A RETROSPECTIVE STUDY OF ADVANCED CARCINOMA OF THE CERVIX TREATED WITH A HYPOFRACTIONATED RADIATION THERAPY PROTOCOL AT THE DEPARTMENT OF RADIATION ONCOLOGY, UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG, SOUTH AFRICA

A DESERTATION SUBMITTED TO THE FACULTY OF MEDICINE IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR A DEGREE OF MASTER OF MEDICINE AT THE UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

BY

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A dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine in Radiation Oncology.

May, 2014

DECLARATION

I, Ahmed Abdi Komen declare that this dissertation is my own work. It is submitted for the degree of Master of Medicine in Radiation Oncology; Faculty of Health Sciences, University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Signed……..

……Day of……2014

DEDICATION

To my family.

PRESENTATIONS

This MMed study was chosen for oral presentation at the South African Society of Clinical and Radiation Oncology (SASCRO) and South African Society of Medical Oncology (SASMO) National Congress which took place in August, 2013.

ABSTRACT

Background

Carcinoma of the cervix is a common cancer among women in developing countries and with the rising HIV environment the burden of cervical cancer might be even greater, stretching the limited resources even further. This retrospective descriptive study evaluates the potential of the hypofractionated departmental protocol for stage 3b carcinoma of the cervix in terms of toxicity, local control, and compares toxicity for HIV negative and positive patients with a mean follow-up of one year. This study also compares the outcome for unilateral to bilateral pelvic sidewall fixed tumours.

Methods and Materials

Medical records of 104 sequential patients with stage 3b carcinoma of the cervix treated with departmental hypofractionated protocols between 2010/2011 were reviewed. The patients were only sequential after meeting the criterion of being local with a contact telephone number. Patients were treated with two-dimensional standard pelvic portals of external beam radiation therapy of 2.5Gray daily to a total of 40Gray and intracavitary radiotherapy high dose rate of 9Gray weekly to a total of 18Gray. All cases were stratified by HIV status as being HIV positive or negative and by local disease spread as being unilaterally fixed or bilaterally pelvic sidewall fixed tumours. The patient's treatment duration and

haemoglobin levels at the start of radiation were also retrieved from her medical records. Outcome was evaluated after six months, using the Papanicolaou smear and clinically, by using the Response Evaluation Criteria In Solid Tumors criteria version 1.1. Toxicity scoring was done by using the Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group criteria. Maximum toxicity information during treatment and follow-up was obtained from patient files. Statistical analysis was done using STATISTICA version 10. The Student's T-test was used for mean age and toxicity comparison between HIV positive and negative patients. Survival analysis was done using the Kaplan Meier statistical method.

Results

The 600 days overall survival and disease free survival were 94.92% and 59.04% respectively. Comparison of unilateral and bilateral pelvic sidewall fixed tumour disease free survival was 63.94% and 48% (p=0.12926) respectively. Seventy one (68.3%) patients were HIV negative while 33 (31.7%) were HIV positive. Human Immunodeficiency Virus positive patients had a mean age of 45.76 years, while the mean age for HIV negative patients were 55.95 years (p=0.000066). There was no statistically significant difference (p=0.49713) in disease free survival between patients completing radiation therapy in ≤24 days (57.03%) versus >24 days (58.76%). There was no statistically significant difference in the outcomes between HIV positive and negative patients for the up to 600 day's follow-up period. However, haemoglobin levels were prognostic, as the comparison between

patients with haemoglobin levels of ≤10g/dl and >10g/dl overall survival was 80.05% and 98.81% (p=0.00055), and disease free survival was 0% and 68.57% (p=0.02130) respectively at 470 days. The treatment was well tolerated and there was no difference in toxicity between HIV positive and HIV negative patients. No patient developed acute grade 3-4 skin and genitourinary toxicity. One patient developed acute grade 3 gastrointestinal tract toxicity. Although the follow-up period was rather short to assess late complications, three patients who were HIV negative had late grade 3 skin toxicity, no patient had late genitourinary toxicity and four had late gastrointestinal tract toxicity. Among the four who had late gastrointestinal tract complications, three were HIV negative while one was HIV positive.

Conclusion

For this short follow-up study, the departmental hypofractionated protocol has potential and has already reduced long waiting periods for radiotherapy treatment in our department from six months to two to three months. The treatment is tolerable with a comparable outcome as conventional standard fractionation for stage 3b carcinoma of the cervix. However, long follow-up is recommended to ascertain long term outcome and late complications. As other studies have shown, carcinoma of the cervix is seen at an earlier age among HIV positive patients and screening is recommended. Interestingly, haemoglobin levels are prognostic among stage 3b carcinoma of the cervix, in patients treated with hypofractionation.

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The staff of the Radiation Oncology Department of the Charlotte Maxeke Johannesburg Academic Hospital and the Head of the Department, Prof Sharma, for their support. It was due to the meticulous recording of patient data in the files that I was able to gather the requisite information for this study.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF ACRONYMS, ABBREVIATIONS AND SYMBOLS

AP..... Anterior posterior
AP/PA .....Anterior Posterior/Posterior Anterior
CD4 ..... Cluster of differentiation 4
CMJAH .....Charlotte Maxeke Johannesburg Academic Hospital
CR ..... Complete Response
DFS .....Disease free survival
EBRT .....External beam radiation therapy
EORTC..... Eastern cooperative oncology group
FIGO .....Federation International de Gynaeologic et Obstetrique
G/dl.....Gram per deciliter
GIT .....Gastrointestinal tract
GLOBOCAN ..... Global cancer facts and figures
GU .....Genitourinary
Gy..... Gray
HAART .....Highly active antiretroviral therapy
HDR .....High Dose Rate
HIV..... Human immunodeficiency virus
ICRT.....Intracavitary radiotherapy
ICRU ..... International commission on radiation units and measurement
IV ..... Intravenous
MV ..... Mega Voltage
n.....Number
OS..... Overall survival
Pap.....Papanicolaou smear
PD.....Progressive Disease
PR..... Partial Response
PSW .....Pelvic sidewall
RECIST..... Response Evaluation Criteria in Solid Tumors

RT.....Radiation therapy

RTOG..... Radiation Therapy Oncology Group

SD.....Stable Disease

TCP ..... Tumour control probability

Tk ..... The onset time (Tk) of acceleration repopulation

y.....Years

1. INTRODUCTION

1.1 Background

Cervical cancer is the third most common cancer in women, and the seventh overall, with an estimated 530 000 new cases being reported worldwide in 2008. More than 85% of the global burden occurs in developing countries where it accounts for 13% of all female cancers (7).

In Africa, cervical cancer is the leading cancer among females and constitutes 23.3% (14).

Southern Africa is one of the high risk regions and the incidence is 26.8 per 100 000 (7).

Overall, the mortality: incidence ratio is 52%, and cervical cancer was responsible for 275 000 deaths in 2008, about 88% of which occurred in developing countries and 53 000 occurred in Africa (7).

In South Africa, according to GLOBOCAN 2008, the incidence of cervix uteri cancer was 5 743 (7).

At the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), we see on average, 750 new cases of cervical cancer patients every year and among them approximately 304 patients are stage 3b (12). According to Federation

International de Gynaecologic et Obestetrique (FIGO) staging, stage 3b cervical cancer means that the tumour extends to pelvic side walls and or causes hydro-nephrosis or a non-functioning kidney (6). Patients with stage 3b as well as renal failure are evaluated differently.

The waiting period was six months when these patients were treated with conventional fractionation, which is 2Gray (Gy) per fraction (12). In our department, stage 3b patients were treated with external beam radiation therapy of 50Gy, plus three fractions of 8Gy intracavitary high dose rate brachytherapy, depending on the renal function and CD4 counts for retro positive patients, with concurrent cisplatinum chemotherapy of $80g/m^2$, three weekly (3). The reason for the long interval from assessment to planning of treatment is due to the burden of the disease compared to the resources available.

With the majority of the carcinoma of the cervix being squamous cell carcinoma, one disadvantage of a long waiting period is that squamous carcinoma is a rapidly multiplying tumour with a potential doubling time (T-POT) of approximately 5 days (17). Hence, from initial assessment to the time of simulation and treatment, most patients are upstaged, with a consequent poorer prognosis.

In order to reduce the waiting period, our department adopted a new hypofractionated protocol for cancer of the cervix stage 3b, which comprises almost half the cases seen at the CMJAH. Waiting times improved and is currently 2-3 months (12). Hypofractionation means giving more than 2Gy per

fraction. The new protocol adopted, involves giving 2.5Gy per fraction of external beam radiation therapy to a total dose of 40Gy to the pelvis and intracavitary high dose rate brachytherapy of 9Gy weekly, to a total of 18Gy without chemotherapy. The treatment is given Monday to Friday (3).

