1.1.1.3.6 Major adverse effects – Pearcey et al

Toxicity	Radiotherapy and Cisplatin		Radiotherapy	
	Grade3	Grade4	Grade3	Grade4
Hematologic	6	-	-	-
Cardiovascular	-	3	-	-
Endocrine	2	-	1	-
Gastrointestinal	11	5	1	-
Genitourinary	3	-	1	-
Infection	-	-	1	-
Metabolic	1	1	-	-
Neurologic	2	-	-	-
Skin	3	-	-	-

1.2 HIV infection and invasive cervical cancer

Cervical cancer in patients with HIV infection has been associated with a more rapid progression to more advanced stages of cervical carcinoma, higher treatment failures, more recurrences and metastasis to unexpected sites (4, 5).HIV infection in advanced stages is associated with certain opportunistic infections/conditions such as severe diarrhoea, non specific dermatosis and genital tract infections. Enhanced mucosal reactions in AIDS patients receiving radiotherapy in oropharyngeal cancer (30) and Kaposi's sarcoma (7) have been reported. These as well as the poor general condition of patients with HIV infection may worsen complications of radiation therapy thereby contributing to treatment interruption.

HIV seropositive patients with invasive cervical cancers however, have not been evaluated in detail regarding the radiation response, its toxicities, patient compliance and patterns of survival. Standard treatments for this set of patients have not been defined (7). HIV positive women with cervical cancer may be at increased risk for treatment complications and a shortened life expectancy. It is not yet clear if the therapeutic ratio for chemoradiotherapy as in HIV negative patients is maintained or altered in HIV infected patients. HIV positive cervical cancers are known to have poor response to radiotherapy and early recurrence resulting in poorer overall survival (4, 6).

Gichangi P. et al (31) prospectively looked at the impact of HIV on acute morbidity and pelvic tumour control following radiotherapy for cervical cancer. Concurrent chemotherapy was not used in this study. 218 patients of whom 20% were HIV positive were evaluated. It was noted that HIV infection was associated with a 7- fold higher risk of multisystem toxicity: skin, gastrointestinal and genitourinary tract systems. HIV infection was also an independent risk factor for treatment interruptions. HIV infection was independently and significantly associated with a 6-fold higher risk of residual tumour post external beam radiotherapy.

Another small retrospective study of 42 HIV positive cervical cancer patients looked at toxicity and outcome following treatment with radiotherapy (32). Thirty-two (76%) were planned for radical radiation therapy. However, the compliance was poor with only 22 patients completing the prescribed radiotherapy and only 50% of these achieved complete response. Grade 3-4 acute gastrointestinal toxicity was seen in 14% of patients and grade 3 acute skin toxicity was seen in 27% of patients, leading to treatment delays.

Studies in anal cancer also showed that HIV positive patients have a poorer tolerance to combined therapy and a shorter time to cancer related death as well as a strong trend to poorer initial response rates (33). HIV positive patients with anal cancer with CD4 counts more than 200, treated with chemoradiation have excellent disease control with acceptable morbidity whereas those with CD4 counts less than 200 had markedly increased toxicity including intractable diarrhea, decreased counts and skin toxicity (34).

1.2.1 Management of cervical cancer in HIV positive patients

Although the stage of cancer may not predict CD4 levels, immune status does influence subsequent outcome. Patients with CD4 counts greater than 500/mm^3 have had more favorable disease courses; therefore, the management decisions in HIV infected women with cervical carcinoma should carefully consider pretreatment immune function, since positive serostatus alone may not necessarily and uniformly confer a dismal outcome (35). HIV related immunodeficiency may strongly influence the natural history of cervical carcinoma, and HIV positive patients need not demonstrate other signs of immunosuppression such as opportunistic infection for their neoplasm to be adversely affected by HIV (35).

The characteristics of HIV disease in cervical cancer may be different when compared with HIV positive patients with other AIDS related cancers. First, women with invasive cervical cancer are less immunosuppressed than women with other AIDS opportunistic illnesses and may be expected to have CD4 counts twice as high as those with Kaposi's sarcoma and Non Hodgkin's Lymphoma. Secondly, the diagnosis of cancer is more likely to precede the diagnosis of HIV infection. Finally, the cause of death was more likely to be attributed to cancer than to other manifestations of HIV infection (36).

The management of HIV positive patients with cervical cancer is among the most challenging tasks faced by the oncologic team. In general the same principles that guide the oncologic management of cervical cancer in immunocompetent patients should be applied. However extremely close monitoring for both therapeutic efficacy and unusual toxicity must be instituted (35).

TABLE 1.2.1.1 Treatment recommendations for cervical carcinoma in HIV infected women.

Stage IA1	Cold knife therapeutic cone biopsy if fertility desired: Otherwise simple hysterectomy
Stage IA2 Stage IB1	Radical hysterectomy with pelvic lymphadenectomy Alternatively, radiation therapy in poor surgical candidates
Stage IB2 Stage IIA	Radiation therapy +/- simple hysterectomy; or Radical hysterectomy with pelvic lymphadenectomy; or Neoadjuvant chemotherapy + radical surgery
Stage IIB-IVA	Radiation therapy +/- chemosensitisation
Stage IVB	Chemotherapy +/- radiation therapy
Recurrent Disease	Pelvic exenteration (central disease), otherwise Palliative chemotherapy

Maiman M. Management of cervical neoplasia in Human Immunodeficiency Virus Infected women; Journal of the National Cancer Institute, Monographs No.23, 1998.

1.3 Highly Active Antiretroviral Therapy (HAART) and its impact on prognosis in HIV infected patients

There have been substantial improvements in the management of HIV infection and these have had important effects upon the incidence, prognosis and treatment of malignancy in HIV seropositive people. Potent combinations of antiretroviral therapy have reduced rates of AIDS and death. HAART is associated with profound and sustained suppression of HIV viral replication, a dramatic reduction in opportunistic infections, AIDS defining illnesses and mortality amongst HIV-infected persons as well as a reduction in AIDS associated malignancies (37).

The role of radiation in the management of HIV associated malignancies is changing with improvements in antiretroviral therapy. Chemoradiation remains central to the management of HIV associated anal and cervical cancers and with prolonged survival, other solid tumours (37)

Clinicians managing these patients need to be aware of the enhanced sensitivity to irradiation and be fully conversant with the important drug interactions and toxicities of antiretroviral agents.