Hypofractionation involves giving a smaller number of larger doses per fraction. Treatment regimens involving fewer fractions, is clearly more convenient for patients and is of benefit in resource constraint health systems. Overall treatment time is important for fast growing tumours and as for carcinoma of the cervix, local tumour control is decreased by 0.5% each day that the overall treatment time is prolonged past 49 days (8).

A recent study by Huang *et al.,* (2012) (41), verifies the fact that accelerated repopulation does exist in cervical cancer and has a relatively short onset time. Higher dose and shorter treatment duration were associated with higher tumour control probability (TCP). According to his study the best TCP fit was achieved with an onset time (Tk) of acceleration of 19 days and a number of tumour clonogens(K) of 139 (41). This suggests that hypofractionation could be a potential choice of treatment for carcinoma of the cervix.

1.2 Chemotherapy and locally advanced carcinoma of the cervix

Earlier studies showed chemotherapy survival benefit in stages1b-IV carcinoma of the cervix (45, 46 and 48). However, Vale *et al*., (2008) (49), showed in a systematic review and meta-analysis of individual patient data from 18 randomised trials, that the benefit of chemotherapy decreases with stage progression. Indeed, stages 3 and 4 had a 5 year survival benefit of only 3% (49). Based on the above observation and the fact that most of our patients at CMJAH with locally advanced disease being unable to tolerate chemotherapy, patients with stage 3b on the departmental hypofractionated protocol do not receive concurrent chemotherapy.

1.3 High dose rate brachytherapy of twice 9Gy each

Studies by Patel *et al*., (1992) , Sood *et al*., (2002) and more recently from our department by Wondemagegnhu *et al*., (2007) have showed that two fractions of HDR brachytherapy of 9Gy each is safe and effective in the management of carcinoma of the cervix (50, 51 and 52).

My study aimed to evaluate the outcome of this departmental hypofractionated protocol in terms of local control, early and late toxicity and also to compare HIV positive and negative patients with a mean follow-up of six months. I also compared the outcome for unilateral pelvic sidewall involvement to more advanced tumours.

1.4 SCIENTIFIC RATIONALE

There are very few studies on the hypofractionation for cancer of the cervix. None of the studies was done in South Africa. This is a common cancer among the women in developing countries and with the rising HIV environment; the burden of cervical cancer might be even greater, stretching the limited resources even further. Thus, it is important to evaluate hypofractionated protocols and their potential.

1.5 OBJECTIVES

With respect to hypofractionated radiation for advanced cervical cancer, my study had four aims:

1. To evaluate the early and late toxicity with a mean follow-up of six months.
2. To asses local control after six months using Pap smear results post treatment.
3. To compare local control and toxicity among HIV positive and negative patients.
4. To compare outcomes of unilateral fixed to more advanced cervical tumours.

2. METHODOLOGY

2.1 STUDY LOCATION

The Radiation Oncology Department of the University of the Witwatersrand, South Africa based at the CMJAH. This is a tertiary referral hospital for the Southern Gauteng Province.

2.2 STUDY SUBJECTS

One hundred and four sequential patients treated with the departmental hypofractionated protocol between 2010 and 2011 were evaluated.

2.3 STUDY DESIGN

This was a retrospective descriptive study comprising two consecutive years.

2.4 SAMPLE SIZE

The specific number of patients (n=104) selected was due to:

1) A study period of one year

2) A particular disease stage investigated

3) A particular schedule of a hypofractionated radiation protocol being assessed

4) A minimum follow-up period of six months

2.5 STUDY SAMPLING METHOD

Patients included were as follows:

1) Local patients with contact telephone numbers, treated with the hypofractionated protocol
2) The first 104 patients treated on this hypofractionated protocol were included in the study if they met the criterion described in point 1 above.

2.6 STUDY PERIOD

The total study period was two years: 2010-2011.

2.7 INCLUSION CRITERIA

- Squamous cell carcinoma histology of cervix only.

-Stage 3b with normal renal function.

-Hypofractionated protocol in previously untreated patient.

-Both HIV positive and negative patients.

-All ages.

-Telephonically available for follow-up.

2.8 EXCLUSION CRITERIA

-No follow-up (no telephone).

2.9 STUDY MATERIALS

A retrospective review of hospital records of patients treated with the hypofractionated protocol. The records analysed include:

- Patient files
- Laboratory records
- Death certificates if applicable

2.10 STUDY PROCEDURES

2.10.1 Obtaining patient records

The cancer of the cervix stage 3b cases that were treated with the hypofractionated protocol were identified through a review of records kept for each patient at our records office /statistics department. The hospital numbers were used to trace the patient case notes and laboratory data.

2.10.2 Ascertainment/authentification of records

To avoid missing patient files/records and to confirm authenticity of the said record, the principal investigator liaised with the records officers. Attempts were made to contact patient/family by phone if information was not in the file. Failing telephonic information, home affairs was contacted for a death certificate.

2.11 ETHICAL CONSIDERATIONS

Ethical clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) with certificate number M110908 and permission of the CEO of the CMJAH was obtained before starting the study, as per university and hospital requirements.

2.11.1 Study record confidentiality

All data and materials extracted from the patients files/records was done with utmost respect and confidentiality. No patient identifiers was extracted or analyzed and all care taken into account to ensure that only the principal investigator had access to raw patient records through creation of a password protected Microsoft excel data flow sheet. The patient numbers used to extract the raw patient data into the excel sheets was not transcribed into the STATISTICA database for statistical analysis; instead each record packet was assigned a new study number. As such only the principal investigator was able to link the primary data with the secondary data. The data shall be used for the sole purpose of writing this dissertation and for scientific publications.

2.12 Statistical analysis

Statistical analysis was done using STATISTICA Version 10. Basic descriptive and frequency statistics of categorical and nominal data and comparisons using

the Students T-test was done. Survival statistical analysis using the Kaplan Meier statistical method was used to derive survival comparisons. A p value of less than 0.05 was taken as significant.

2.13 Toxicity analysis

Toxicity was assessed based on RTOG/EORTC scoring system. See appendices B and C (5).

2.14 Study variables

The following data were reported for all case records reviewed:

1. Demographic data including age and race.
2. Haemoglobin levels at the start of radiation therapy.
3. Human Immunodeficiency Virus status and whether on HAART at the start of radiation therapy.
4. Histology.
5. Stage 3b unilateral pelvic side wall invaded or more advanced disease.
6. Kidney ultrasound findings at the start of radiotherapy whether hydronephrosis was present or not.
7. Papanicolaou smear result 6 months post radiation therapy.
8. Disease free survival and overall survival at 6 months.
9. Radiation toxicity, for both early and late gastrointestinal, genitourinary, skin and mucosa.

2.15 Assessment record review during treatment and follow-up.

Patients were followed according to departmental protocol for carcinoma of the cervix. Patients were reviewed once a week for toxicity during treatment, six weeks post treatment and then three monthly for the first year. Papanicolaou smears were done at six months post treatment. During follow-up, history and physical examination was done, including bimanual pelvic and rectal examinations. If required, imaging was done to confirm distant disease.

2.16 Study data collection instruments

All primary data extracted from raw patient records were entered into a Windows excel based data flow sheet. Data was cleaned up and verified, and all patient identifiers were removed prior to data being transcribed into a STATISTICA data base as secondary data ready for analysis using the STATISTICA software version 10.

2.17 Study limitations

This study was retrospective and unfortunately, some records were not kept well and therefore missing.