Examples of important overlapping side effects that may complicate radiotherapy include myelosuppression caused by Zidovudine and neuropathy caused by Didanosine. The metabolic effects of protease inhibitors include inhibition and induction of hepatic microsomal enzymes resulting in important pharmacokinetic interactions with chemotherapy as well as lactic acidosis that may mimic tumour progression. Oncologists need to be aware of the immunological and virological consequences of their therapies. The effects of chemotherapy on lymphocyte subsets and plasma HIV viral loads have been studied but no data is available as yet describing the effect of radiotherapy on these parameters (37, 38,). A study done at Johannesburg Hospital by Msemo et al (40) showed a significant drop in CD4 counts in both HIV negative and HIV positive patients following pelvic radiotherapy and concurrent chemotherapy for carcinoma of the cervix.

1.4 Toxicity of chemoradiotherapy

A higher radiation dose increases the probability of tumour control but results in more treatment sequelae (41-43). Acute toxicity is currently defined as toxicity which occurs during or up to 90 days after radiotherapy. There is only sparse literature on the acute toxicities of chemoradiation in HIV positive patients.

1.4.1 Toxicity of chemotherapy

Cisplatin toxicity is mainly evidenced by nausea and vomiting, mild to moderate myelosuppresion, nephrotoxicity and neurotoxicity (peripheral neuropathy, auditory impairment). Nausea and vomiting has been alleviated with the introduction of 5-hydroxytryptamine-3 ($5HT_3$) receptor antagonists, for example Granisetron and Ondansetron and in addition corticosteroids and more recently Aprepitant. Cisplatin induced nephrotoxicity can be minimized by prehydration with normal saline. Cisplatin induced myelosuppresion (anaemia, leucopaenia and thrombocytopaenia) is usually mild and reversible.

1.4.2 Acute toxicity of chemoradiotherapy

Although the side effects of chemoradiotherapy with weekly cisplatin or cisplatin plus 5 FU are tolerable for most patients, the addition of concurrent chemotherapy to radiotherapy markedly increases haematological and gastrointestinal side effects and adds to the overall complexicity of treatment. In a meta-analysis of 19 trials (39) ,when cisplatin containing chemotherapy were analysed separately, the reported rates of acute grade 3 and 4 toxicity ranged from 4-47% for haematologic toxicity, 0-15% for gastrointestinal toxicity and 1-8% for genitourinary toxicity.

The acute toxicity of chemo radiotherapy for cervical cancer has been reported in several phase II and III studies. Comparing the various studies is difficult because of the differences in the chemotherapeutic regimens, the radiotherapy delivered, and whether or not surgery was performed.

1.4.3 Studies reporting on acute toxicity and compliance

Tan et al 2004 (44)

74 patients with carcinoma of the cervix treated with radiotherapy given concurrently with weekly cisplatin chemotherapy were evaluated for acute treatment related toxicity and were graded prospectively at weekly intervals during chemoradiotherapy using the National Cancer Institute Common Toxicity Criteria. The most common adverse effect was diarrhoea (80.6%), malaise (66.7%), and nausea (62.5%). The most common hematological toxicity was anaemia, with 41.7% developing grade 1 or 2 toxicity. Only three (4.2%) patients had Grade 3 or 4 toxicity. One patient had grade 3 thrombocytopaenia, another had grade 4 neutropaenia and the third patient had grade 3 diarrhoea. A statistically significant correlation was found between maximum treatment related toxicity, larger treatment volumes and disease stage.

A total of 70.2% patients completed the planned number of chemotherapy cycles, with a further 20.3% receiving at least 3 cycles. The most common reason for failure to complete planned chemotherapy was gastrointestinal toxicity.

Serkies et al 2004 (45)

112 patients with cervical cancer were treated with concurrent cisplatin and radiation. A total of 454 cisplatin cycles were administered with a median of 4 cycles per patient (range1-6). The planned 5 cisplatin cycles were administered to 50 patients (45%). The full and timely planned cisplatin dose was administered to 29 patients (26%). For 29% of patients, the interval between cycles was prolonged because of toxicity (10%) and/or for reasons not related to toxicity (9%). Of the 55% of patients who did not undergo the planned 5 cisplatin cycles, 31% was due to treatment toxicity and 21% was due to noncompliance with the treatment schedule or reasons other than toxicity. Grade 3 or 4 leucopaenia occurred in 6 patients, grade 3 or 4 gastrointestinal toxicity in 16 patients.

2.0 THIS STUDY

2.1 BACKGROUND

In the radiation oncology unit of Johannesburg Hospital, concomitant chemoradiation with cisplatin is the standard treatment for patients with carcinoma of the cervix. The use of concomitant chemoradiation therapy has not been established in HIV positive patients. Compliance, toxicity and response data are not available and the benefit of combined therapy in this group of patients has not been demonstrated to date. This study is part of a multicenter International Atomic Energy Agency sponsored study.

2.2 OBJECTIVES

Primary end point:

To compare incidence of Grade 3 and 4 toxicities from the treatment of cancer of the cervix with radiotherapy alone versus radiotherapy plus standard cisplatin based concurrent chemoradiation in HIV positive patients.

Secondary Endpoints:

Tumour response at 3 months

2.3 MATERIALS AND METHODS

2.3.1 Inclusion criteria

This study was conducted at the University of Witwatersrand, Department of Radiation Oncology, Johannesburg Hospital, Johannesburg, South Africa. The local Human Research Ethics Committee approved this study. To be eligible to participate in this study, patients had to comply with the following inclusion criteria:

1. HIV positive
2. Histologically confirmed cervical cancer FIGO Stages IB to IIIB (without hydronephrosis)
3. Age over 18 years
4. Karnofsky scale more than or equal to 60%
5. Haemoglobin more than or equal to 10g/dl with or without transfusion, White Cell Count more than or equal to 4000/μL, Platelets more than or equal to 140 000/μL
6. Adequate renal function with creatinine 97.24μm/l or calculated creatinine clearance >60ml/min by the Cockroft and Gault formula (46)
7. Total bilirubin ≤ 34.2 μm/l ; SGOT <30 U/L
8. Expected good compliance to follow up
9. Written informed consent for HIV testing and for treatment

2.3.2 Exclusion criteria

1. Previous radiotherapy to pelvic region
2. Uncontrolled previous malignancy
3. Any severe medical ailment that may interfere with the proposed treatment
4. Previous chemotherapy in the last 1 year
5. Severe psychiatric disorder, pregnancy or breast feeding
6. Patients with hydronephrosis

2.3.3 Staging Workup

1. Complete history and physical examination
2. Complete blood count
3. Renal function tests(Urea and creatinine)
4. Liver function tests
5. Serum electrolytes
6. Chest X-ray
7. Ultrasound abdomen and pelvis (to assess status of the kidneys)
8. Histopathology of the tumour
9. CD4 counts

2.3.4 Treatment

2.3.4.1 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 in 23 fractions 5 days /week.