3. RESULTS

Table 1 Patient characteristics

Characteristic	Number of patients (%)
Total number (n)	104 (100%)
Age (y)	
Mean	52.72
Range	23-89
Race (n)	
Blacks	102 (98.08)
White	1 (0.96)
Coloured	1 (0.96)
Haemoglobin at the start of RT	
Mean (g/dl)	11.66
Range (g/dl)	7.5-15.2
≤10g/dl (n)	21(20.19)
>10g/dl (n)	83(78.81)
Tumour extension to pelvic wall (n)	
Unilateral PSW	53 (50.96)
Bilateral PSW	45 (43.27)
No PSW	6 (5.77)
Hydronephrosis(n)	
No hydronephrosis	57 (54.81)
Unilateral	32 (30.77)
Bilateral	15 (14.42)

HAART status among HIV positive (n)	
On HAART	14 (42.42)
Not on HAART	18 (54.55)
Not known	1 (3.03)
Duration of treatment (days)	
Mean	25.97
Range	21-54
≤ 24 days (n)	40 (38.46)
>24 days (n)	62 (59.66)
Energy (n)	
Cobalt	16 (15.38)
6mv	49 (47.12)
15mv	15 (14.42)
18mv	21 (20.19)
Missing	3 (2.88)
Technique (n)	
AP/PA	99 (95.19)
Four field	5 (4.81)
Pap smear results (n)	
Negative	71 (68.3)
Positive	0 (0.00)
Not done	33 (31.7)

PSW (pelvic side wall); AP/PA (anterior posterior/posterior anterior)

Table 2 **Overall pattern of recurrence**

Failure site	Number of patients (%)
No recurrence	79 (75.96)
Local only	12 (11.5)
Local + distant	1 (0.96)
Distant only	2 (1.92)
Not evaluable	10(9.62)

Table 3 Comparison of mean age between HIV negative and HIV positive patients

	HIV NEGATIVE	HIV POSITIVE
MEAN AGE (YEARS)	55.95	45.76

p=0.000066

Table 4 Clinical response after six months using a clinical assessment modelled on the RECIST criteria as explained in appendix D

Response	Patients (%)
Total number	104 (100)
Complete	73 (70.19)
Partial	6 (5.77)
Stable	8 (7.69)
Progressive	8 (7.69)
Not evaluable	9 (8.65)

3.1 PATIENT AND DISEASE CHARACTERISTICS

3.1.1 Age

The mean age of the patients at the time of presentation was 52.72 years (range 23-89 years).

3.1.2 HIV status

Seventy one (68.3%) patients were HIV negative while 33 (31.7%) were HIV positive. The mean age of HIV negative patients was 55.95 years while that of HIV positive patients was 45.76 years, which was statistically significant with a p value=0.000066.

3.1.3 Race distribution

One hundred and two patients (98.08%) were black, one patient (0.96%) was white and one (0.96%) was coloured.

3.1.4 Haemoglobin levels

The mean haemoglobin was 11.66g/dl (range 7.5-15.2 g/dl). Twenty one patients had haemoglobin levels of less or equal to 10g/dl and 83 patients had haemoglobin levels of more than 10g/dl.

3.1.5 Parametria tumour involvement

Fifty three patients (50.96%) had unilateral pelvic side wall tumour involvement, forty five patients (43.27%) had more advanced tumours, extending to both pelvic side walls. Six patients (5.77%) had no tumour extension to the pelvic side walls and stage 3b based on having hydronephrosis.

3.1.6 HAART status among HIV positive patients

At the start of treatment only 14 patients (42.42%) were on HAART. Eighteen patients (54.55%) were not on HAART while one patient's data was missing.

3.1.7 Papanicolaou smear results after six months

All the Pap smears that were done after six months among 71 patients (70.19%) were negative for intraepithelial malignancy. Two patients (1.92%) died post treatment before the six month follow-up, while 29 patient's Pap smears were not done due to vaginal stenosis post radiation treatment.

3.1.8 Duration of treatment

The mean number of days of receiving treatment was 25.97 days (range 21 -54 days). Forty (38.46%) patients (38.46%) completed radiation therapy on or before 24 days while sixty two patients (59.66%) completed treatment after 24 days. Unfortunately two patient's (1.92%) data was missing.

3.1.9 Overall pattern of recurrence

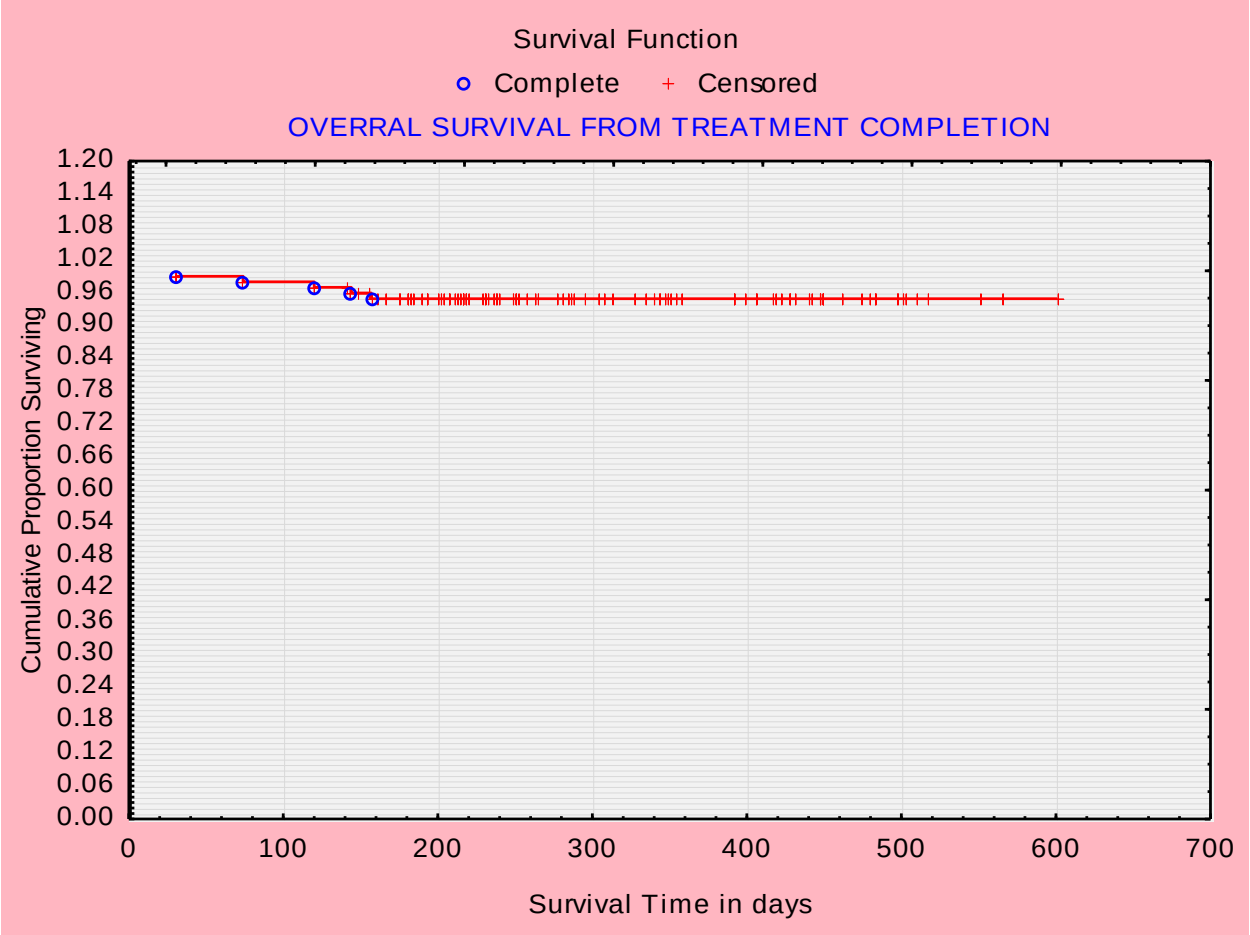
Seventy nine patients (75.96%) had no local or distance recurrence of disease. Twelve patients (11.5%) had local recurrence, one (0.96) patient had both local and distance disease and two patients (1.92%) had only distant metastases. Ten patient's (9.6%) data was missing. The local recurrences were mainly a mass in the vaginal wall, parametria and a tumour in the periurethral area. Distant metastases were mainly lung metastases, seen in two patients and one patient had both lung metastasis and a par-aortic mass.

3.2 SURVIVAL RESULTS

At six months after completion of radiation therapy 73 patients (70.19%) achieved a complete response, six patients (5.77%) had a partial response, eight patients (7.69%) had no response (stable disease) and a further eight patients (7.69%) had progressive disease on follow-up. One patient died a few days post treatment while eight patient's data were missing and hence not evaluable.