The field size was determined at simulation. AP/PA fields or a four field box technique were used depending on patient's separation.

Anterior posterior fields

Superior border – Mid L5 vertebra

Inferior border

- No vaginal involvement - Bottom of obturator foramen
- Vaginal involvement less than ½ - Bottom of ischial tuberosity
- If lower 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, then inguinal nodes were treated to beyond the acetabular margin.

Lateral fields

Superior and inferior borders as in the anterior-posterior fields

Posterior border

- IB2 to IIB- S2-S3 interspace
- IIB with outer half of parametrium involved to IIIB- entire sacral hollow

Anterior border

Anterior to the pubic symphysis

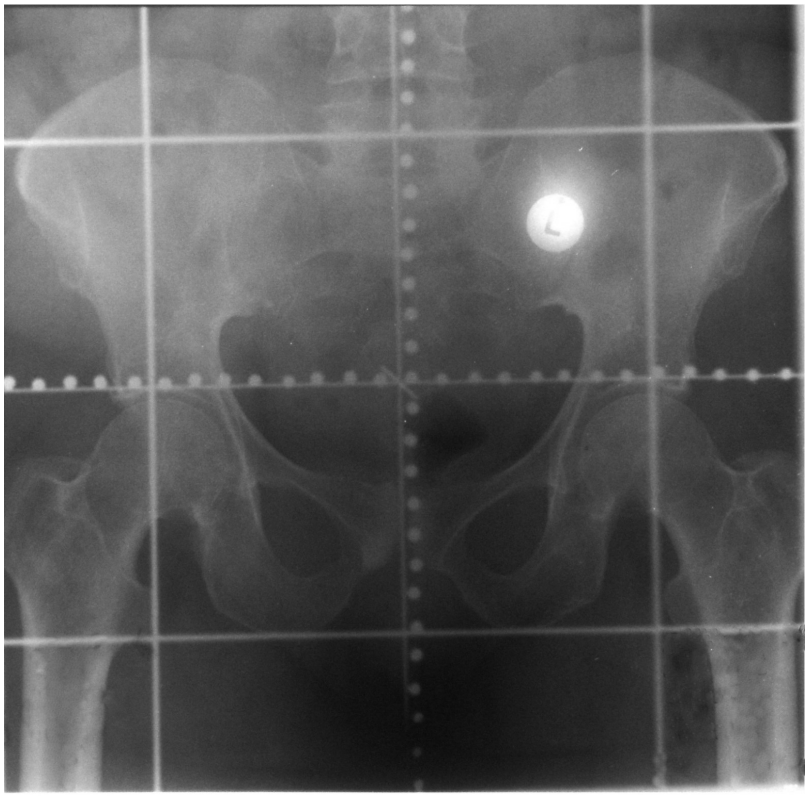


Figure 2.3.4.1.1 Anterior-posterior simulation film

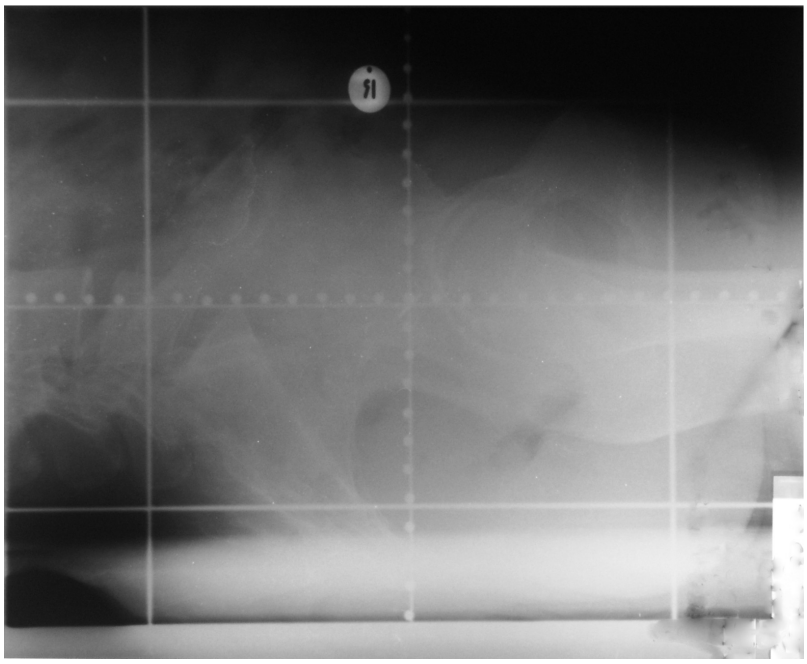


Figure 2.3.4.1.2 Lateral simulation film

2.3.4.2 Brachytherapy

Three intracavitary applications with High Dose Rate Brachytherapy, 8 Gy to point 'A', were given.

In most of the patients a rigid intrauterine tandem (Nucleotron (trademark) 6cm, 4cm or 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.