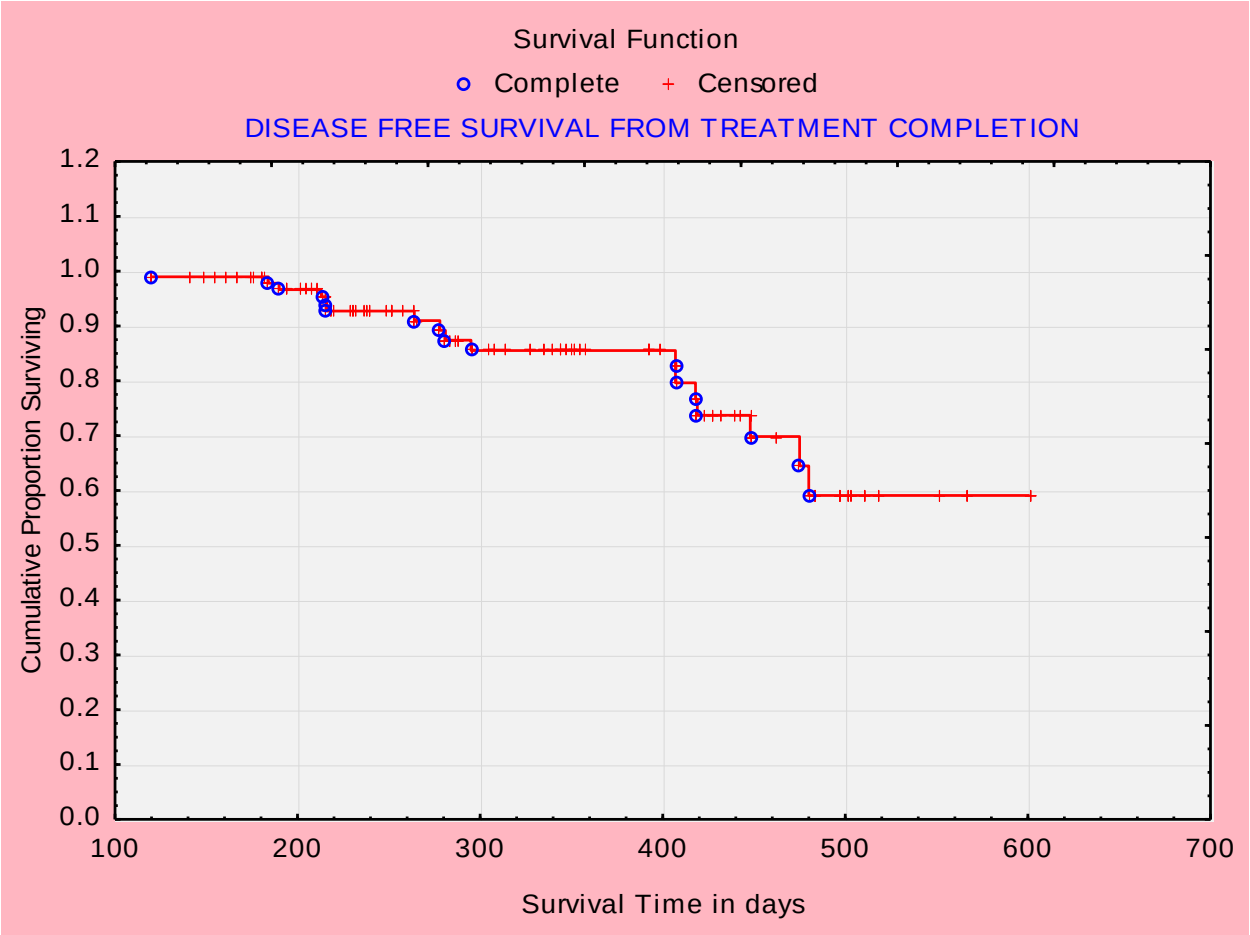
3.2.1 Overall and disease free survival

The 600 days cumulative overall survival after treatment completion was 94.92% as shown in Graph 1, while DFS over the same number of days was 59.04%, as shown in Graph 2.



Graph 1 Overall survival after treatment completion

600 Days overall survival =94.92%

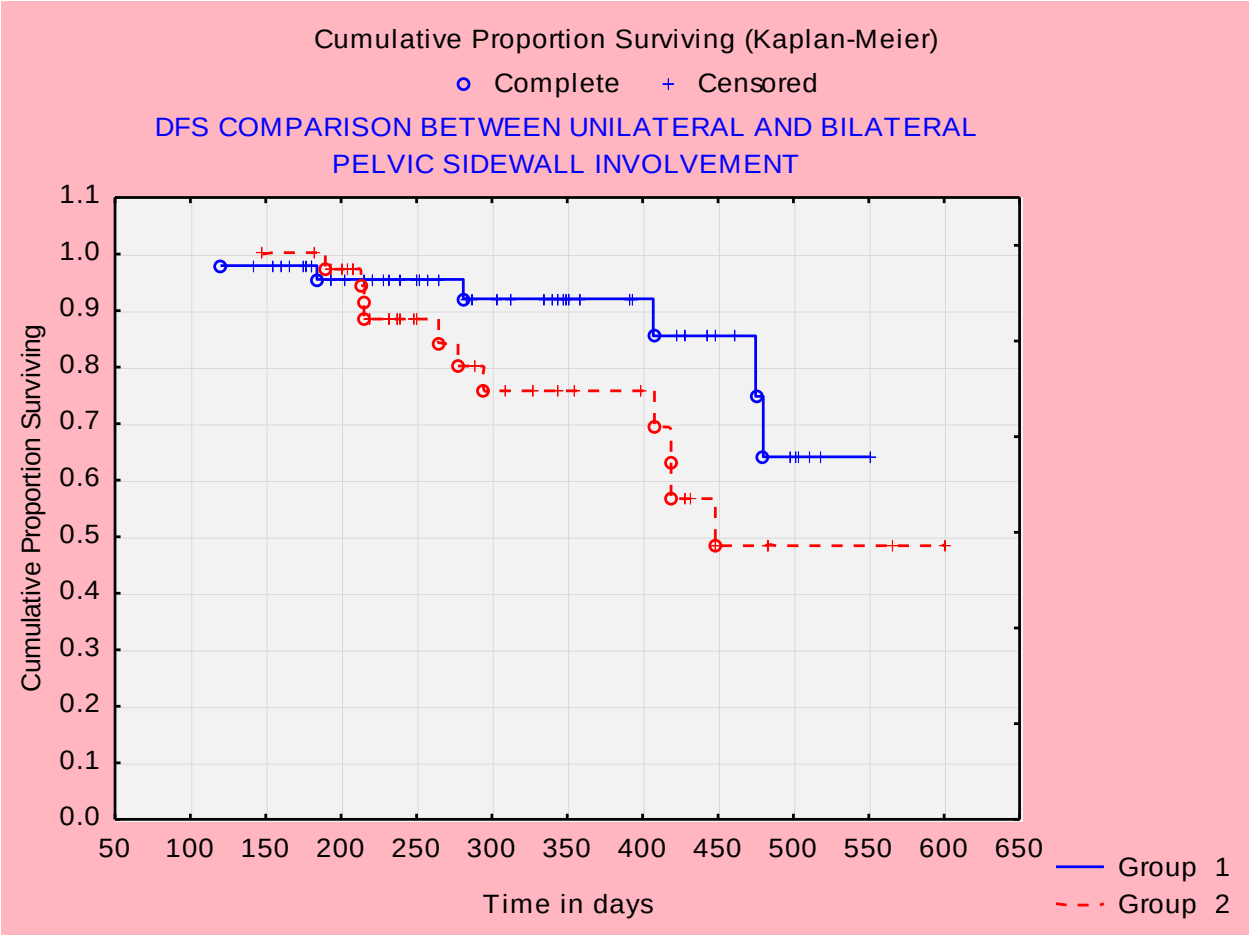


Graph 2 Disease free survival after treatment completion

600 Days disease free survival=59.04%

3.2.2 Disease free survival comparison between unilateral and bilateral pelvic sidewall fixed tumours

Comparison of DFS between unilateral and bilateral pelvic side wall (PSW) involvement at 600 days was as follows: DFS for unilateral PSW involvement=63.94% and DFS for bilateral PSW involvement=48.79% (p =0.129) as seen in the Graph 3.