Figure 2.3.4.2.1 Lateral brachytherapy insertion radiograph

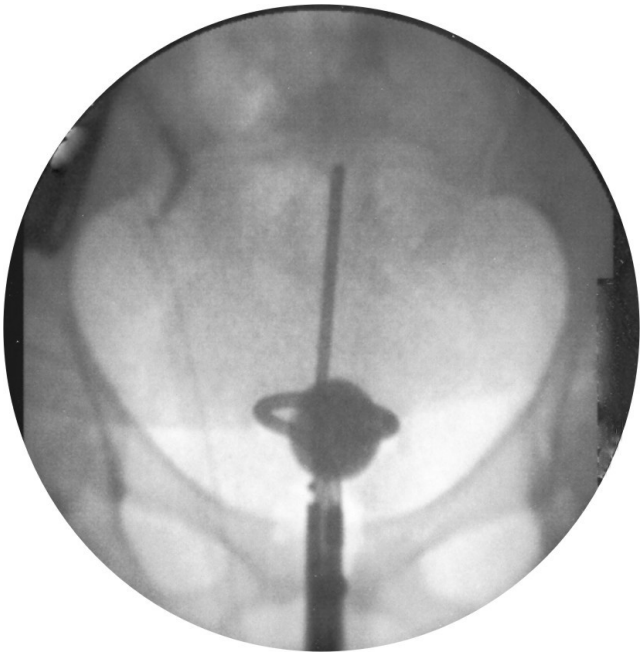


Figure 2.3.4.2.2 Anterior-posterior brachytherapy insertion radiograph

2.3.4.3 Concurrent Chemotherapy

Intravenous infusion of Cisplatin 30mg/m^2 weekly during external beam radiation with proper hydration and antiemetics was given to the patients randomized to the chemotherapy arm. Prehydration was given using one litre of normal saline infusion supplemented with calcium gluconate, magnesium sulphate and potassium chloride.

Prophylactic antiemetics consisted of Dexamethasone (8 mg intravenously) and Granisetron (kytril) 1mg intravenous. Cisplatin added to one litre normal saline was given after prehydration and prophylactic antiemetics. Cisplatin was omitted if the patient developed a WBC of less than 2000/μL, platelets of less than 100 000/μL or a raised creatinine of more than 97.24μm/L, or calculated creatinine clearance less than 60 mls/min.

2.3.5 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.

Weekly investigations done during treatment included:

1. Complete blood count
2. Serum urea, electrolytes and creatinine
3. Serum calcium, magnesium and phosphates
4. CD4 counts
5. Viral loads
6. Liver function tests

2.3.6 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.

2.3.7 Data analysis

The data was analyzed using SSPS version 16.0. Differences between groups in the severity of adverse effects were evaluated using the Pearson's chi-square test. The t-test for equality of means was used to determine similarity of continuous variables at randomization. The paired sample t-test was used to compare the magnitude of drop of CD4 counts at the beginning and end of treatment in each arm. Differences were considered statistically significant if the 'p'value was less than 0.05.

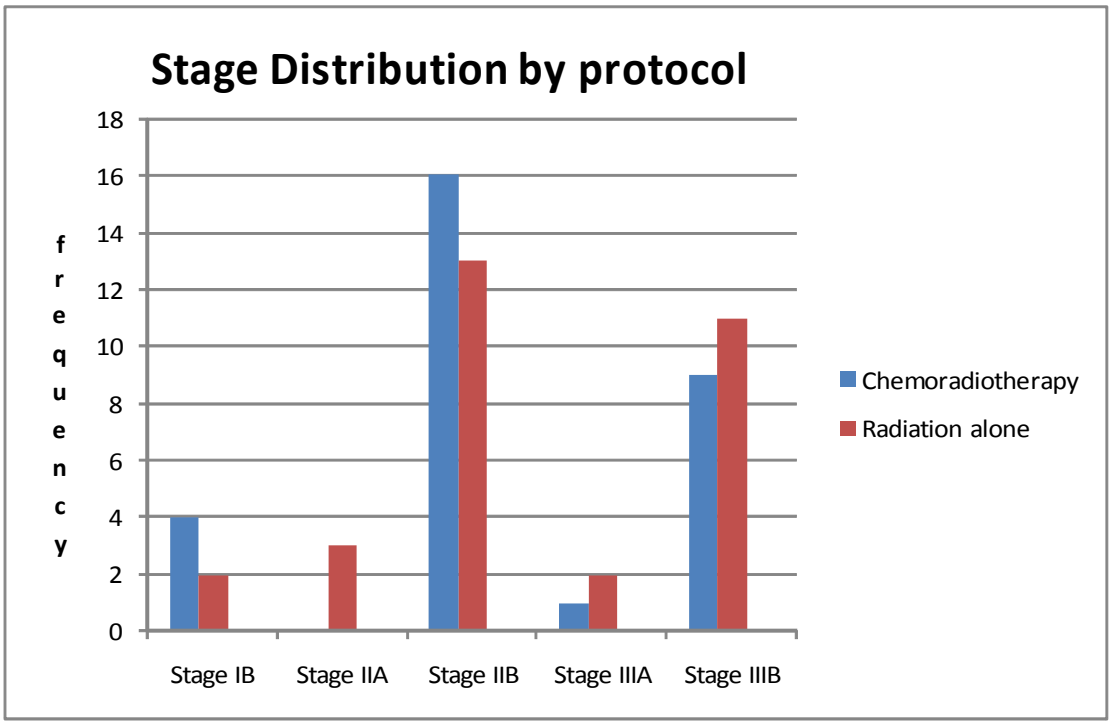
3.0 RESULTS

3.1 PATIENT CHARACTERISTICS

64 patients were recruited to the study. 31 patients were randomized to the chemoradiation arm and 33 patients to the radiation alone arm. The two groups of patients were comparable with respect to prognostic factors (Table 3.1.1). Stage IIB was the most common stage (Figure 3.1.1). The mean CD4 count was 410.5 in the chemoradiation arm vs. 358.4 (p=0.436) in the radiation only arm at randomization. Only 6 patients were on antiretroviral therapy at start of treatment, 3 in each arm.

TABLE 3.1.1 Patient characteristics_

	Chemo radiation			Radiation only			p value
	Min	Max	Mean	Min	Max	Mean	
Age	26	55	41.37	22	51	37.71	.068
Karnofsky Performance	80	100	90	80	100	90	.740
Haemoglobin	10.1	14	11.883	10.1	15.2	12.084	.522
WCC	4300	12700	7497.6	4000	27000	8427.1	.363
Platelets	187000	726000	366 200	198000	613000	358 516	.772
CD4	107	1005	410.5	95	1359	358.4	.436
Creatinine	45	94	72.40	51	91	66.13	.040



p=0.343

Figure 3.1.1 Stage distribution by protocol

3.2 TREATMENT DELIVERY

3.2.1 Radiotherapy Delivery

Of the 64 patients recruited to the study, 6 in the chemoradiation arm and 5 in the radiation only arm did not receive any treatment and were therefore not evaluated (Table 3.2.1.1). Only 51 of the 64 patients completed the radiation treatment as prescribed. Of the 13 who did not complete the treatment, 6 patients died before starting treatment, 3 absconded before treatment, 1 absconded after having started radiation treatment, 1 died during treatment from a respiratory tract infection, 1 received treatment in private and 1 received an altered fractionation regimen after disease progression. (Table 3.2.1.1). Of the patients who did not receive treatment according to protocol, 6 were randomized to the chemoradiation arm and 7 to the radiation alone arm.

The majority of the patients in this study were treated with AP/PA fields and only 12 were treated with 4 fields, 7 in the chemoradiation arm and 5 in the radiation alone arm (p= 0.343) (Table 3.2.1.2).

The median total duration of treatment was 40.12 days in the chemoradiation arm and 37.76 in the radiation alone arm (p=0.405). (Table 3.2.1.3) One patient in the chemoradiation arm had a treatment split for 4 weeks due to lower gastrointestinal and skin toxicity. Another patient in the chemoradiation arm had a split after 2 fractions of radiation before any chemotherapy was given due to suspected pyometria. This, however, was not treatment related. In the radiation only arm one patient absconded treatment for 3 and a half weeks after receiving 5 weeks of treatment.

TABLE 3.2.1.1 Treatment Delivery

	Chemoradiation	Radiation only	Total
Completed prescribed treatment	25	26	51
Absconded during treatment	1	0	1
Died during treatment	0	1	1
Absconded or died before treatment	5	4	9
Treated in private	0	1	1
Treated palliatively due to progression	0	1	1
Total	31	33	64

Table 3.2.1.2 Treatment Fields

Treatment Fields	AP/PA	FOUR FIELD
Radiation Only	24	5
Chemoradiation	18	7
Total	42	12

p = 0.343

Table 3.2.1.3 Treatment duration

	< 8 weeks	>8 weeks	Mean
Chemoradiation	22	2	40.12
Radiation alone	26	1	37.76

(p =0 .405)

3.2.2 Cisplatin Administration

The number of chemotherapy cycles received by patients in the chemoradiation arm ranged between 0 and 5 cycles (Table 3.2.2.1**)**. A total of 96 chemotherapy cycles were administered, with a median of 4 cycles per patient. 76% of patients received at least 4 cycles of chemotherapy.

The full five intended courses of cisplatin were administered in 10 (40%) patients. 9 (36%) patients received 4 cycles, 4 (16%) received 3 cycles, none received 2, 1 (4%) received 1 and 1 (4%) received no chemotherapy though randomized to the chemotherapy arm. This patient had developed sepsis after 2 fractions of radiation therapy before any chemotherapy was administered but was included in the chemoradiation arm in the analysis.

The planned five cisplatin cycles were not administered in 15 patients. Chemotherapy was not administered either due to logistical reasons (3 observations), non compliance (3 observations) or treatment toxicity (11 observations, renal toxicity-9 observations and leucopoenia-2 observations) (Table 3.2.2.2).

TABLE 3.2.2.1 Cycles of chemotherapy received in the chemoradiation arm

Chemotherapy cycles	Number of patients n=25	%
0	1	4
1	1	4
2	0	0
3	4	16
4	9	36
5	10	40

TABLE 3.2.2.2 Reasons for omitting chemotherapy

Reason	Number of observations
Logistical	3
Absconded	3
Low WBC	2
High creatinine, low creatinine clearance	9
Sepsis	5 (1 patient did not receive all 5 cycles)

3.3 TOXICITY

Toxicity was usually mild and reversible (Table 3.3.1 and 3.3.2**)**. Haematologic toxicity was the most common toxicity. The incidence of grade 3 leucopoenia was 5, 4 in the chemoradiation arm and 1 in the radiation alone arm.; this was statistically significant (p=0.025). There was no grade 4 leucopoenia in either arm. A drop in haemoglobin levels was recorded 17 times in the chemoradiation arm and 22 times in the radiation alone arm. Grade 3 or 4 toxicity occurred twice and both these were in the radiation alone arm (p=0.157).

Skin toxicity was the next most common toxicity being recorded 44 times, 17 in the chemoradiation arm and 27 in the radiation only arm (p=0.389). However moderate (grade 3) or severe (grade 4) toxicity occurred only 8 times of which 6 were in the radiation alone arm; this was not statistically significant (p=0.142).

Lower gastrointestinal toxicity occurred 28 patients, 12 in the chemoradiation arm and 16 in the radiation alone arm (p=0.890). Two incidences of lower gastrointestinal grade 3 or 4 reactions occurred and both were in the chemoradiation arm (p=0.144).

Upper gastrointestinal toxicity occurred 15 times, 6 in the radiation alone arm and 10 in the chemoradiation arm. There was one incidence of grade 3 toxicity and no grade 4 upper gastrointestinal toxicity. This occurred in the chemoradiation arm (p=0.305).

Bladder toxicity was recorded 15 times, 9 in the chemoradiation arm and 6 in the radiation alone arm (p=0.444). There was no grade 3 or 4 bladder toxicity. Two patients had moderate to severe vaginal mucositis, 1 in the chemoradiation arm and the other in the radiation alone arm. Grade 1 or 2 renal toxicity with raised creatinine levels occurred 7 times, 4 in the chemoradiation arm and 3 in the radiation alone arm (p=0.646). There was no moderate or severe renal toxicity.

No neurotoxicity or ototoxicity was observed.

During chemoradiation there was a significant drop in CD4 counts both in the chemoradiation group and the radiation alone arm (Figure 3.3.1). At the commencement of treatment the mean CD4 count in the chemoradiation arm was 321.06cells/mm^3 compared to 62.56cells/mm^3 at treatment completion (p=0.0001). In the radiation alone arm the mean CD4 count at commencement of treatment was 248.09cells/mm^3 and at completion 68.17cells/mm^3 (p=0.002). The mean difference in CD4 counts at the beginning and end of treatment was 188.7cells/mm^3 in the radiation alone arm, and 258.2cells/mm^3 in the chemoradiation arm (p=0.294). The magnitude of drop was similar in both arms.

Thus moderate and severe toxicities were comparable in both arms except for leucopaenia which was more frequent in the chemoradiation arm.