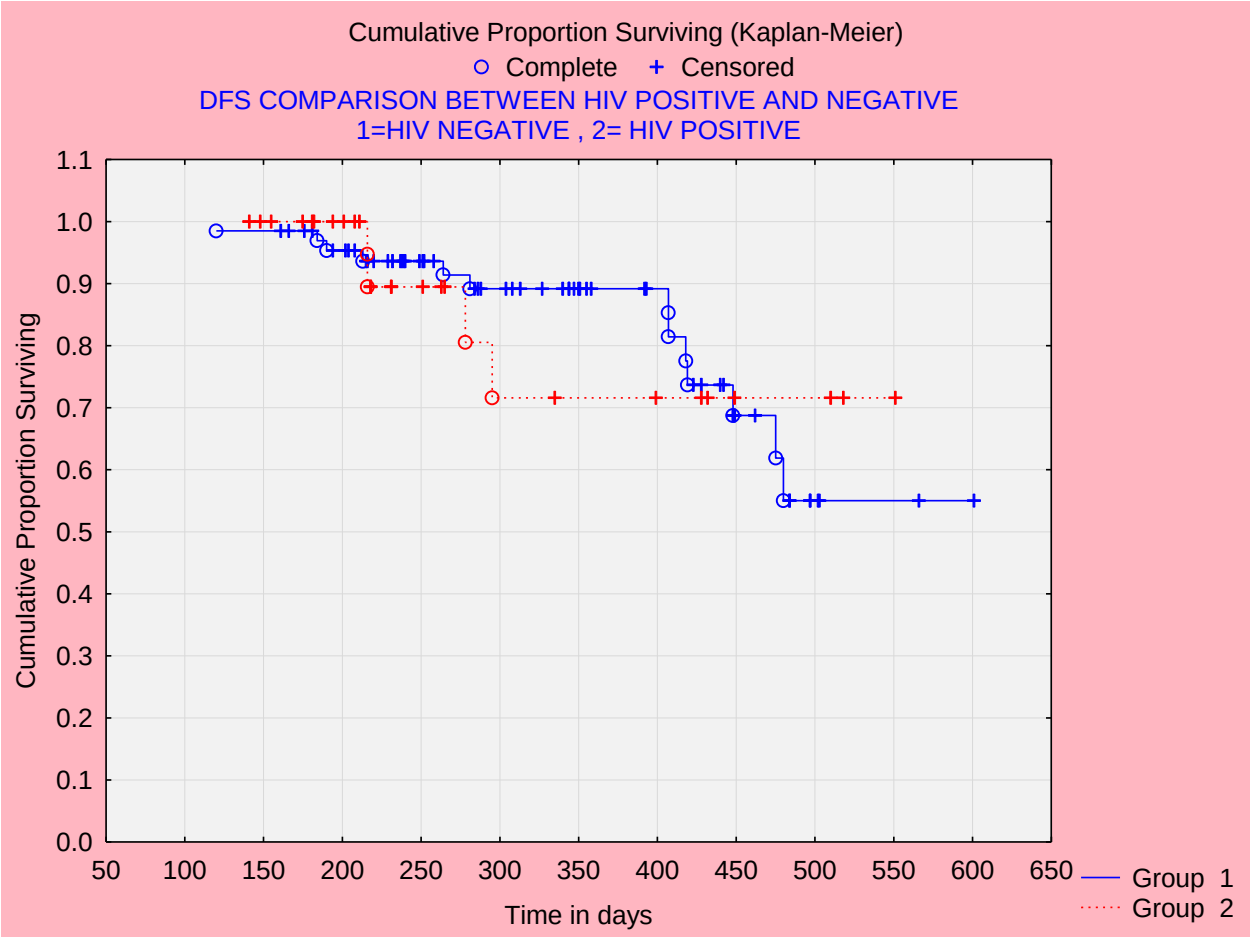


Graph 3 Disease free survival comparison between unilateral and bilateral pelvic sidewall tumour involvement

Group 1 indicates the unilateral PSW involvement and Group 2 indicates the bilateral PSW involvement.

3.2.3 Disease free survival comparison of HIV negative and HIV positive patients who were treated with radiotherapy

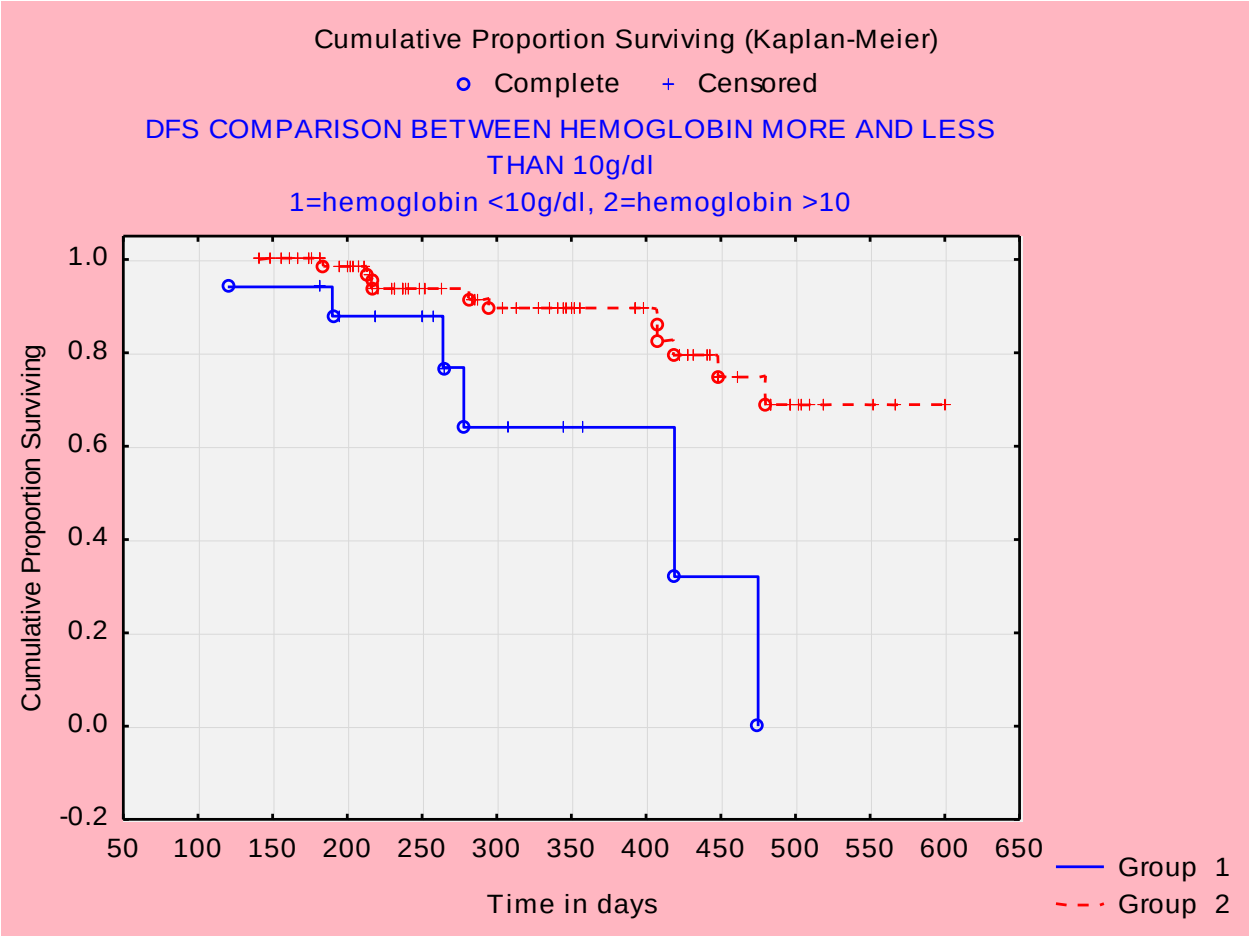
In the DFS comparison between HIV negative and HIV positive radiation treated patients at 600 days, the DFS for HIV negative patients was=55.13% and the DFS for HIV positive patients was=71.41%, with p=0.7229, as show in Graph 4.



Graph 4 Disease free survival comparison of HIV negative and HIV positive patients who were treated with radiotherapy