TABLE 3.3.1 Adverse Effects

Adverse Effect	Radiation arm Incidence of toxicity				Chemoradiation arm Incidence of toxicity				p Value of total Toxicity
Toxicity Grade	1	2	3	4	1	2	3	4	
Upper Gastrointestinal	4	2	0	0	5	4	1	0	0.943
Lower Gastrointestinal	10	6	0	0	3	7	2	0	0.890
Haemoglobin	15	5	2	0	10	7	0	0	0.176
WCC	13	6	10	0	15	6	4	0	0.330
Platelets	0	0	0	0	1	0	0	0	
Neutrophils	1	2	0	0	0	0	0	0	0.176
Renal toxicity	2	1	0	0	3	1	0	0	0.646
Bladder	4	2	0	0	8	1	0	0	0.444
Skin	9	12	4	2	7	8	2	0	0.389
Mucous Membranes (Vaginal mucositis)	0	1	0	1	0	0	1	0	0.157

Table 3.3.2 Grade 3 and 4 Adverse Effects

Adverse Effect	Radiation arm Incidence of toxicity			Chemoradiation arm Incidence of toxicity			p value
Toxicity Grade	3	4	**Total**	3	4	**Total**	
Upper Gastrointestinal	0	0	0	1	0	1	0.305
Lower Gastrointestinal	0	0	0	2	0	2	0.144
Haemoglobin	2	0	2	0	0	0	0.157
WCC	1	0	1	4	0	4	0.025
Platelets	0	0	0	0	0	0	
Neutrophils	0	0	0	0	0	0	
Renal toxicity	0	0	0	0	0	0	
Bladder	0	0	0	0	0	0	
Skin	4	2	6	2	0	2	0.142
Mucous Membranes (Vaginal mucositis)	0	1	1	1	0	1	0.981

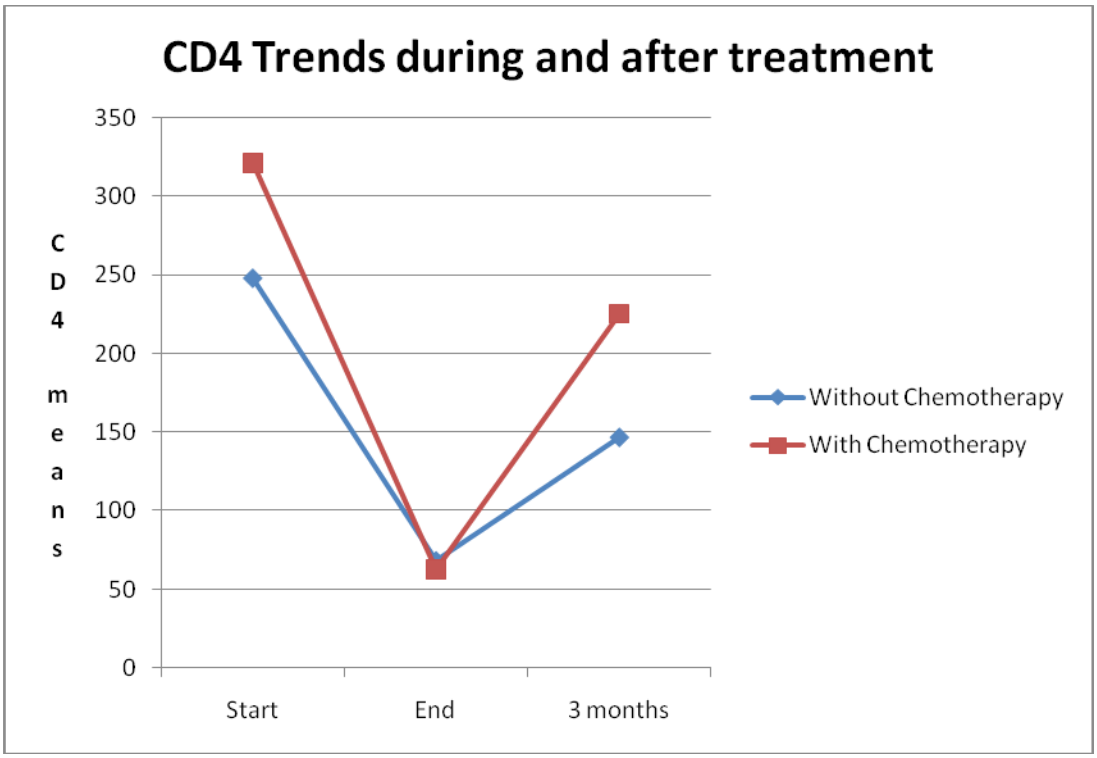


Figure 3.3.1 CD4 trends during and after treatment

3.4 Treatment Efficacy

51 patients were evaluable for response at 3 months, 25 in the chemoradiation arm and 26 in the radiation alone arm. 41 of the 51 evaluable patients at 3 months had complete responses to treatment, 20 (80%) in the chemoradiation arm and 21 (80.7%) in the radiation alone arm. 5 patients in both arms had incomplete responses (p=0.777) (Table 3.4.1).One patient in the chemoradiation arm died of progressive disease at 3 months and 1 patient in the radiation arm died from lung metastasis at 3 months post treatment despite adequate local control.

TABLE 3.4.1. Response to treatment

Response to treatment	Chemoradiation (25)	Radiation alone (26)	Total (%)
Complete	20	21	41 (80)
Incomplete	5	5	10 (20)

p=0.777

4.0 DISCUSSION

The publication of five randomized trials and a meta-analysis showing the superiority of cisplatin based chemoradiotherapy over radiotherapy alone has resulted in the introduction of combined modality treatment into daily practice. However, these regimens have not been evaluated in detail in HIV positive patients with regard to the radiation response, its toxicities, patient compliance and patterns of survival. Historically, there has been some reluctance to treat HIV patients according to these standardized regimens (concurrent chemoradiation) because of concerns regarding the possibility of unacceptable toxicity.

The principal grade 3 and 4 adverse effects in this trial were leucopaenia (4 in the chemoradiation arm, 1 in the radiation arm) and cutaneous reactions (2 in the chemoradiation arm, 6 in the radiation alone arm). However, only the incidence of Grade 3 and 4 leucopaenia was significantly higher in the chemoradiation arm. In a meta-analysis of randomized trials of cisplatin based chemoradiotherapy (47), there was increased acute toxicity predominantly haematologic and gastrointestinal in the combined chemoradiotherapy groups. However the acute toxicity tended to be short lived and resolved by appropriate medical treatment.