3.2.4 Disease free survival comparison between patients with haemoglobin levels ≤10g/dl and >10 g/dl

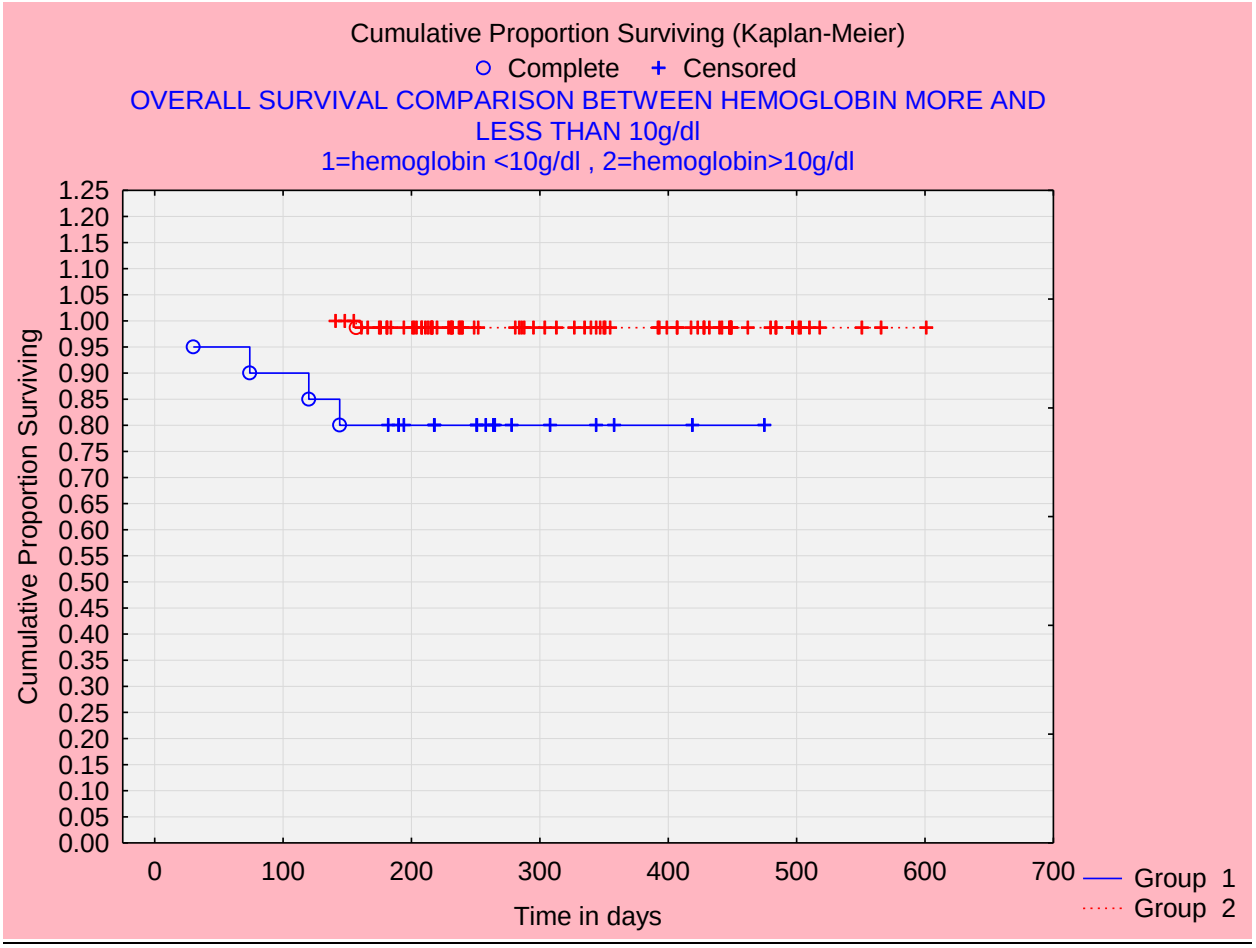
The DFS for patients with haemoglobin levels of more than 10g/dl was 68.57%, while there was no patient with haemoglobin levels of less or equal to 10 g/dl who survived after 470 days (p=0.0213), as shown in Graph 5.



Graph 5 Disease free survival comparison between patients with haemoglobin ≤10g/dl or >10g/dl

3.2.5 Overall survival comparison between patients with haemoglobin levels ≤10g/dl and >10g/dl

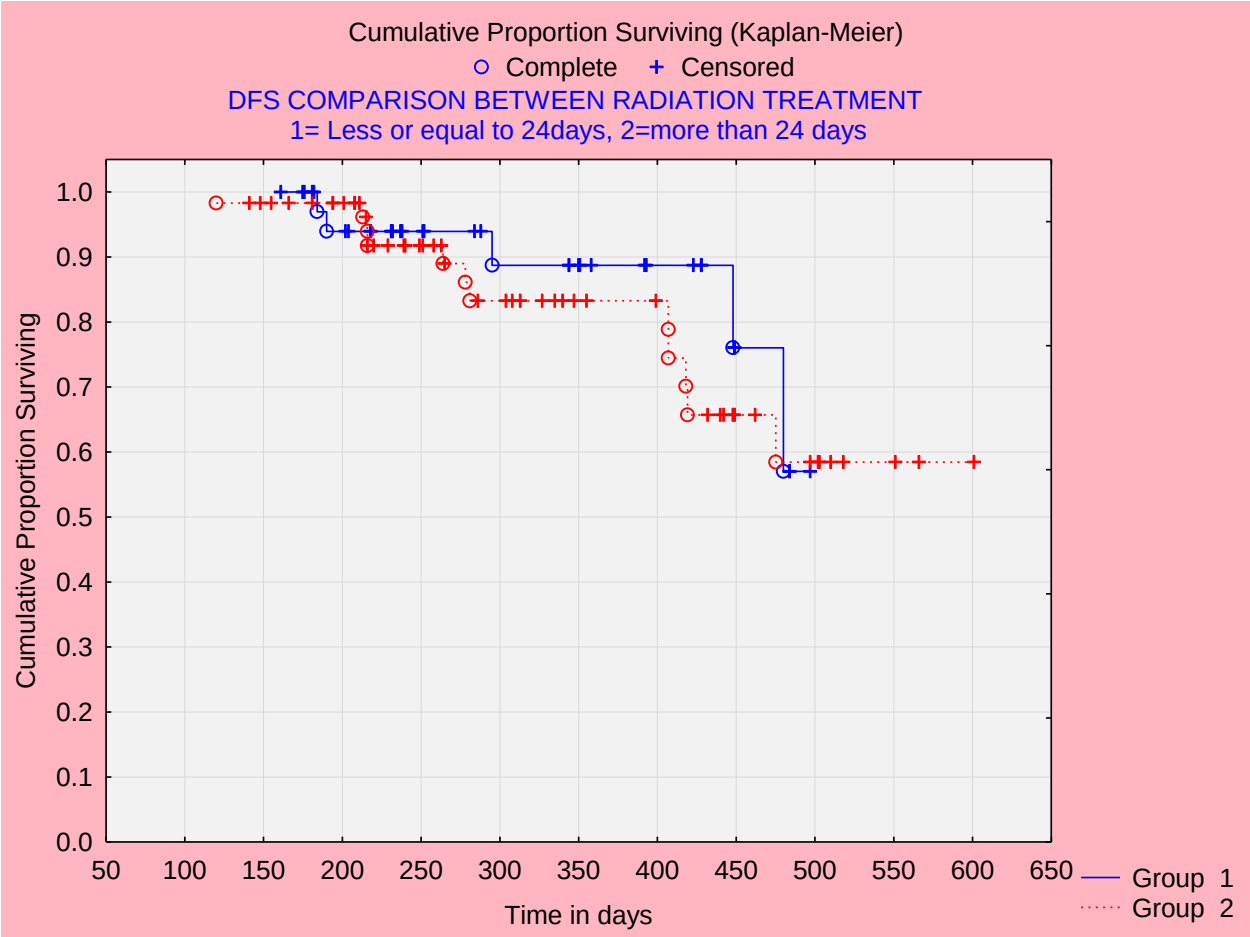
Overall survival was 98.81% for patients with haemoglobin levels of more than 10g/dl, while patients with haemoglobin levels of less or equal to 10g/dl had an OS=80.05% (p=0.00055), as show in Graph 6.



Graph 6 Overall survival comparison between patients with haemoglobin levels of ≤10g/dl or >10g/d

3.2.6 Disease free survival comparison between patients who completed radiotherapy ≤24days and >24 days

There was no statistical difference in the DFS between patients who completed treatment within 24 days and patients who were on radiotherapy for more than 24 days, as indicated by Graph 7.



Graph7 Disease free survival comparison between patients who received radiation ≤24days and for >24 days

The DFS for radiation treatment duration of ≤24 days =57.03% and similarly, the DFS for radiation treatment duration of >24 days =58.76%, with a p value of 0.49713.

3.3 TOXICITY

Table 5 Overall acute reactions

ACUTE REACTIONS

REACTION	TOTAL	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
SKIN	77	25	23	54	0	0
GU	32	69	0	32	0	0
GIT	39	61	2	36	1	0

Table 6 Overall late reactions

LATE REACTIONS

REACTION	TOTAL	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
SKIN and/or VAGINA	62	34	4	53	5	0
GU	0	0	0	0	0	0
GIT	5	91	0	1	4	0

3.3.1 Acute skin reactions

Seventy seven patients developed acute skin reactions. Twenty three patients had grade 1 and 54 patients had grade 2 acute skin complications. No patient developed acute grade 3 or 4 toxicity. Human Immunodeficiency Virus status did not have an effect on acute skin complications (See table 7).

Mean time=23.59 days

Minimum=8 days

Maximum=63 days

Table 7 Acute skin reactions comparing HIV negative to HIV positive patients

ACUTE SKIN TOXICITY	HIV NEGATIVE	HIV POSITIVE	TOTAL
GRADE 0	16	9	25
GRADE 1	17	6	23
GRADE 2	37	17	54
GRADE 3	0	0	0
GRADE 4	0	0	0
TOTAL	70	32	102

The mean time to acute skin reaction was 23.59days (Range 8-63 days).