Though this study is small, these toxicity rates were lower than those experienced in other published studies e.g. 23% leucopoenia in the cisplatin and radiotherapy arm in the study by Rose et al.. Table 4.1 illustrates that patients in this study did not experience greater haematological toxicity than the other three studies. Cutaneous effects (skin toxicity) were however higher in this study (15.7% total, 8% chemoradiation and 23% radiation only) compared to the studies by Rose et al, Pearcey et al and Keys et al. One factor that might have potentially increased cutaneous toxicity is the high number of patients with advanced disease requiring larger treatment fields and the use of anterior posterior fields (Table 3.2.1.2) in most of our patients as well as the theory that HIV positive patients have increased sensitivity of the normal tissues to radiotherapy resulting in excessive acute normal tissue reactions (7, 30, 31, 33). Two patients developed severe vaginal mucositis. In previous studies this has been explained by poor radiation tolerance of mucosal surfaces possibly due to colonization with candida albicans (30).

The response rates to chemoradiation in HIV positive patients with cancer of the cervix have not been reviewed in the literature. However a study by Kim et al. (33), compared disease response and tolerance to chemoradiotherapy in HIV positive and HIV negative patients with anal cancer. In this study, acute major toxicity differed significantly (HIV positive 80% vs. HIV negative 30%; $p = 0.005$). Only 62% of HIV positive patients were rendered disease free after initial therapy vs. 85% in HIV negative patients. Cleator S et al, in another study on 12 patients with HIV infection and anal cancer recommended combined modality therapy in these patients and noted that although toxicity is considerable, it is such that reduction in the intensity of radiation or chemotherapy is not merited and indeed would be expected to compromise local control rates (48).

TABLE 4.1 Grade 3 and 4 toxicity in comparison to other trials using weekly Cisplatin

Toxicity	**GOG 123** RT+CDDP n=183 (%)	**NCIC** RT+CDDP n=127 (%)	**GOG 120** RT+CDDP n=176 (%)	**This study** RT+CDDP n=25 (%)	**This study** Total toxicity in both arms (%)
Leucopaenia	-	-	23	16	9.8
Thrombocytopenia	-	-	2	0	0
Other haematologic	21	4.7	15	0	3.9
Gastrointestinal	14	13	12	12	5.9
Genitourinary	2	2	5	0	0
Cutaneous	0	2	2	8	15.7
Neurologic	1	2	1	0	0

Thus, although HIV positive patients are thought to demonstrate an increased sensitivity of normal tissues to radiotherapy resulting in increased acute adverse effects, this was not observed in this study. The lack of increased morbidity could be due to the relative immunocompetence of the patients in this study (Table 3.1).

Most HIV positive cervical cancer patients are asymptomatic for HIV infection and HIV infection is identified by routine screening. They usually have higher CD4 counts compared to patients with other AIDS defining cancers (36). Hoffman et al, in studies on anal cancer reported markedly increased morbidity if the pretreatment CD4 cell count was less than 200cells/mm^3 following standard therapy (34). During chemoradiation there was a significant drop in CD4 counts both in the chemoradiation group and the radiation alone arm. The magnitude of drop was similar in both arms. At 3 months the mean CD4 counts increased in both groups but however there was failure to recover to pretreatment levels. A review of literature did not reveal any studies that looked at the immunological and viral consequences of chemoradiation. In immunocompetent patients receiving combination chemotherapy CD8 cells, B cells and natural killer cells all decline but recover within 3 months of completing chemotherapy, however the recovery of CD4 cells is protracted. The CD4 cell count is only one third of the pretreatment level at 3 months after completing treatment and may not have recovered to pretreatment levels after 1 year (37). Since HIV infection affects immune function primarily by infection and destruction of CD4 cells, there is concern that prolonged CD4 suppression by chemotherapy may have a major adverse influence on the course of HIV disease (38).

In studies on HIV patients receiving combination chemotherapy and HAART, the CD4 T-lymphocyte count falls by approximately 50% but recovers rapidly within 1 month after treatment and reflects a global fall in T cells as the percentage of CD4 T cells remains unchanged throughout (38). Studies in HIV seropositive patients have shown that without HAART the viral load increases during chemotherapy (49).With the concomitant use of chemotherapy and HAART there is no increase of viral load during chemotherapy (38).

The median total duration of treatment was 40.12 days in the chemoradiation arm and 37.76 in the radiation alone arm (p=0.405. According to the American Brachytherapy society recommendations for treatment for cervical cancer the total treatment duration should be less than 8 weeks, because treatment prolongation can adversely affect local control and survival.(50) In this study most patients completed radiation therapy within 8 weeks (Table 3.9). 2 in the chemoradiation arm and 1 in the radiation alone arm received treatment for more than 8 weeks. Of the 3 patients who had treatment interruptions 2 had residual tumour at 3 months post completion of treatment. A few other patients had short treatment delays for personal and logistic reasons. These treatment durations were shorter than those used in most randomized trials.

The median treatment duration in the study by Rose et al was 63 days; in the study by Keys et al. it was 50 days, and in the NCIC CTG study it was 48 days. Significant loco-regional failure due to treatment prolongation is often seen if the treatment period is beyond 50 days (50-54). Treatment prolongation contributes to loss of loco-regional control by allowing clonogenic repopulation (52).

TABLE 4.2 Chemotherapy cycles in comparison to other studies with weekly cisplatin

No. of Chemotherapy cycles	GOG 120 n=176	This study n=25
0	0.6%	4%
1	1.1%	4%
2	1.1%	0%
3	4.0%	16%
4	10.2%	36%
5	33.5%	40%
6	49.4%	0%

Table 4.2 compares the cisplatin cycles delivered in this study to the study by Rose et al.

In this study only 40% of patients received the planned 5 cycles of chemotherapy with only 76% of patients receiving at least 4 cycles of chemotherapy and 92% of patients received at least 3 cycles of chemotherapy. This outcome was related to both treatment toxicity and other reasons. This however may be significant as there is some evidence that the benefit from chemoradiotherapy is apparent as long as patients receive at least 3 cycles of treatment (25, 55). In the GOG 120 study (23), 93% of patients received at least 4 cycles of chemotherapy, with 49.4% receiving the full 6 cycles of chemotherapy. Likewise in the second GOG study (21), 90% of patients who underwent preoperative radiation received four or more courses of cisplatin. In the NCIC CTG study (26) 86% of patients assigned to concurrent weekly cisplatin received >90% of the recommended dose (five cycles) and toxicity accompanying radiation combined with weekly cisplatin precluded the delivery of planned radiation in only 6% of patients.