3.3.2 Acute genitourinary toxicity

Thirty two patients developed acute grade 2 genitourinary reactions. No patient developed grade 1, 3, or 4 reactions. Patient's HIV status did not affect acute genitourinary reaction (See table 8).

Time to developing acute genitourinary toxicity:

Mean time=19.03 days

Minimum=2 days

Maximum=51 days

Table 8 Acute genitourinary reactions comparing HIV negative to HIV positive patients

ACUTE GENITOURINARY TOXICITY	HIV NEGATIVE	HIV POSITIVE	TOTAL
GRADE 0	43	26	69
GRADE 1	0	0	0
GRADE 2	26	6	32
GRADE 3	0	0	0
GRADE 4	0	0	0
TOTAL	69	32	101

The mean time to acute maximum genitourinary complication was 19.03 days (range2-51 days). All the patients who developed acute genitourinary toxicity had radiation induced cystitis and were treated with CITRO-SODA.

3.3.3 Acute gastrointestinal toxicity

Thirty nine patients developed acute gastrointestinal complications. Two patients had grade 1, 36 patients had grade 2 and 1 patient developed grade 3 gastrointestinal toxicity. The patient who developed grade 3 toxicity had diarrhoea which required intravenous fluid. Human Immunodeficiency Virus status did not affect acute gastrointestinal complications (See table 9).

Time to developing acute gastrointestinal toxicity:

Mean=15.5 days

Minimum=1 day

Maximum=27 days

Table 9 Acute gastrointestinal reactions comparing HIV negative to HIV positive patients

ACUTE GASTROINTESTINAL TOXICITY	HIV NEGATIVE	HIV POSITIVE	TOTAL
GRADE 0	44	17	61
GRADE 1	2	0	2
GRADE2	21	15	36
GRADE3	1	0	1
GRADE 4	0	0	0
MISSING	1	0	1
TOTAL	69	32	101

The mean time to acute GIT complication was 15.5days (Range 1-27 days).

3.3.4 Late complications

3.3.4.1 Late skin/vulvo-vaginal complications

Sixty two patients developed late skin complications of which four had grade 1, 53 had grade 2 and 5 had grade 3 toxicity. The patient's HIV status did not affect late skin/vulvo-vagina complications. All the patients who developed grade 3 toxicities had radiation proctitis (See table 10).

Mean time=218.74 days

Minimum=147 days

Maximum=391days

Table 10 Late skin/vulvo-vaginal reactions comparing HIV negative to HIV positive patients

LATE SKIN TOXICITY	HIV NEGATIVE	HIV POSITIVE	TOTAL
GRADE O	25	9	34
GRADE 1	3	1	4
GRADE 2	34	19	53
GRADE 3	5	0	5
GRADE4	0	0	0
TOTAL	67	29	96

The patients' late skin complications were assessed to a maximum follow-up of 391 days.

3.3.4.2 Late genitourinary toxicity

No patient developed late genitourinary complication up to a maximum follow-up of 390 days.

3.3.4.3 Late gastrointestinal toxicity complications

Five patients developed late GIT complications of which one had grade 2 and four had grade 3 toxicity. Patients' late toxicity was assessed up to a maximum 278 days. All the patients who had grade 3 toxicity had radiation induced proctitis which was confirmed by procto-sigmoidoscopy. The patients'HIV status did not affect late GIT complications (See table 11).

Time to late gastrointestinal toxicity

Mean time=241.75 days

Minimum=202 days

Maximum=278 days

Table 11 Late gastrointestinal toxicity reactions comparing HIV negative to HIV positive patients

LATE GIT TOXICITY	HIV NEGATIVE	HIV POSITIVE	TOTAL
GRADE 0	64	27	91
GRADE 1	0	0	0
GRADE 2	0	1	1
GRADE 3	3	1	4
GRADE4	0	0	0
TOTAL	67	29	96

The mean time to late complication was 241 days (Range 202-278 days)

4. DISCUSSION

4.1 Papanicolaou smear

The use of Pap smears for cervical and vagina cytology as a follow-up study is controversial because of the bizarre post irradiation cellular morphology that renders it difficult to distinguish post irradiation changes from residual or recurrent malignant cells (20, 21). In my study, 73patients' (70.19%) Pap smears were done six months post irradiation and all the results were cytologically negative for intraepithelial malignancy. Two patients died post treatment before six months and hence the Pap smear was not done. Twenty nine patients did not comply with post irradiation advice as to using a vaginal dilator and therefore on the sixth month visit, the vagina was stenosed and hence the Pap smear was not done. However, clinical assessment using speculum and per vaginal examination revealed different results from Pap smears. Using modified RECIST criteria (44), 73% of the patients had a complete response, 6 had a partial response, and 8 had progressive disease while 9 patients were not evaluable at six months as one died while 8 had missing information. In asymptomatic patients, clinical assessment seemed to be a better tool of assessment than a Pap smear at six months. This could be due to a number of reasons including how the Pap smear was taken and the skills involved. Indeed, in a study done at the MD Anderson Cancer Centre on 1 000 patients treated with either surgery or radiation therapy for stage 1B cervical cancer, post treatment Pap smears did not detect a single asymptomatic recurrence among 133 patients with recurrent disease (22).

4.2 Outcome and haemoglobin

Many studies have demonstrated the prognostic significance of haemoglobin levels in terms of disease free survival and overall survival (23, 24, 25, 26, and 27). In a review article of published data Vaupel *et al*., (28) concluded that maximum oxygenation of the tumour is expected with haemoglobin in the range of 12 to 14 g/dl for women and that higher levels of haemoglobin may not necessarily be better. In this study, I compared OS and DFS among patients with haemoglobin levels ≤10 and ≥ 10. The haemoglobin levels were measured at the start of radiotherapy. Patients with haemoglobin levels of more than 10g/dl had a 98.8% OS while patients with haemoglobin equal or less than 10g/dl had an 80.05 %OS, (p=0.00055). Disease free survival among patients with haemoglobin levels of more than 10g/dl was 68.57%, while no patient was disease free after 470 days with haemoglobin levels of less or equal to 10g/dl (p =0.02130). My study confirms and demonstrates the prognostic importance of haemoglobin levels in patients receiving radiotherapy.

4.3 Human Immunodeficiency Virus status and outcome

Campbell *et al.,* (1999) (29) observed in his study on carcinoma of the cervix treated with radiation therapy, that HIV positive patients had more advanced tumours and that the duration of remission was shorter than in the HIV negative patients. Furthermore, women who are HIV positive also had a higher risk for

tumour recurrences after treatment and a higher risk of death as a consequence of the malignant process.

In my study, there were 71 patients (68.3%) who were HIV negative and 33 patients (31.7%) who were HIV positive. The mean age of HIV positive patients was 45.76 years, while the mean age for HIV negative women was 55.95 years (p=0.000066). Carcinoma of the cervix is seen at an earlier age among HIV positive patients as compared to in HIV negative patients in our department. There was no difference in DFS among the HIV positive (71.4%) and HIV negative (55.13%) patients, (p=0.72296). However, the duration of remission among HIV positive patients was shorter as compared to HIV negative patients. The HIV positive patients were disease free after 300days, while the HIV negative patients were disease free after 475 days. This concurs with Campbell's study (29).

4.4 Overall outcome

Five year overall survival rates of 65-75%, 35-50% and 15-20% are reported for patients treated with radiotherapy alone for stage 2b, 3b, and 4 tumours respectively (30, 31, 32, 33). In other studies on stage 3b carcinoma of the cervix treated with conventional fractionation, the five year overall survival rates reported ranged from 25-48% and pelvic failure rates ranged from 38-50% (34, 35).

A retrospective study by Muckasden *et al,*. (2002) (13) from the Tata Memorial Hospital in India reported that the five year DFS was 59% and the OS was 50% at a mean follow- up of 40 months. Furthermore, a phase 1-2 study from Brazil by Viegas *et al.,* (2004) reported that the three year OS was 76% and the five year OS was 59% (18).

In my study, the OS for up to 600 days follow-up was 94.92% and the DFS was 59.04%. The follow-up period was very short and longer follow-up is recommended. Despite the short follow-up, both the OS and the DFS compares well with conventional radiotherapy results found in the literature with a projection towards better survival.

4.5 Impact of prolonged treatment time

Several studies have described lower pelvic tumour control and survival rates in invasive carcinoma of the uterine cervix when the overall time in a course of irradiation is prolonged (36, 37, 38, and 39). Girinsky et al(38) in386 patients with stage 2b or 3 carcinoma of the cervix ,observed that the 10 year local recurrence free survival rate decreased when overall treatment time exceeded 52 days. A 1.1% loss of pelvic tumour control per day was also observed in their regression analysis. Perez et al (40) also observed that there was a strong correlation between overall treatment time and survival.

A recent study by Huang *et al.,* (41) verifies the fact that accelerated repopulation does exist in cervical cancer and has a relatively short onset time. Higher dose and

shorter treatment duration were associated with higher TCP. They achieved the best fit with onset time Tk of 19 days.

In this study, the patients were treated with a departmental hypo-fractionated protocol, in which the mean duration of treatment time was 25.97 days (range 21-54 days).There was no difference in 600 days DFS (57.03% versus 58.76%, p=0.49713), and overall survival (97.43% versus 93.21%, p=0.38410**)** between patients who completed radiation therapy in less or equal to 24 days and more than 24 days as treatment times for the two groups were similar. Longer follow-up is required to ascertain the benefit of shorter treatment time.

4.6 Outcome of unilateral versus bilateral pelvic sidewall tumours

Patterns of care studies in stage 3a/3b patients indicate that survival is depended on the extent of the disease, with unilateral PSW involvement predicting a better outcome than bilateral involvement (42). Other studies have also correlated outcome with the tumour bulk, unilateral versus bilateral parametria or PSW involvement (32, 33). Souhami *et al.,* (1987) (15) reported on the results of patients with stage 3b disease treated with radiation therapy alone. Patients with bilateral parametria disease involvement had a significantly lower survival than those with unilateral disease (43% versus 15%), (p=0.005). Lanciano *et al*., (1991) (43) also reported a significantly worse outcome in patients with bilateral parametria disease.

A Study by Arthur *et al.*, in1995 (1) from Virginia, showed that stage 3b cancer of the cervix comprises of a heterogeneous group of diseases with different prognostic indices. They derived at a tumour burden scoring system by which FIGO stage 3b disease can be clinically divided into two prognostic groups. The five year local regional control was 62.9% and 40% for the low and high tumour burden groups respectively (1).

A retrospective study by Hei-Yu *et al*., (2009) from Taiwan reporting on the aggressive characteristics of cervical cancer in young women also showed that parametria involvement is prognostic in early FIGO stage 1A-2A cervical cancer patients who underwent surgical procedure between Jan 1983 and Dec 2007. Parametrial involvement for stages 1A and 2A was 33.3% versus 12.0% respectively, (p=0.001) (9). My study shows a trend towards a better DFS after 600 days follow-up in patients with unilateral as compared to bilateral PSW involvement (63.94% versus 48.79%), (p=0.12926). However, longer follow-up is recommended.

4.7 Toxicity

The incidence of major late sequelae of radiation therapy for stage 2b and 3 carcinoma of the cervix is between 10%-15 % (53). However, a study by Bosset *et al*., (1997), reported the rate of late rectal morbidity was between 2-25% in radiotherapy patients (2). From a study by Swaroop *et al*., (1998), it appeared that the time of development of bleeding per rectum is between 6 months to one year

after completion of radiation therapy and is caused by friable mucosal angiogenesis (16). However, Yegappan *et al*., (1998) have reported a mean duration of 19.9 months for toxicity after radiotherapy for development of bleeding per rectum (19). According to studies reported in the literature, late urinary tract complications are seen frequently 3- 5 years after treatment (19, 57, 58). Radiation cystitis is observed in 6-15% of patients receiving pelvic radiotherapy (10, 11, 4). Pedersen *et al.*, (1994) (54) recommended that actuarial estimates rather than frequency of sequelae be reported. Montana *et al.*,(1986) (35), Perez *et al.*,(1999) (55) and Pourguier *et al.*, (1982) (56) have noted that the incidence of radiation complications depended on the dose delivered.

Hypo-fractionated studies for carcinoma of the cervix by Muckasden *et al.*, (2000) (13) and Viegas *et al*., (2004) (18) showed comparable sequelae as conventional radiation therapy. Although, in the study by Viegas *et al*., (2004) (18) concurrent chemo-radiation was given at 2.5Gy twice daily to a total of 40Gy plus 35Gy Low Dose Rate brachytherapy delivered to point A. Chemotherapy consisted of 15mg/m^2 Cisplatin and 400mg/m^2 5-Fluorouracil intravenous infusion. The study by Muckasden *et al.*, (2000) (13) used standard pelvic portals to a total dose of 39GyEBRT in 13 fractions plus intra-cavity brachytherapy.

In my study, there was no patient with acute grade 3 or 4 skin and/or GU complications. Only one patient had acute grade 3 GIT toxicity. The patient had diarrhoea which required admission and intravenous fluid support.

Five patients who were also HIV negative, developed late grade 3 skin complications. There was no patient with late bladder complications up to a

maximum follow-up of 390 days. Four patients had late grade 3 GIT complications. Among them one patient was HIV positive while three were HIV negative. All of these patients had radiation induced proctitis based on procto sigmoidoscopy and were treated with formalin injection and sucralfate enemas. The earliest radiation proctitis was seen after 202 days.

The difference in toxicity between HIV positive and HIV negative patients was not statistically significant.

5. CONCLUSIONS

Given the limitations of this study, viz, retrospective study, short observation time (600days) and the crude assessment by clinical examination, these preliminary outcomes are promising. A DFS of 59% and a low severe complication rate compares favourably with conventionally treated patients with stage 3 cervical cancer. The protocol is resource sparing (reduced long waiting for radiotherapy in our department from 6 months to 2-3 months) and if long term results are satisfactory, the protocol may be recommended for use in resource constrained departments. The reduced overall treatment time may confer an advantage in reducing tumour re-population during treatment.

As other studies have shown, carcinoma of the cervix is seen at an earlier age among HIV positive patients and screening of HIV positive women for cervical cancer is recommended. Furthermore, haemoglobin levels are also found to be prognostic among stage 3b cervical carcinoma patients treated with hypofractionation, as it is in patients treated with conventional fractionation. Importantly, monitoring and correction of anaemia is highly recommended.

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APPENDIX A

FIGO staging of carcinoma of uterine cervix

I Cervical cancer confined to the uterus (extension to corpus should be disregarded).

IA Pre–clinical invasive carcinoma, diagnosed by microscopy only.

IA1 measured stromal invasion < 3 mm in depth and < 7 mm in horizontal spread.

IA2 measured stromal invasion > 3 mm and not > 5 mm with horizontal spread of < 7 mm.

IB clinically visible lesion confined to the cervix or microscopic lesion > IA2.

IB1 clinically visible lesion < 4 cm in greatest dimension.

IB2 clinically visible lesion > 4 mm in greatest dimension.

II cervical carcinoma invades beyond uterus, but not to the pelvic wall or to the lower third of vagina.

IIA Tumour without parametrial invasion.

IIB Tumour with parametrial invasion.

III Tumour extends to pelvic wall, and/or involves the lower third of vagina, and/or causes hydronephrosis or non-functioning kidney.

IIIA Tumour involves lower third of vagina, no extension to pelvic wall.

IIIB Tumour extends to pelvic wall and/ or causes hyderonephrosis or non-functioning Kidney

IVA Tumour invades mucosa of bladder or rectum and/or extends beyond the true pelvis.

IVB Distant metastasis

APPENDIX B– RTOG acute radiation morbidity scoring criteria

Organ Tissue	[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 that may produce an inflammatory serosanguinous discharge/may experience moderate pain requiring analgesia.	Confluent fibrinousmucositis /may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
Lower G.I including pelvis	No change	Increased frequency or change in quality of bowel habits not requiring medication/ rectal discomfort not requiring analgesics	Diarrhoea requiring parasympatholytic drugs (e.g. Lomotil)/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics	Diarrhoea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subactue obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
Genitourinary	No change	Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication.	Frequency of urination or nocturia that 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

APPENDIXC - RTOG/EORTC late radiation morbidity scoring scheme

Organ Tissue	0	Grade 1	Grade 2	Grade 3	Grade 4	5
Skin	None	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Market atrophy; gross telangiectasia	Ulceration	
Mucous membrane	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucous	Marked atrophy with complete dryness. Severe telangiectasia	Ulceration	Death directly related to radiation late effects
Small/Large intestine	None	Mild diarrhea, mild cramping; bowel movement 5 times daily, slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement >5 times daily; excessive rectal mucous or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/ Perforation Fistula	Death directly related to radiation late effects.
Bladder	None	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria	Severe frequency & dysuria; severe generalized telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (,150cc)	Necrosis/Contracted bladder (capacity<100cc) Severe hemorrhagic cystitis	Death directly related to radiation late effects.

Appendix D

4.3. Clinical response after six months using clinical assessment modelled on recist criteria explained here.

4.3.1. Evaluation of target lesions

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

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

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

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