In a prospective study that assessed the eligibility for chemoradiotherapy in patients presenting with cervical cancer in the developing world, it was noted that HIV positive patients were more likely to have multiple factors preventing safe administration of cisplatin based chemotherapy (56).

Despite the fact that at 3 months the response rates were similar in the both arms, further follow up is required to assess survival functions and local control. About 20% of our patients had residual disease at 3 months. HIV infection is associated with higher pelvic failure (4, 6). One hypothesis is that HIV infection may alter cervical cancer cell kinetics resulting in a more radioresistant tumour. Another hypothesis is that HIV is associated with anemia (57). Chronic and transient hypoxia makes tumours radioresistant and is an adverse prognostic factor for both local control and survival outcome.

5.0 STUDY LIMITATIONS

- The study was small thus making the study less robust. These findings need to be replicated in more extensive studies.
- Documentation of the parameters reported is prone to observer variation as documentation was done by several people.
- The use of clinical documentation of disease response is subjective. More objective measures such as pre and post treatment magnetic resonance imaging could not be utilized due to cost limitations. Pap smears were done at 6 months post treatment and therefore was not assessed in this analysis.

6.0 CONCLUSION

This study has shown that concurrent weekly cisplatin chemotherapy is well tolerated when given to HIV positive patients and that no unexpected toxicities were observed beyond those generally associated with single agent cisplatin. Thus radical chemoradiation in conventional doses can be given safely in HIV positive patients with invasive cervical cancer. Toxicity was usually mild and reversible. The principle adverse effects in this trial were leucopaenia and cutaneous reactions. Leucopaenia was the only toxicity which was significantly higher in the chemoradiation arm.

Many patients did not receive the planned cisplatin dose due to various factors not related to toxicity. Chemoradiotherapy is a resource intensive treatment, involving considerable input from doctors, nurses, radiographers and pharmacists and a high degree of coordination is necessary for treatment to be delivered effectively.

In general the same principles that guide the oncologic management of immunocompetent patients should be applied to HIV patients. These findings are based on a relatively small patient population and a short follow up period. These results need to be replicated in more rigorous extensive studies. Follow up over a longer period of time is needed to assess survival outcomes of these HIV patients with invasive cervical cancer.

These studies will assist in the design of appropriate treatment strategies for invasive cervical cancer in HIV positive patients as these patients are likely to increase in number as the HIV pandemic continues growing and life expectancy increases due antiretroviral therapy.

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APPENDIX A

FIGO Staging of carcinoma of the uterine cervix

Stage 0		Carcinoma in situ, cervical intraepithelial neoplasia Grade III.
Stage I		The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded.
Ia		Invasive carcinoma which can be diagnosed only by microscopy. All macroscopically visible lesions — even with superficial invasion — are allotted to Stage Ib carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0 mm and a horizontal extension of not > 7.0 mm. Depth of invasion should not be > 5.0 mm taken from the base of the epithelium of the original tissue — superficial or glandular. The involvement of vascular spaces — venous or lymphatic — should not change the stage allotment.
	Ia1	Measured stromal invasion of not > 3.0 mm in depth and extension of not > 7.0 mm.
	Ia2	Measured stromal invasion of > 3.0 mm and not > 5.0 mm with an extension of not > 7.0 mm.
Ib		Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than Stage Ia.
	Ib1	Clinically visible lesions not > 4.0 cm.
	Ib2	Clinically visible lesions > 4.0 cm.
Stage II		Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina.
	IIa	No obvious parametrial involvement.
	IIb	Obvious parametrial involvement.
Stage III		The carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer- free space between the tumour and the pelvic wall. The tumour involves the lower third of the vagina. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to other causes.
	IIIa	Tumour involves lower-third of the vagina, with no extension to the pelvic wall.
	IIIb	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney.
Stage IV		The carcinoma has extended beyond the true pelvis, or has involved (biopsy-proven) the mucosa of the bladder or rectum. A bullous oedema, as such, does not permit a case to be allotted to Stage IV.
	IVa	Spread of the growth to adjacent organs.
	IVb	Spread to distant organs.

APPENDIX B

Karnofsky Performance Scale

100 Normal, no complaints, no evidence of disease

90 Able to carry on normal activity. Minor symptoms of disease.

80 Normal activity with effort: some symptoms of disease

70 Cares for self: unable to carry on normal activity or active work

60 Requires occasional assistance but is able to care for needs.

50 Requires considerable assistance and frequent medical care.

40 Disabled: Requires special care and assistance.

30 Severely disabled: hospitalization is indicated, death not imminent.

20 Very sick, hospitalization necessary: active treatment necessary.

10 Moribund, fatal processes progressing rapidly.

APPENDIX C
RTOG Acute Toxicity Criteria

	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 edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
MUCOUS MEMBRANE	No change over baseline	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
UPPER G.I	No change	. Anorexia with <=5% weight loss from pretreatment baseline/ nausea not requiring antiemetics/ abdominal discomfort not requiring parasympatholytic drugs or analgesics	Anorexia with <=15% weight loss from pretreatment baseline/ nausea &/ or vomiting requiring antiemetics/ abdominal pain requiring analgesics	Anorexia with >15% weight loss from pretreatment baseline or requiring N-G tube or parenteral support. Nausea &/or vomiting requiring tube or parenteral support/abdominal pain, severe despite medication/hematemesis or melena/ abdominal distention (flat plate radiograph demonstrates distended bowel loops	Ileus, subacute or acute obstruction, perforation, GI bleeding requiring transfusion/abdominal pain requiring tube decompression or bowel diversion
LOWER G.I. INCLUDING PELVIS	No change	Increased frequency or change in quality of bowel habits not requiring medication/ rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g., Lomotil)/ 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 distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
GENITO-URINARY	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 anesthetic (e.g., Pyridium)	Frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/ without clot passage	Hematuria requiring transfusion/ acute bladder obstruction not secondary to clot passage, ulceration or necrosis
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	-------

APPENDIX D

Ethics clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Msadabwe

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M040913**
PROJECT	A Randomised Clinical Study t Compare Standard Radical Concomitant Chemo-Radiation Against Radical Radiotherapy.....
INVESTIGATORS	Dr SC Msadabwe
DEPARTMENT	School of Clinical Medicine
DATE CONSIDERED	04.10.01
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 04.10.04 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof R Lakier

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES