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A Prospective Randomized Study Comparing Three-Fraction Regimens of HDR Brachytherapy with concomitant chemo-radiotherapy for Cancer of the Cervix Stage IIB and IIIB

A thesis submitted to the faculty of Health Sciences,

University of the Witwatersrand, in fulfilment of the requirements

for the Degree of Master of Medicine in Radiation oncology

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DECLARATION

I, W. Tigeneh, declared that this research report work is my own. It is being submitted for the degree of Master of Medicine in Radiation Oncology in the University of the Witwatersrand, Johannesburg. This thesis has not been submitted before for any examination or degree at this or any other University.

Signed on _____ October 07

Wondemagegnehu Tigeneh

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W. Tigeneh

Johannesburg, South Africa

DEDICATION

This work dedicated to my beloved wife, FANTU, for unconditional support; and to my beloved son and daughter, SURAFEL & ARSEMA, for being the highlight of my days.

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LIST OF ACRONYMS

ABS: American Brachytherapy Society

AP: Anterior-posterior

BED: Biological Effective Dose

BRT: Brachytherapy

Ca: Cancer

CCRT: Concurrent Chemo-radiotherapy

CDDP: Cisplatin

CTV: Clinical Target Volume

DFS: Disease free survival

EBRT: External beam radiotherapy

ECOG: Eastern Cooperative Oncology Group

EFH: Extra Fascial hysterectomy

5-FU: 5-Flurouracil

FIGO: Federation International de Gynaecologic et Obestetrique

Fx: Fractionation

Gy: Gray

GIT: Gastro-intestinal tract

GOG: Gynaecology Oncology Group

HU: Hydroxyurea

HWT: Height, Width & Thickness

HIV: Human immunodeficiency viruses

HDR: High dose rate

ICRT: Intracavitary radiotherapy

ICRU: International commission on radiation units and measurement

IV: Intravenous

LDR: Low dose rate

LN: Lymph node

LQED: Linear quadratic effective dose

OS: Over all survival

Pap: Papanicolaou smear

PALN: Para aortic lymph node

PSW: Pelvic sidewall

PTV: Planning target volume

RTOG: Radiation Therapy Oncology Group

SOMA Scale: Subjective Objective Management & Analytic scale

SWOG: South West Oncology Group

ABSTRACT

Purpose

Cancer of uterine cervix is one of the leading malignancies affecting the South African female population. In recent years, High Dose Rate (HDR) brachytherapy in combination with External Beam Radiotherapy (EBRT) has been popular in the management of cancers of uterine cervix. Various fractionations regimens of HDR are used in different centres. This randomized prospective study reports the treatment results and incidence of bladder and rectal complications following radical treatment of carcinoma of cervix with standard EBRT and 2, 3 or 4 fractions of HDR brachytherapy.

Methods and Materials

Sixty-six patients with biopsy proven stage IIB and stage IIIB cancer of cervix were recruited. All patients were treated radically and received EBRT 50 Gy in 25 fractions at 2 Gy per fraction. Almost all patients received concomitant Cisplatin 80 mg/m^2 3 weekly. Patients were then randomized into one of the three-fractionation regimens of HDR: 6.5 Gy × 4; 8 Gy × 3; and 9 Gy × 2. Each HDR application was evaluated separately. AP and lateral radiographs were taken. ICRU rectum, bladder, and PSW reference point were identified. Using the linear quadratic formula, the biologically effective dose to the tumour using an α/β ratio of ten (Gy_{10}) was calculated at point A in order to determine a dose response relationship for local control. The biologically effective dose to organs at risk was calculated using an α/β ratio of 3 and this was used to assess the complication rates of the treatment. Patients were evaluated using SOMA Lent toxicity criteria during the treatments, at 6 weeks and finally at 6 months when Pap-smears were performed to assess local control.

Results

Sixty-six patients were entered in this study. Fifty-nine completed chemo-radiotherapy and attended both 6 weeks and 6 months follow up and evaluations. The

mean age of the patients was 51.6 years and the mean duration of the treatment was 47.2 days. Of the 59 patients who completed treatment and had six months follow up, 29 patients were stage IIB and 30 were stage IIIB. The overall complete response rate for the whole group was 88%. The response rate was 90% in arm I, 85.7% in arm II, and 88.8 in arm III, which was not statistically significant (p=0.463). The following prognostic factors were analysed to assess their influence on local control and found to be not significant: stage (IIB vs. IIIB) (p=0.995), age above and below 50 years (p=0.532), treatment duration (p=0.6508), and number of fields used (p=0.603). The adverse effects of radiation-induced toxicity depended on age group (p=0.01), number of fields (p=0.001), and BED Gy_3 dose to organ at risk were statistically significant (p=0.001). The rectal, grade 3 and 4 radiation induced toxicity were observed to be increased when the BED Gy_3 dose was above 105 Gy_3. Similarly, bladder grade 3 & 4 toxicity rate were increased with BED Gy_3 dose of 120 Gy_3 (p=0.001).

Conclusion

Limiting the number of HDR brachytherapy applications from 4 or 3 to 2 fractions has the potential benefit of improving patient compliance. Two HDR applications of 9 Gy each is most cost effective and resource sparing to the institution compared to 3 or 4 insertions.

This study showed that 9 Gy × 2 fractionations HDR brachytherapy with concomitant chemo-radiotherapy was equally effective in short term local control and incidence of treatment related complications compared to other 2 fractionation regimens during 6 months follow up.

INTRODUCTION

Carcinoma of the uterine cervix is the second most common neoplasm in women worldwide and is the most frequent cancer among women in Africa, Asia and South America [1]. It is the most common malignancy in South African black and coloured females with a lifetime (1 – 74 years) risk of 1 in 41 and the 2nd and 5th most common cancer in Asian and white females, respectively[2] . Over the past decade, between 550 and 640 new patients with carcinoma of the cervix were seen at Johannesburg Hospital annually[3] .

Radiotherapy (RT) plays a major role in the treatment of invasive uterine cervical carcinoma. Early invasive tumours are managed with either radical surgery or RT. Locally advanced tumours are also treated with RT. Optimal treatment results require a combination of dedicated planned external beam RT (EBRT) and intracavitary brachytherapy (ICRT). The curative potential of radiotherapy in the management of carcinoma of the cervix is greatly enhanced by the use of intracavitary brachytherapy. The success of brachytherapy may be attributed to the delivery of a high radiation dose to the tumour while sparing the surrounding normal tissues[4].

Low-dose-rate (LDR) ICRT has a long history in the treatment of cervical cancer. The term "brachytherapy" refers to a strategy of implanting sealed radioactive sources either in close proximity to or in contact with the target tissue. High-dose-rate (HDR) brachytherapy was initiated in the late 1950s with a radiation source of ^{60}Co and has been increasingly used for the treatment of cervical cancer[5].

The use of HDR brachytherapy is the result of technological developments in the manufacture of high-intensity radioactive sources, sophisticated computerized remote after loading devices and treatment planning software. Several advantages of HDR brachytherapy, including rigid immobilization, outpatient treatment, patient convenience, accuracy of source and applicator positioning, individualized treatment with source optimization and complete radiation protection for personnel have been claimed[4][6]. These factors have promoted the outpatient management of HDR

brachytherapy procedures and have increased the possible number of brachytherapy procedures that can be performed daily. However, the move to HDR brachytherapy significantly increases the expenses for staff, equipment and need a change of the iridium source every three months.

External beam radiotherapy

RT is the cornerstone and the treatment of choice for Federation International de Gynaecologic et Obstetrique (FIGO) stage IIB, IIIA, IIIB or IVA carcinoma of the cervix and is an excellent alternative to surgery in selected patients with stage IA, IB, or IIA diseases[4],[7]. RT for primary cervical cancer consists of a combination of EBRT and brachytherapy, except in the stage IA disease where brachytherapy alone may be used[7].

Ideally, pelvic radiotherapy begins with EBRT, which is designed to shrink the primary tumour and to improve the geometry for the brachytherapy insertions that follow. The pelvic field is usually 15 cm by 15 cm, extending to 2 cm laterally to the bony pelvis and inferiorly to the border of the obturator foramen or 2 – 3 cm below the lower tumour extent. The superior margin can be extended to cover the common iliac nodes or even higher if Para-aortic lymph node metastases are evident[8].

Brachytherapy

A number of studies have shown that HDR brachytherapy with concomitant chemo-radiotherapy is safe and effective in the management of cervical cancer[9]. In different countries and centres, various fractionation regimens have been studied. In a paper presented by Patel et al (1992), 412 patients diagnosed with stage III or large stage I and II, biopsy proven cancer of the cervix were treated with EBRT and then randomized to receive either HDR 18 Gy in 2 fractions of 9 Gy each or 35 Gy by continuous application of LDR brachytherapy. The five years survival, local control, and distant failure were not significantly different and there was no evidence of increased toxicity in HDR brachytherapy group[10].

A study done in Bangkok Thailand[11] which comparing LDR and HDR Brachytherapy in the treatment of invasive uterine cervical cancer, showed that the 3 years overall survival rate for the LDR and HDR was 70.9% and 68.4% (p = 0.75) respectively. Subgroup analysis stratified by stage showed non-statistically significant differences in terms of overall survival, pelvic control and relapse free survival rates between the two groups. The high number of distant failures suggests that other modalities such as systemic concurrent or adjuvant chemotherapy might improve results, especially in patients with stage IIB and IIIB disease.

Over the last decade, the treatment of cervical carcinoma with radiation has become increasingly sophisticated with evidence-based guidelines generated from randomized trials. In contrast, radiation therapy techniques, including the design of treatment fields, total dose of EBRT and BT, timing of BT, type of implant, dose rate, and ways of evaluating the quality of treatment have been based on past clinical practice. Several authors have reported on the inadequacy of EBRT alone in maximizing local control. In analysis of 565 patients with varies stages of cervical carcinoma treated in the Patterns Care Study, Coia et al reported improved survival (67%) and pelvic tumour control (78%) for patients receiving intracavitary BT than for patients who had no intracavitary BT application, for whom the 4-year survival rate was 36% and the in-field failure rate 57%[12][13]. Hanks reported a higher incidence of pelvic recurrences in patients with stage III cervical carcinoma treated with external beam alone than in patients who received BT in addition to EBRT. Figure 1 shows the local control rates with EBRT alone compared to a combination of EBRT and BT[12].

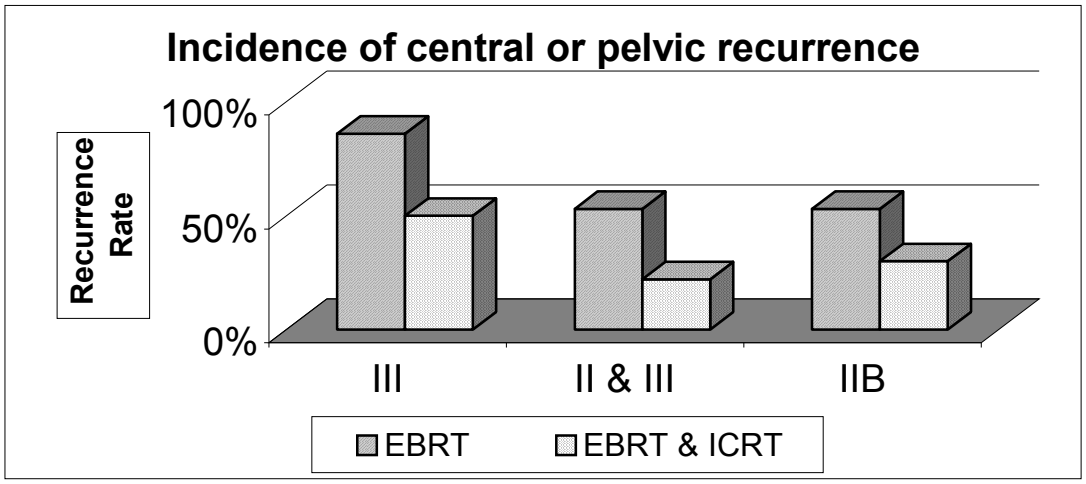


Figure 1. Carcinoma of uterine cervix: incidence of central or pelvic recurrence[12]

High Dose Rate Brachytherapy Fractionation

Various HDR fractionation schedules have been used worldwide in different radiotherapy centres. Examples of the various fractionation regimens used are shown in Table1 below.

Table 1. HDR fractionation schedules[14]

Author	**Whole-pelvic dose**	**HDR fx[1]**	**BED Gy_{10}**	**LQED 2 Gy/ fx**
Wong	40 Gy in 20 fx	7 Gy × 3	86 Gy_{10}	72
		6 Gy × 4	88 Gy_{10}	73
Sood	45 Gy in 25 fx	9 Gy × 2	89 Gy_{10}	74
Ferrigno	45 Gy in 25 fx	6 Gy × 4	92 Gy_{10}	77
NCIC trial	45 Gy in 25 fx	8 Gy × 3	96 Gy_{10}	80
GOG standard	45 Gy in 25 fx	8 Gy × 3	101 Gy_{10}	85
ABS recommendation	45 Gy in 25 fx	4 to 8 fx 5.3 to 7.5 Gy	98 – 109 Gy_{10}	82 – 91

[1] Fx – fraction, NCIC – National Cancer Institute Of Canada, GOG – Gynaecology Oncology Group, ABS – American Brachytherapy Society.

Sood and colleagues[15][16] reported encouraging results of concomitant chemo-radiotherapy (CCRT) using HDR-intracavitary brachytherapy (ICBT) for locally advanced uterine cervical cancer. They used HDR of 9 Gy each in 2 fractions with CCRT and demonstrated an excellent 3 years actuarial local control of 85%. The actuarial severe late complication rate (≥ grade 3) was 6%.

More recently in 2001, a study was done at the Albert Einstein College of Medicine[16] which showed that 2 fractions of HDR brachytherapy of 9 Gy each with and without concomitant chemo-radiotherapy to the pelvis were safe and effective in the management of patients with carcinoma of uterine cervix. Patients were treated with a median dose of EBRT of 45 Gy in 1.8 Gy per fraction daily. This was followed by a parametrial boost in patients with disease extension to the parametrium or to the pelvic sidewall to the median dose of 9 Gy, while the midline structures were shielded. The local control rate and rates of complications were similar to those reported by Patel et al[10][12].

Several randomized studies have demonstrated that CCRT significantly improves the treatment outcome compared to radiotherapy alone for patients with locally advanced uterine cervical cancer[17][18]. The efficacy of CCRT in the treatment of cancer of the cervix has been confirmed by five phase III randomized studies as published in the New England Journal of Medicine in 1999[17]. As can be seen from Table 2, four out of five studies used brachytherapy in addition to the EBRT concurrent chemotherapy[19].

In recent years HDR brachytherapy with EBRT has become popular in the management of carcinoma of uterine cervix, because it eliminates many problems associated with LDR brachytherapy[20][21]. The number of HDR brachytherapy fractions recommended by American Brachytherapy Society (ABS)[22] panel as shown in Table 1 ranged from 4 to 8; but as proven and shown by some studies, even two fractions of HDR brachytherapy in addition to the EBRT are safe and effective in the management of this disease.

The planning target volume (PTV) of brachytherapy in principle must encompass the extent of primary tumour plus a safety margin. The treated volume is limited by the maximum tolerance of critical organs. Thus, in extended disease, the whole primary tumour extent may not be completely covered by the treated volume and would not get an adequate dose to control the disease. The isodose curve distribution of EBRT and BT as well as dose limiting structure around the GTV were mentioned as the main factors leading to an inadequate dose to the tumour volume.

In definitive radiotherapy, the target volume is usually related to the GTV at the diagnosis and /or at the time of brachytherapy. For the tumour, extension to the proximal part of the parametria (proximal stage IIB) must be included in the CTV as far as possible taking into account the dose to critical organs. In cases where the tumour extends far into the parametria (distal stage IIB) there is no clear agreement on the determination of the CTV for the brachytherapy. Endocavitary brachytherapy alone can only cover the tumour extension, which is directly adjacent to the cervix. For the above reasons, the University of the Witwatersrand Radiation Oncology Department modified FIGO staging system as following. Stage IIB cancer of the cervix, subdivided in to two groups: proximal stage $IIB_{(proximal),}$ and distal Stage $IIB_{(distal)}$ and; stage IIIB was further divided in to 3 subgroups; early- to those with one side pelvic wall involvement, intermediate- bilateral pelvic side wall involvement with out hydronephrosis and late – those who have hydronephrosis. Among those stage IIB (distal) and IIIB (early), according to departmental protocol are treated radically and have been included in this study.

Table 2 Randomized Trials of Concurrent Chemotherapy with External Beam and Brachytherapy in Cervical Cancer[19]

Trial	Stage	No. of patients	Treatment Arm	Brachytherapy	Median FU	OS in%	DFS in %
Morris et. al RTOG 90-01	IIB-IVA; IB/IIA > 5 cm	193	RT[2], CDDO & 5-FU	YES	43	73	67
Whitney	IIB-IVA	193	RT	YES		58	40
GOG 85		177	RT, CDDP &5-FU	YES	91	55	57
Rose et al GOG 120	IIB-IVA	191	ROTH	YES	35	43	47
		176	RT & CDDP	YES		70	67
		173	RT, CDDP, 5-FU&HU	YES		69	64
Key et al GOG 123	IB Bulky	177	RT & HU	YES	35.7	45	47
		183	RT & CDDP, EFH	YES		83	79
		186	RT & EFH	YES		74	63

[2] RT – Radiotherapy, CDDP – Cisplatin, 5-FU – Fluorouracil, HU – Hydroxyurea, EFH – Extra facial hysterectomy, OS – Overall survival, DFS – Disease free survival, FU – Follow-up.

Radiobiology and Physics of Brachytherapy

Based on the linear quadratic model, the biological effective dose (BED) to point A is a contribution from EBRT and HDR brachytherapy. The BED for the tumour may be determined for tumours using an α/β ratio of 10, which is used for early responding tissues. The total BED at rectal and bladder reference points may be determined by using an α/β ratio of 3 which is used for late responding tissues. The equation written below may be used in the calculation for total BED dose to gross tumour volume (GTV) as a contribution of both EBRT and brachytherapy as well as to critical organs (rectal and bladder) as seen in appendix c[16].

ICRU reference points

Brachytherapy for cervical cancer is based on intrauterine and or intravaginal sources. Intracavitary therapy is often used in combination with external beam therapy. In particular, it would be desirable, whenever possible, to use the concept of target volume, treatment volume, and irradiated volume as defined for external beam radiotherapy. However, due to the high dose-gradient around the source (throughout the tumour and target volume), the specification of the target absorbed dose in terms of dose absorbed either at one or several reference points within the target volume is not considered meaningful. Therefore, the approach used in external beam therapy cannot be used[23]. Based on clinical experience, different systems for the treatment of cervical carcinoma have been proposed. Three basic systems have been developed; the Stockholm system, the Paris system, and the Manchester system. Systems used throughout the world are derived from these 3 basic systems[24].

The Manchester system (Paterson and Parker, 1934), derived from the original Paris system, was first utilized in 1920. It was designed to deliver a constant dose-rate to defined points near the cervix, irrespective of variation in the size and shape of the uterus and vagina. In the Manchester system, an application was specified in terms of the dose in roentgen delivered at specific points such as point A and B as shown in Figure 2.

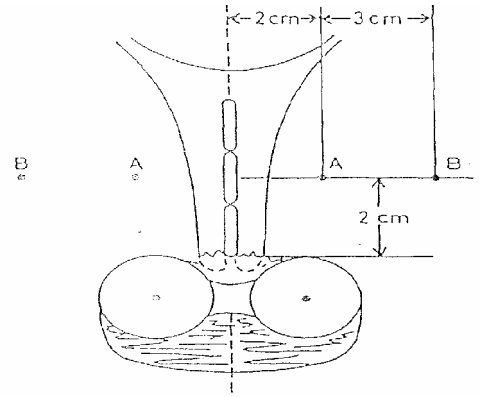


Figure 2. ICRU point A and point B[24]

Related to rectum and bladder, two reference points are defined which are located relatively close to the sources – the ICRU-bladder reference point and the ICRU-rectum reference points.

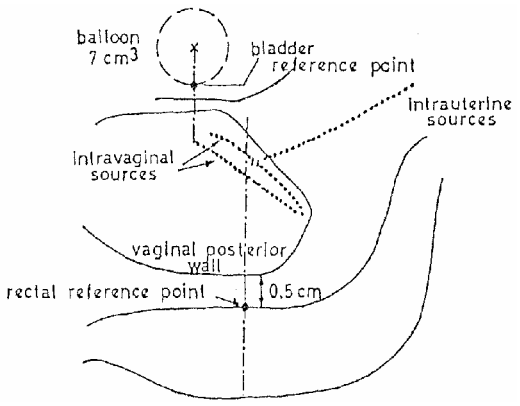


Figure 3. Rectum and bladder ICRU reference points lateral view[24]

These points are reproducible and reliable. However, they do not necessarily represent the maximum dose to these organs at risk.

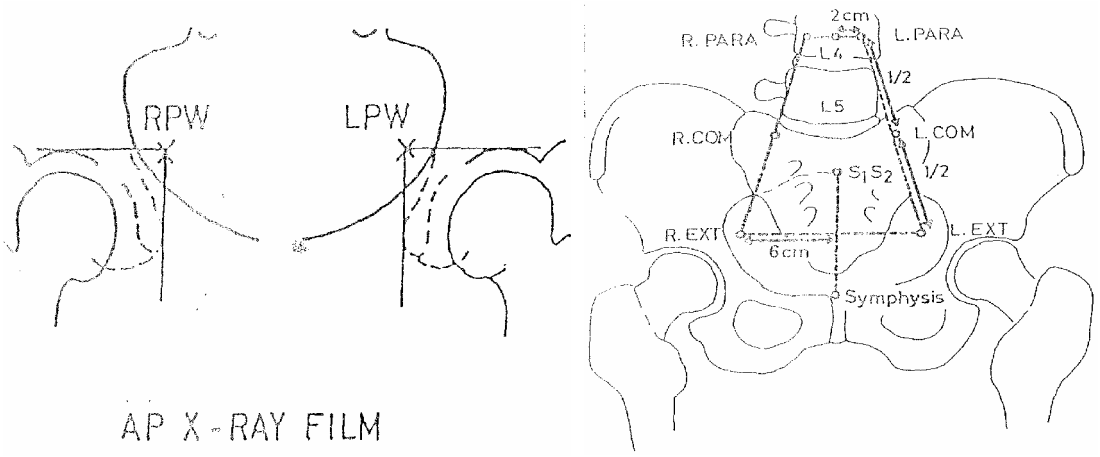


Figure 4. The pelvic wall reference points and the points in the lymphatic trapezoid[24]

Related to bony structures and lymph node topography, 2 set of reference points relatively far from the source are defined; the pelvic wall reference points and the points in the lymphatic trapezoid (see Figure 4). These indicate the dose to the lateral margins of the true pelvis and to the different lymph node regions: external iliac, common iliac and low Para-aortic.

Organ at Risk and its Localization

Organs at risk are those whose tolerances and vicinity may affect planning doses; in cervix cancer these include the rectum, bladder, urethra, and sigmoid colon. The determination and specification of the absorbed dose to organs at risk are obviously useful with respect to normal tissue tolerance limits. Chassagne and Horiot[25] have proposed reference points for the expression of the absorbed dose to the bladder and to the rectum. The bladder reference point is obtained thus: The balloon of a Foley catheter is filled with 7 ml of radio-opaque fluid. The catheter is pulled down to bring the balloon against the urethra. On the lateral radiograph, the reference point is obtained on an antero-posterior line drawn through the centre of the balloon. The reference point is taken on this line at the posterior surface of the balloon[24],[25].

The rectal reference point may be obtained from the lateral radiograph using an anterior-posterior line source or from the middle of the intravaginal source. The point is located on this line at 5 mm behind the posterior vaginal wall and can be visualized by means of an intra-vaginal mould or by opacification of the vaginal cavity with radio-opaque gauze used for the packing. On the AP radiograph, the reference point is at the lower end of the intrauterine source or at the middle of the intravaginal source[24].

The pelvic-wall reference point[24] can be visualized on an AP and lateral radiograph and is related to fixed bony structures. This point is intended to be representative of the observed dose at the distal part of parametrium and at the obturator lymph node. On an AP radiograph, the following 2 lines intersect the pelvic-wall reference point: the horizontal line tangential to the highest point of the acetabulum and the vertical line tangential to the inner aspect of the acetabulum[24].

Evaluation of the absorbed dose at the reference points, related to well defined bony structures and lymph node areas is particularly useful when intracavitary therapy is combined with EBRT.

ADVERSE EFFECTS

The main complications following the treatment of cancer of the cervix involve the bowel and urinary tract, with an overall actuarial five year severe complication rate of 8 – 10%[20], [26], [27]. Late sequelae of radiotherapy occur mainly during the first 3 – 5 years following treatment and this rate decreases in subsequent years. Gastrointestinal complications usually occur earlier than urinary complications at 30 months versus 48 months[26][27].

There is a continuous risk of all types of complications as demonstrated in Eifel series of 1784 patients with an estimated rate of 0.34% per year after treatment. Rectal complications increased by 1% during the first 2 years and then decreased to 0.06% per year; while bladder complications increased by 0.7% during the first 3 years, and later it was stabilizing at 0.25% per year[27][28].

Radiotherapy related side effects are categorized as directly linked to either the radiotherapy techniques and doses or secondary to other factors such as prior surgery, concomitant chemotherapy, or co-morbid condition such as diabetes, hypertension and pelvic inflammatory disease[26], [27], [28].

Total dose

Perez[29] showed that the most significant factor affecting the incidence of complications was the total dose of irradiation to the pelvic organs by both pelvic irradiation and the intracavitary insertion. The incidence of complications significantly increased when the dose exceeded 80 Gy. A more recent analysis with a larger number of patients (up to 1456) confirmed the role of total dose in the development of complications[26]. For the bladder, a dose below 80 Gy correlated with less than 3% probability of morbidity while this rate reached 5% with higher doses[24]. The incidence of morbidity from recto-sigmoid complications is significantly increased when the total dose exceeded 75 Gy: 4% with doses below 75 Gy and 9% with higher doses. The dose to the lateral pelvic wall was a significant

factor influencing the small intestine complication rate: the complication rate was less than 1% with a total of 50 Gy or less, 2% with 50 to 60 Gy, and 5% with higher doses[30].

Volume

Using a combined EBRT and brachytherapy approach, the complications observed are closely correlated with the volume treated. Barillot[30] reviewed 642 patients treated between 1970 and 1994 with radiotherapy alone for uterine cervical carcinomas. The analysis was divided into 3 periods. Comparisons of the 3 time-periods showed a significant reduction of the external radiation dose, in the use of a parametrial boost, the use of vaginal cylinders and the height, width, and thickness volume[30]. The rate of grade 3 complications dropped from 16% to 6% over time[29].

Influence of Dose Rate

Stage for stage the local control rates in the LDR and HDR groups were similar[22],[24]. The overall local control achieved in the LDR group was 79.7% as compared to 75.8% in the HDR group. The five-year survival figures in the LDR and HDR groups were also comparable[31].

The only statistically significant difference found was in the incidence of overall rectal complications. These were 19.9% for the LDR group, compared to only 6.4% for the HDR group. However, the incidences of more severe grade 3 – 4 complications were not significantly different between the 2 groups (2.4% versus 0.4%) respectively[29]. In addition, HDR brachytherapy has some advantage over LDR brachytherapy in cancer of cervix[22][29]. These advantages may be listed as follows:

A. HDR eliminates radiation exposure hazard for caregivers, visitors and eliminates the need for source preparation and transportation.

B. HDR allows for shorter treatment times that results in;

I. Less patient discomfort, because prolonged bed rest is eliminated.

II. It is possible to treat patients who may not tolerate long periods of isolation and those who are at risk for acute cardiopulmonary toxicity due to prolonged bed rest.

III. There is lower risk of applicator movement during therapy.

IV. Reduced hospitalization (due to outpatient therapy) results in cost shifting.

V. Possibly allows greater displacement of nearby normal tissues (by packing or using rectal retractor), which could potentially reduce the rectal and bladder morbidity.

VI. It is possible to treat a larger number of patients in institutions that have a high volume of cervical cancer patients but insufficient inpatient facilities (for example, in some developing countries).

C. Allows the use of smaller diameter sources than are used in LDR;

I. This reduces the need for dilation of the cervix and the need for heavy sedation or general anaesthesia. High-risk patients who are unable to tolerate general anaesthesia may now be more safely treated.

II. It is physically easier to insert applicator into the cervix.

D. Allows for treatment-dose-distribution optimization. The variation of dwell time with the single stepping source strength and source positions allows for greater control of the dose distribution and potentially less morbidity.

E. Allows integration of EBRT and HDR, which can lead to a shorter overall duration of treatment and potentially to improved tumour control.

The curative potential of radiation therapy in the management of carcinoma of cervix is greatly enhanced by the use of intracavitary brachytherapy. The correct application

and execution of the brachytherapy component of radiotherapy is crucial for maximizing the local control of cervical cancer[12].

Table 3. Criteria for optimal application in the intracavitary brachytherapy[12]

Criteria for optimal application in intracavitary brachytherapy
Anterior posterior view
Colpostats high in the fornices along cervix
Radio-opaque markers placed on exocervix corresponding to the flange on the central tandem
Tandem mid line; unrotated
Tandem midway between colpostats
Lateral view
Tandem bisect the colpostats
Sufficient anterior and posterior packing
Foley balloon identified at vesico-urethral junction

The influence of brachytherapy technique has been assessed by a number of centres. Perez found a correlation of poor insertion technique with an increment in the incidence of central failure[29].

Intracavitary gynaecological brachytherapy is typically standardized with the application techniques and dosimetry for a given geometry. This defined loading technique, usually derived from radium loading pattern, creates a pear-shaped distribution when viewed from anterior-posterior and a banana shaped distribution on lateral view[4].

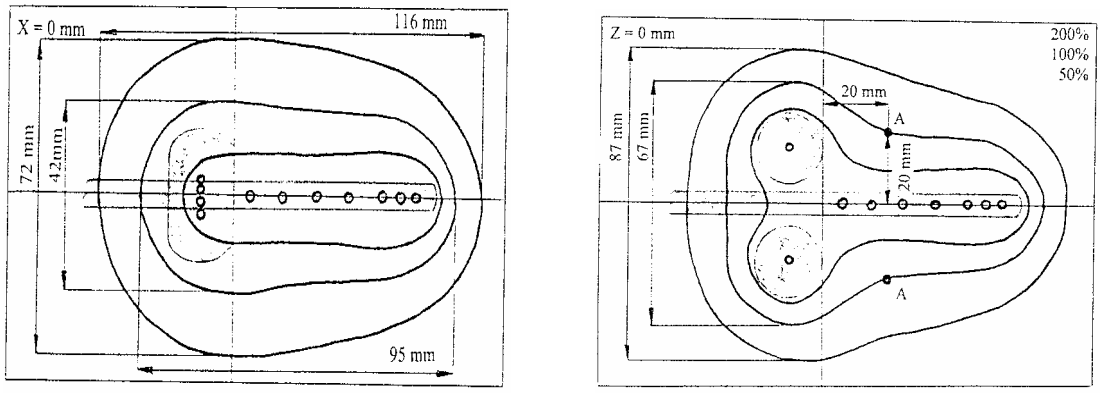


Figure 5. Lateral and anterior-posterior views of isodose distribution of brachytherapy application[6]

Standard dose distribution of brachytherapy application in Figure 5 above shows the 100%, 50%, and 200% isodose lines with a standard Manchester applicator with an ovoid. Point A is the reference point in these standard programs where the dose is prescribed. Limitations are set for the dose to the critical organs: The dose to the ICRU rectum reference point should be less than 70% of the dose at point A and the dose to the ICRU bladder reference point should be less than 80%. As the positions of the rectum and the bladder are radiographically known relative to the application and the gross tumour volume (GTV), these limitations apply for each brachytherapy fraction[4].

BACKGROUND TO THE STUDY

Most of the patients seen at The University of the Witwatersrand (WITS), Radiation Oncology Department outpatient clinics are diagnosed to have locally advanced cancer of cervix (stage II and III)[3]. These patients, according to the department protocol, are treated with 3 or 4 brachytherapy insertions in addition to 50 Gy external beam radiotherapy.

In respect to the management of patients with locally advanced cancer of the cervix, this study was designed to investigate the following;

1. 18 Gy in 2 fractions of HDR brachytherapy is effective and leads to an equivalent local control compared to 24 Gy in 3 fractions and 26 Gy in 4 fractions,
2. the toxicity of treatment using 18 Gy in 2 fractions of HDR brachytherapy is equivalent to the other 2 regimens.

OBJECTIVES

1. To compare the local control with the following 3 HDR brachytherapy fractionation regimens: (a) 2 fractions of 9 Gy each; (b) 3 fractions of 8 Gy each and (c) 4 fractions of 6.5 Gy each, with concomitant chemo radiotherapy,
2. To compare the normal tissue complication rate using these 3 regimes

METHODS AND MATERIALS

Inclusion criteria

1. Biopsy proven squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma of the cervix,
2. Age above 20 and below 75,
3. Performance status ECOG 0 up to 2 (see Table 4),
4. HIV negative,
5. Carcinoma of the cervix FIGO stage IIB (distal) and IIIB (early) , and (see Appendix D)
6. Reliability of the patient for follow up

Table 4. Criteria for performance status on the ECOG performance scale[32]

Scale	Description
0	Normal activity, asymptomatic
1	Symptomatic; fully ambulatory
2	Symptomatic; in bed less than 50% of time
3	Symptomatic; in bed more than 50% of time, not bedridden
4	100% bedridden

Exclusion criteria

1. Age greater than 75,
2. Lower third vagina involvement
3. Patients unavailable for follow up,
4. Metastatic disease,
5. HIV positive patients,

6. Previous hysterectomy,
7. Previous pelvic radiotherapy,
8. Malignancy other than skin cancer not controlled for five or more years,

Justification for exclusion and inclusion criteria

A cut-off age of 75 was selected as these patients often have co-morbidities with limited life expectancy. In addition to this, concurrent chemotherapy is not given routinely to this group of patients according to departmental practice. Patients with lower third vagina involvement were excluded because brachytherapy is individualised for these patients and the isodose distributions produces are not comparable with the standard technique. Patients with Stage IIIB extending to both pelvic sidewall or with hydronephrosis were excluded because they are not treated radically according to the departmental treatment protocol.

Diagnostic work up

1. History and physical examination that included a bimanual pelvic and rectal examination,
2. Cervical biopsy,
3. Full blood count, platelet, urea, and electrolytes,
4. Chest radiography,
5. Abdominal sonar,
6. HIV test, and
7. Cystoscopy and proctosigmoidoscopy (only if clinically indicated).

   See appendix D for staging [33][34]

Note: According to the departmental protocol, both stage IIB (distal) and IIIB (early) will get the same radical dose of EBRT and HDR.

All patients fulfilling the inclusion and exclusion criteria received 50 Gy in 25 fractions of EBRT, and were then, randomized to one of the following three Arms.

Arm I.

Patients received HDR brachytherapy of 4 fractions of 6.5 Gy each. The brachytherapy was given once weekly during the last 4 weeks of EBRT with concomitant chemotherapy.

Arm II

Patients received HDR brachytherapy of 3 fractions of 8 Gy per fraction to point A. The HDR brachytherapy was given during the last 3 weeks of external beam radiotherapy with concomitant chemotherapy.

Arm III

Patients received HDR brachytherapy of 2 fractions of 9 each, with concomitant chemo radiotherapy.

In this study, randomization table were used to assign patients to 1 of 3 groups sequentially. Patients randomized to receive HDR brachytherapy of 2 fractions of 9 Gy each; brachytherapy was given weekly during the last 2 weeks of external beam radiotherapy with concomitant chemotherapy.

The departmental treatment field protocol for EBRT depended on the anterior-posterior separation of each patient. Every patient received either anterior and posterior fields or anterior, posterior, and two lateral fields from either side.

During treatment, the patients were assessed weekly for side effects. Each HDR brachytherapy application was evaluated individually. A rigid intrauterine tandem (nucleotron 6 cm, 4 cm, or 2 cm in length) and a ring applicator (nucleotron 3.4 cm, 3.0 cm, or 2.6 cm in diameter) with a rectal shield were used. The length of the tandem and the diameter of the ring were individualized for each patient. Two

orthogonal radiographs with a dummy source in the applicator were taken (see Figure 6). Transparencies of appropriate magnification indicating the isodose distributions were placed over the applicator image on the screen. This was used to check the isodose distributions. The rectum and the bladder points were calculated according to the ICRU 38 recommendations. From lateral radiograph, the anterior rectal wall was identified with the help of a radio-opaque balloon and the posterior wall of bladder was identified using an indwelling catheter with contrast material in its balloon.

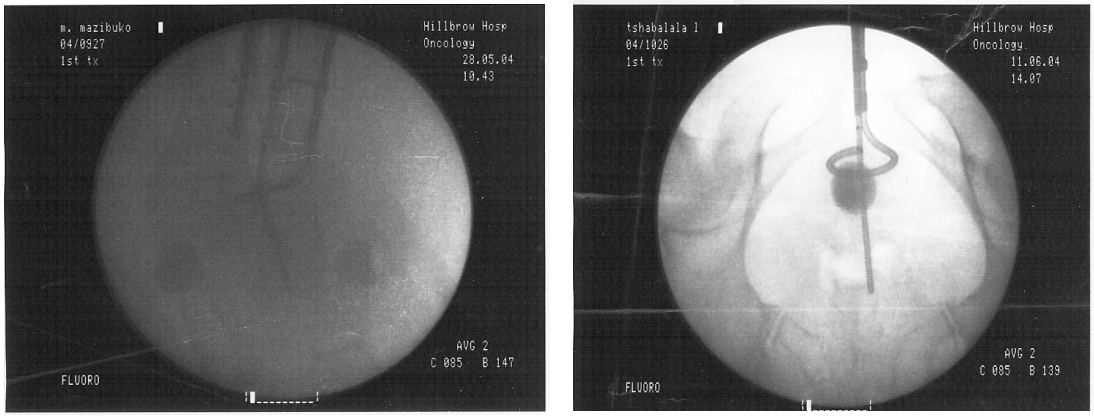
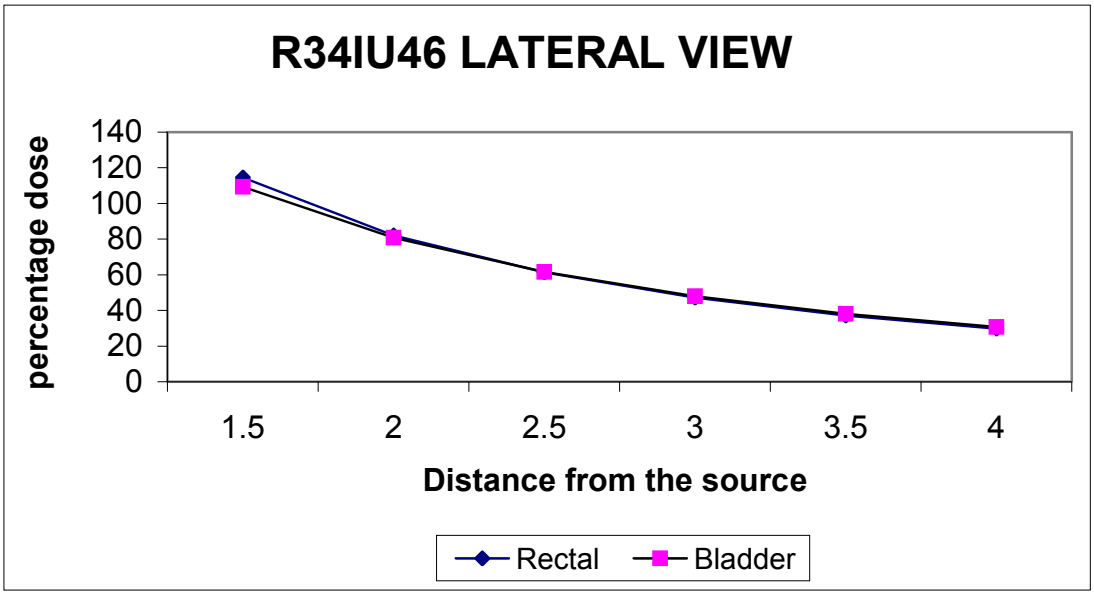


Figure 6. Two orthogonal radiographs of the applicator in situ

The pelvic sidewall reference point was visualized on an anterior-posterior radiograph related to a fixed bony structure (acetabulum). This point was intended to be representative of the absorbed dose at the distal part of parametrium and at the obturator lymph node.

The doses to critical organs (rectum and bladder) were calculated by measuring the distance from the applicator to ICRU reference points from the graph after correcting for the magnification factor. The graph was plotted for each ring size and tandem length.

Figure 7 shows the relationship between the percentage dose prescribed to point A against distance from applicator, ring size 34 and tandem size 46, to the ICRU rectum, bladder, and pelvic sidewall points.



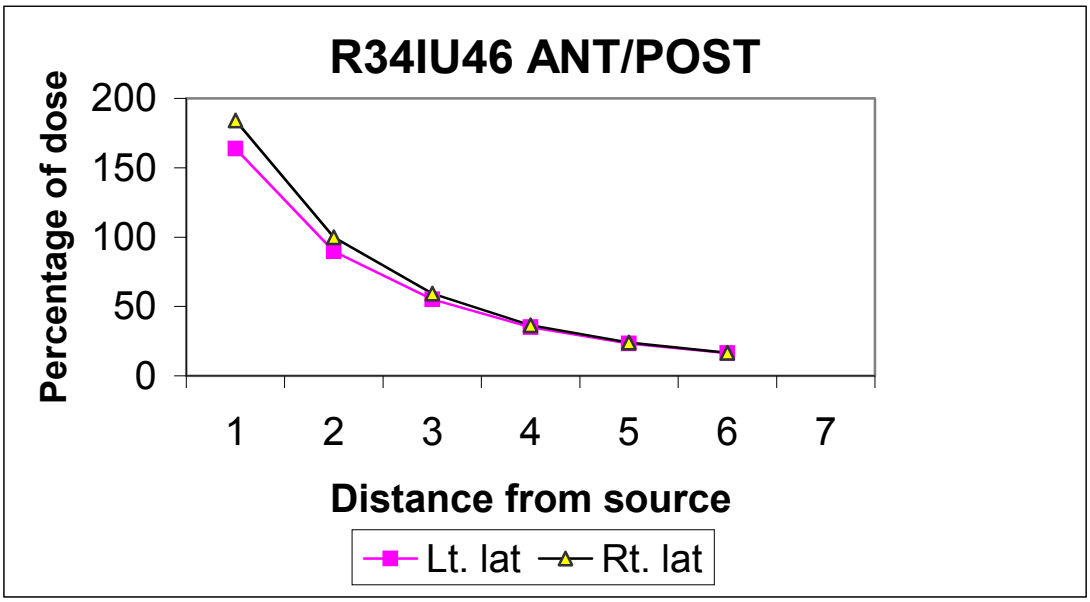


Figure 7. R34IU46 rectal, bladder and PSW reference points (the relationship between the percentage dose to point A and distance from the tandem to ICRU rectum, bladder, and pelvic sidewall points)

By using packing with each application, an attempt was made to increase the distance between the tandem and critical organs. As can be seen from the graph, the dose to the critical organ is inversely proportional to the distance square away from the

tandem. For each HDR application, a calculation was done by measuring the distance from the tandem to the organ at risk by using the magnification factor, and the graph for the bladder, rectum, and the pelvic sidewall points.

For each arm, the contribution of point A dose was calculated as per the linear quadratic model (LQM)[35] from both external beam radiotherapy and intracavitary portions of the treatments. The total biologically effective dose (BED) to the tumour was calculated by using an α/β ratio = 10 (Gy_{10}) (see Table 5).

The BED Gy_{10} can be converted to a linear quadratic effective dose (LQED) for a 2 Gy fraction by dividing the BED dose by 1.2 (the relative effectiveness for a 2 Gy fraction)[23].

Table 5: BED Gy_{10} dose to point A for 3 HDR fractionation regimens

Arm	EBRT Dose Gy/fx[3]	EBRT No. fx	HDR Dose Gy/fx	HDR No. fx	Gy_{10} Point A	LQED Gy_{10} to point A 2 Gy/fx
I	2	25	6.5	4	103	86
II	2	25	8	3	103	86
III	2	25	9	2	94	78

The median BED for late responding tissue for arm I patients was 165 Gy_3.With adequate packing and good application, the bladder and the rectum would usually receive 60 – 80% of the prescribed dose to point A. If the normal tissues received 70% dose, then the 165 Gy_3 term would reduce to about 115 Gy_3. The LQED[6][23] for a 2 Gy fraction to late responding tissue can be calculated by dividing the BED by 1.67 (the relative effectiveness for a 2 Gy fraction to the late responding tissues , 115 Gy/1.67= 69 Gy. This is shown in Table 6 for 3 HDR fractionation schedules.

[3] Fx - fraction, Gy - Gray, No - number, LQED - Linear Quadratic Effective Dose.

Table 6: BED Gy_3 dose and to late responding tissue for three fractionation regimens

Arm	Gy_3 dose to Point A	70% of BED dose in Gy_3 to organ at risk	Late responding tissue LQED in Gy_3 at 2 Gy/fraction to organ at risk
I	165	115	69
II	171	120	71
III	155	109	65

After the completion of the treatment, patients were assessed at 6 weeks in order to evaluate response and acute side effects. At 6 months post–therapy, the patients were further assessed for any side effects and the response to the treatment by doing a Pap smear.

In this study, the treatment outcome and complication were assessed in each arm using the following criteria:

1 The local control of the disease by a Pap-smear at six months post treatment in each arm,

2 The effect of stage, age, ring application and duration of treatment on local control,

3 Toxicity in each arm,

4 The effect of age and number of fields treated on radiation induced toxicity,

5 The doses to the bladder and rectal reference points and their association with radiation induced toxicity.

The Epi Info program 2002 performed all statistical analysis. Duration of treatment was measured from the first day of treatment to the end day of treatment. Patient age, tumour stage, number of portals and duration of treatment were used as prognostic factors for the factors analyses of local control and adverse effects of RT.

Comparisons of categorical variables were performed using the Chi-square test, t test and for more than 2 variables, Analysis Of Variance (ANOVA) test was used. Statistical significance was considered with p-values of less than 0.05 or 95% of significance.

During the HDR application, the widest ring and the longest tandem were used when possible depending on the individual patient anatomy. The size of applicator or the length of the tandem chosen for this study did not depend on the stage of the patient or the size of the lesion, but was dependent on the patient's anatomy. R26IU66 was the smallest width ring that has 2.6 cm diameter and was used for patients who have narrow anatomy. R30IU26 was the shortest tandem used for only one patient who had fibrosis of the cervix. The length of this tandem is only 2 cm. The majority of patients were treated with R34IU66, which has the widest ring (3.4 cm) and the longest tandem (6 cm).

SOMA (Subjective Objective Management and Analytic) scale was used to assess and treat the toxicity induced by radiotherapy[36]. (See appendix B)

RESULTS

Seventy-one patients were entered in the study. Three patients were excluded due to active non-malignant diseases. One patient had active tuberculosis and 2 patients had severe skin reactions and herpes zoster. A repeated HIV test in the latter 2 patients confirmed that they were HIV positive. Two patients withdrew following the first HDR application. The remaining 66 patients were further analysed.

Twenty-two patients were recruited to Arm I; twenty-three to arm II and twenty-one arm III. Sixty-six patients completed the prescribed dose of radiotherapy but only fifty-nine had the six-week and the six-month prescribed evaluation and Pap-smear, and were further evaluated. Of these, thirty-nine (59%) were stage IIB (distal) and twenty-seven (41%) stage IIIB (early).

All 66 patients received HDR and 59 received concomitant cisplatin 80 mg/m^2 3 weekly. The reasons for not receiving chemotherapy (n=7) were low creatinine clearance in 4 patients, 2 could not receive chemotherapy for logistic reasons and 1 patient absconded. Among those 7 patients, 3 of them were in arm I, 2 were in arm II and 2 were in arm III. The only chemotherapy-related side effect noted was mild to moderate nausea and vomiting.

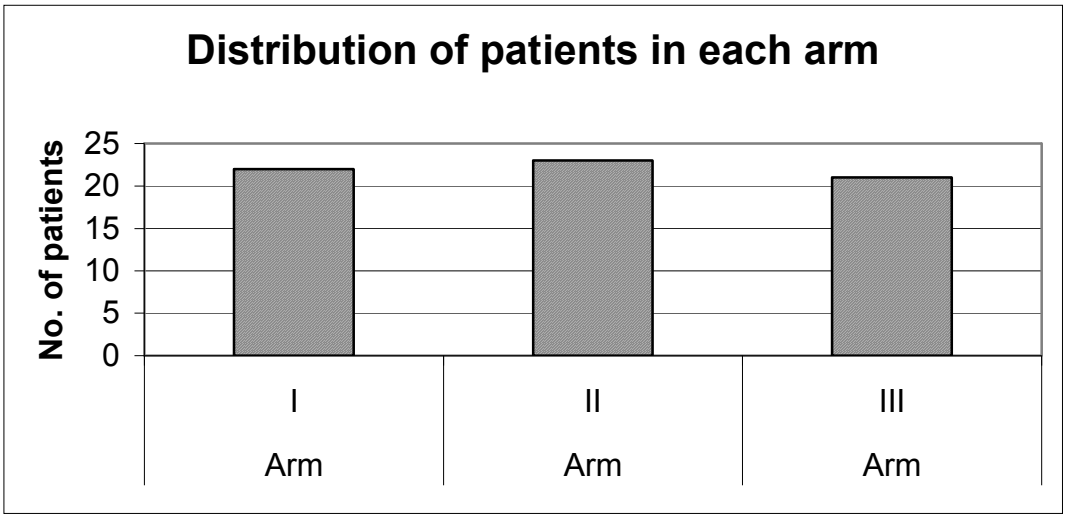


Figure 8. Distribution of patients in each Arm

Further analysis will include only those 59 patients who completed the prescribed dose of chemo radiotherapy and attended the six week and six month assessments and Pap smear.

The distribution of patients by stage and by age group at diagnosis in the various arms was as shown in table 7 below.

Table 7. Distribution of patients by stage in each arm

Arm	Stage IIB (distal)	Stage IIIB (early)	Total
I	11	9	20
II	11	10	21
III	9	9	18

Twenty-nine patients were aged 31 – ≤50 years and 30 were aged 51 – 75 years. There was no statistical significant difference between the mean ages in the 3 arms with p value of 0.995 using the ANOVA. There was no statistically significant differences between 3 arms in terms of stage distribution and the number of chemotherapy cycles given using the Chi-Square test (p=0.678 and 0.532 respectively).

The mean time to completion of treatment was 46.4 days with a range of 35 – 58 days. The duration of treatment was similar in the three arms according to ANOVA test with p value of 0.6508. Ninety-three percent of the cases were squamous cell carcinomas, 5% adenocarcinomas, and the rest were adenosquamous carcinomas (fig 10). Four of non-squamous patients were in arm II and the remaining 2 patients were in arm III.

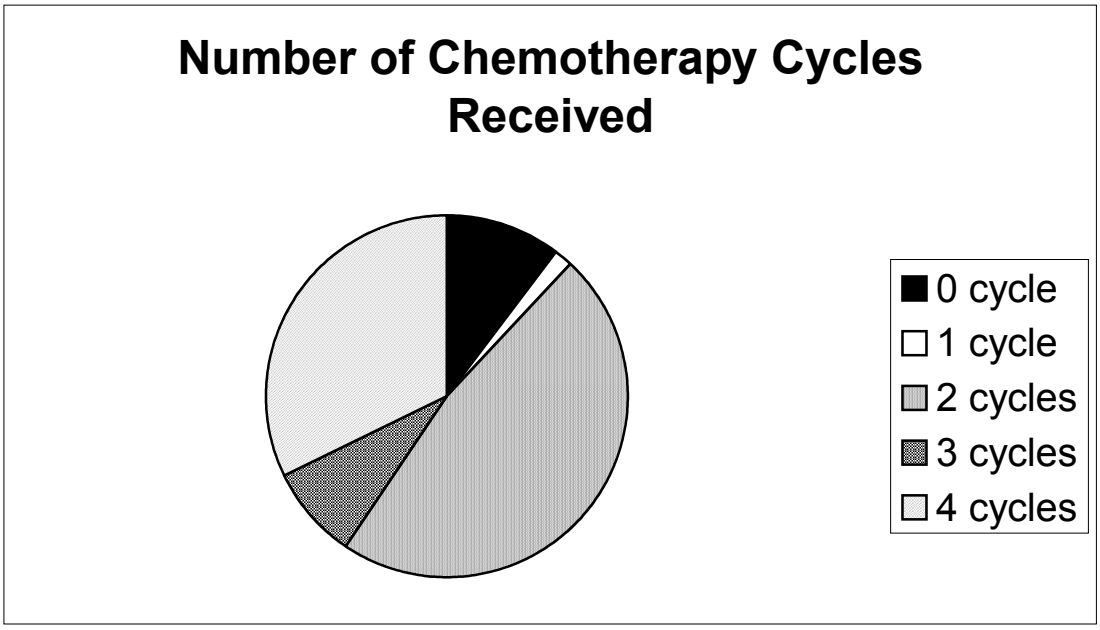


Figure 9. Number of Chemotherapy Cycles Received

One patient received 4 cycles of chemotherapy instead of the standard three weekly cisplatin. She received weekly twice (40 mg/m^2) followed by three-weekly twice (80 mg/m^2), but the patient did not develop any side effects during treatment and thereafter for six months follow up time.

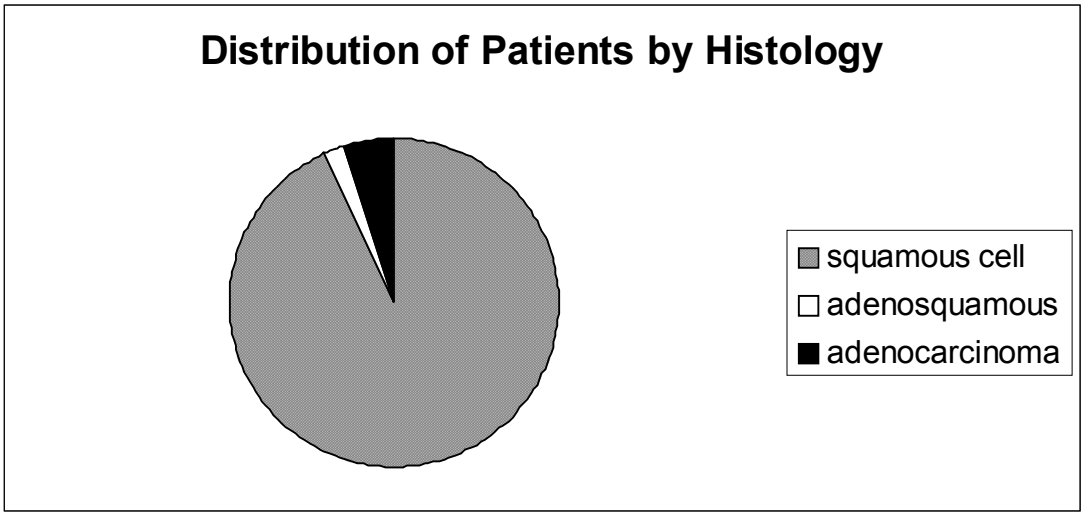
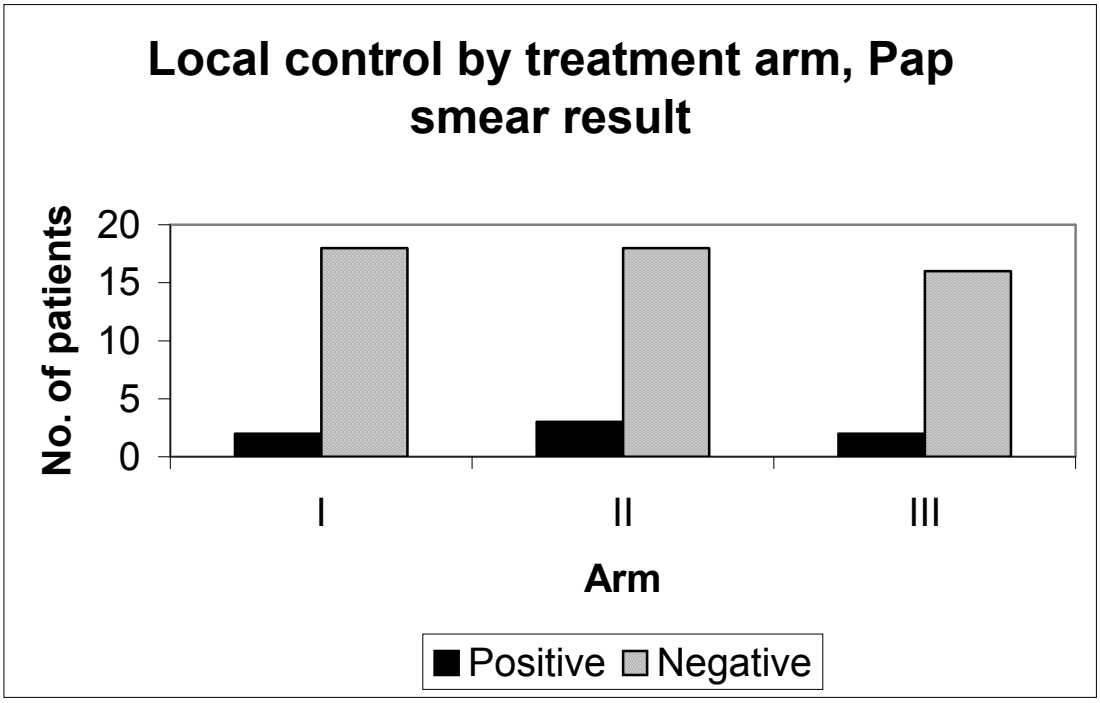


Figure 10. Distribution of patients by histology

Treatment outcome

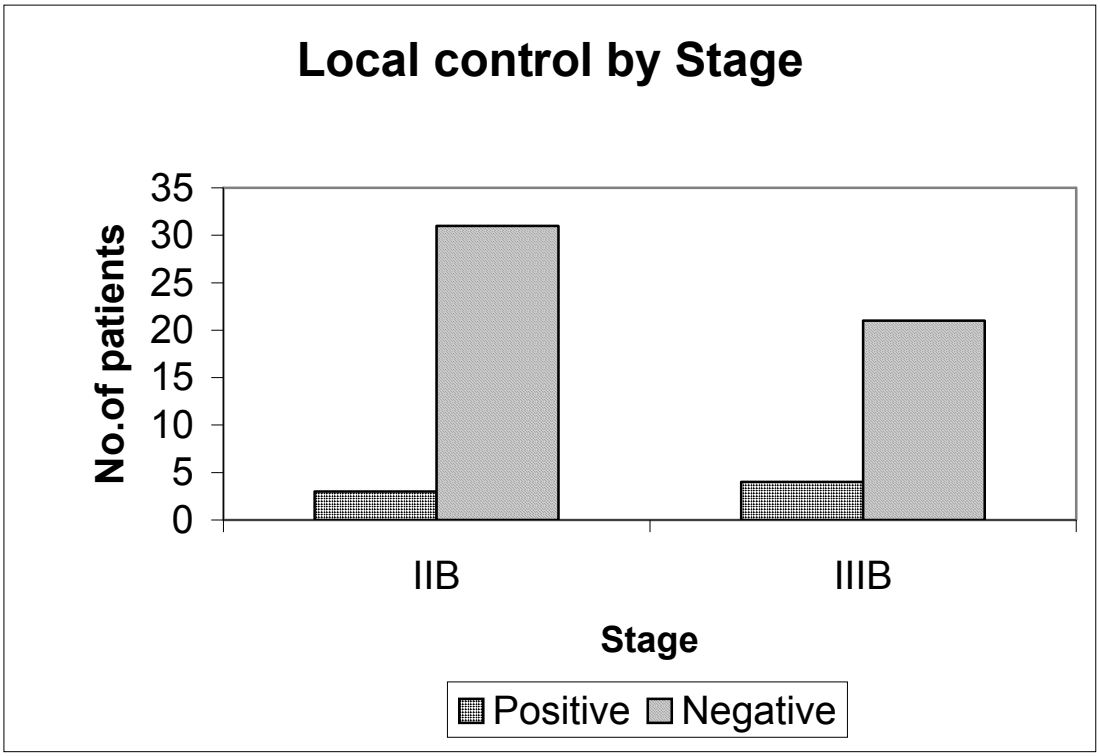
Fifty-nine patients completed the prescribed treatment and were evaluated. Fifty-two had a good clinical response with negative Pap-smears at 6 months. Seven patients had a positive Pap smear with clinical signs of persistence disease. There was no statistically a significant difference in response for treatment in 3 arms as seen in Figure 11 with p value of 0.464.

91% (3/31) of patients with stage IIB (distal) had negative Pap smears at 6 months compared with 84% (4/28) of stage IIIB (early) as shown in Figure 12. This was not statistically significant (p = 0.328).



(p =0.464)

Figure 11. Local control by treatment arm



($p = 0.328$)

Figure 12. Local control by stage

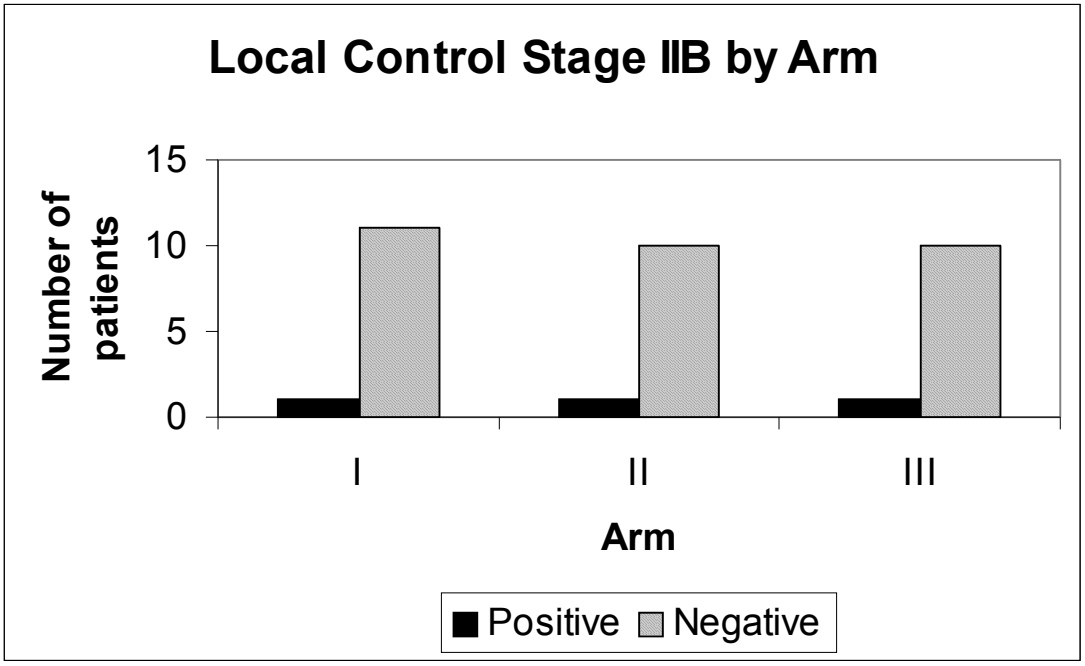


Figure 13. Local control among stage IIB (distal) patients in each Arm

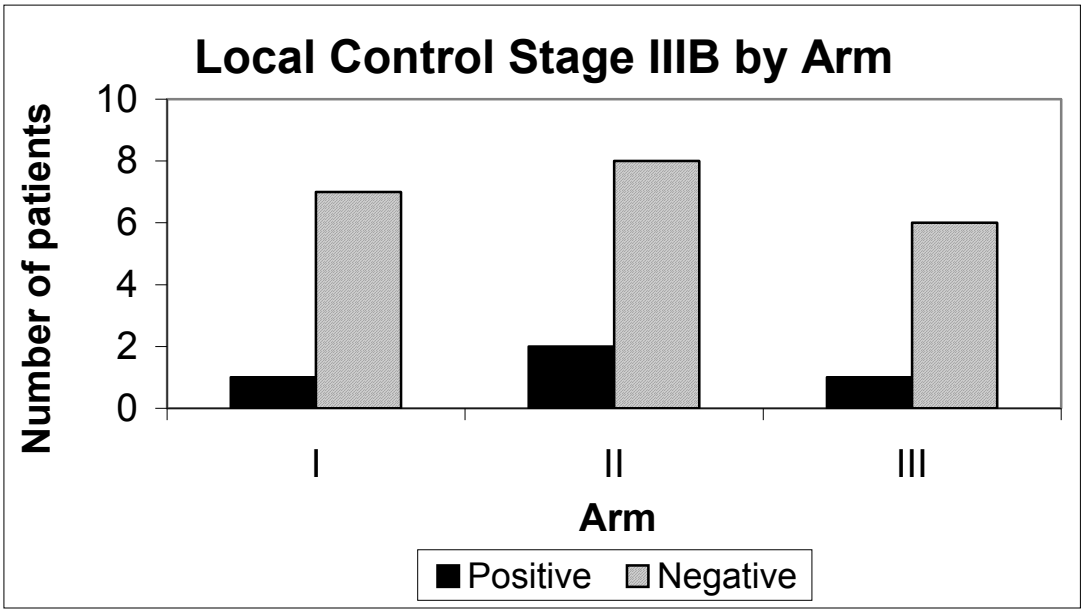


Figure 14. Local control among stage IIIB (early) patients in each Arm

Table 8. Local Control by Age Group

Age group	Total number of patients	Pap-smear negative	Pap-smear positive
31 – 50	28	23	5
51 – 75	31	29	2

(p=0.17)

The number of fields used did not affect local control (p = 0.603) (table 9) nor did the duration of treatment (p = 0.402) (table 10).

Table 9. Relationship between Local Control and Number of Fields

Number of fields	Pap-smear negative	Pap-smear positive
2	31	4
4	21	3

(p = 0.603)

Table 10 Relationship between Duration of Treatment and Local Control

Duration of treatment	Pap-smear negative	Pap-smear positive
35 – 45 days	23	4
46 – 58 days	29	3

($p = 0.402$)

The adverse effects of radiation observed were compared in each arm. Radiation induced grade 3 and 4 bladder and rectum effects were assessed in each arm and plotted in Table 11 and Table 12 respectively.

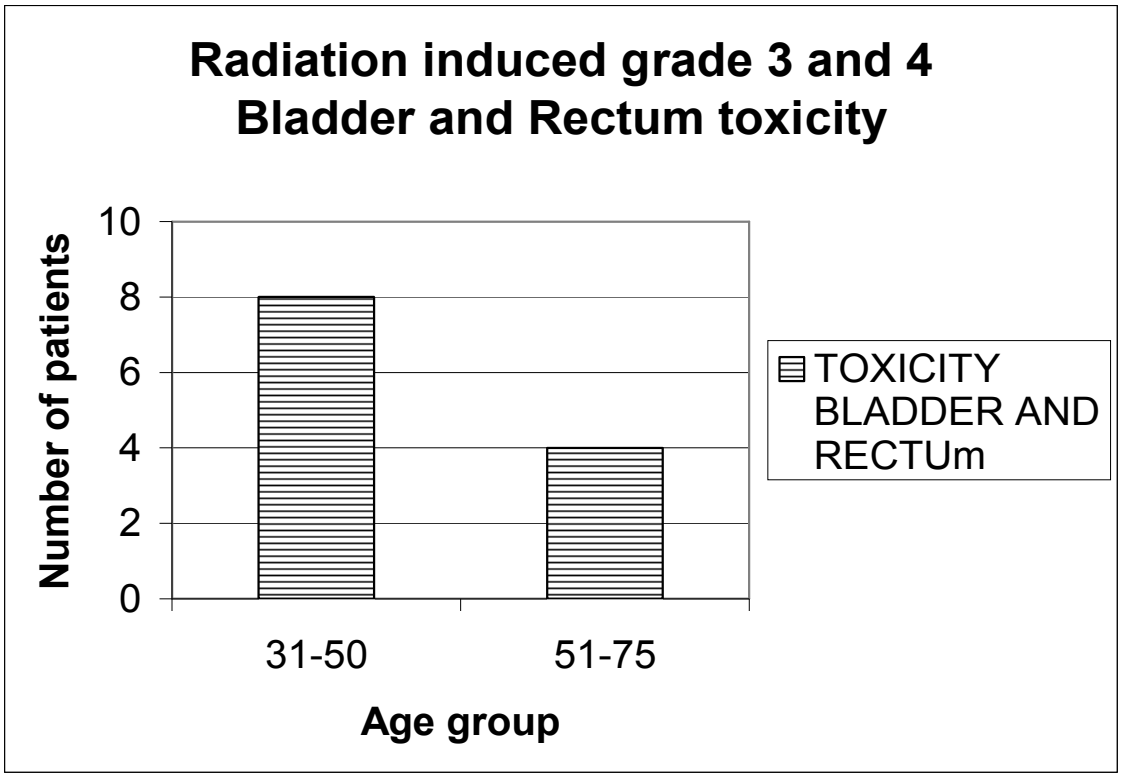
Table 11 Radiation induced bladder toxicity in each arms.

Arms	Radiation induced grade 0-2 bladder toxicity	Radiation induced grade 3 & 4 bladder toxicity
I	19	1
II	16	5
III	17	1

Table 12 Radiation induced rectal toxicity in each arms

Arm	Radiation induced grade 0-2 rectum toxicity	Radiation induced grade 3& 4 bladder toxicity
I	17	3
II	19	2
III	15	3

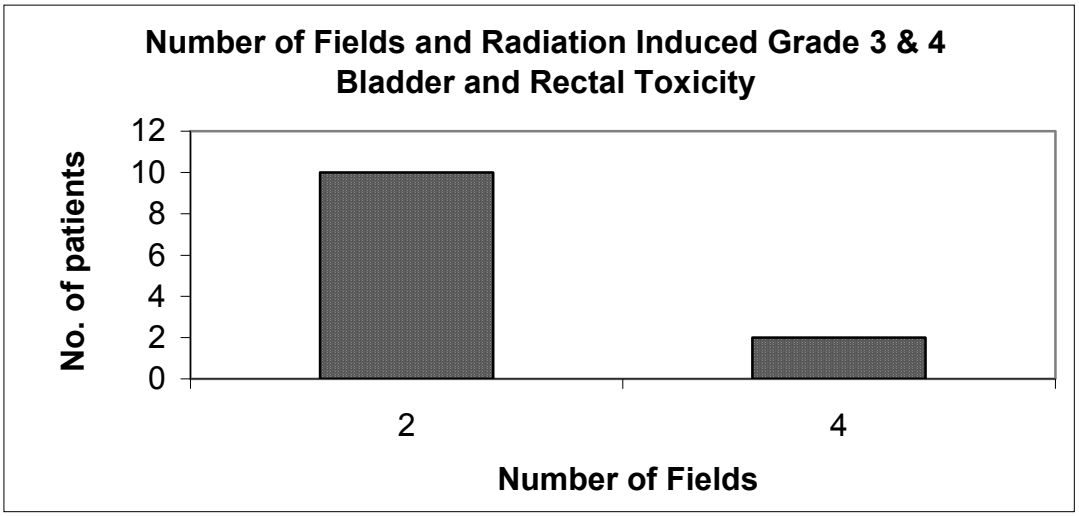
Although the numbers of patients in each age group were nearly equal, of the 12 patients who developed grade 3 and 4 bladder and rectal toxicity, eight patients were below the age of 50 ($p < 0.001$).



($p < 0.01$)

Figure 15 Radiation induced grade 3 & 4 bladder and rectum toxicity in two age groups

The BED to the rectum and bladder ICRU reference point was calculated from both EBRT and intracavitary HDR brachytherapy. Patients treated with two fields EBRT in addition to the HDR brachytherapy had an increased chance of grade 3 and 4 toxicity compared to those treated with four fields ($p = 0.001$).



($p = 0.001$)

Figure 16 Relationship between Number of Fields and Radiation Induced Grade 3 & 4 Bladder and Rectal Toxicity

More rectal complications were observed in patients who received a BED of 105 Gy_3 dose or more.

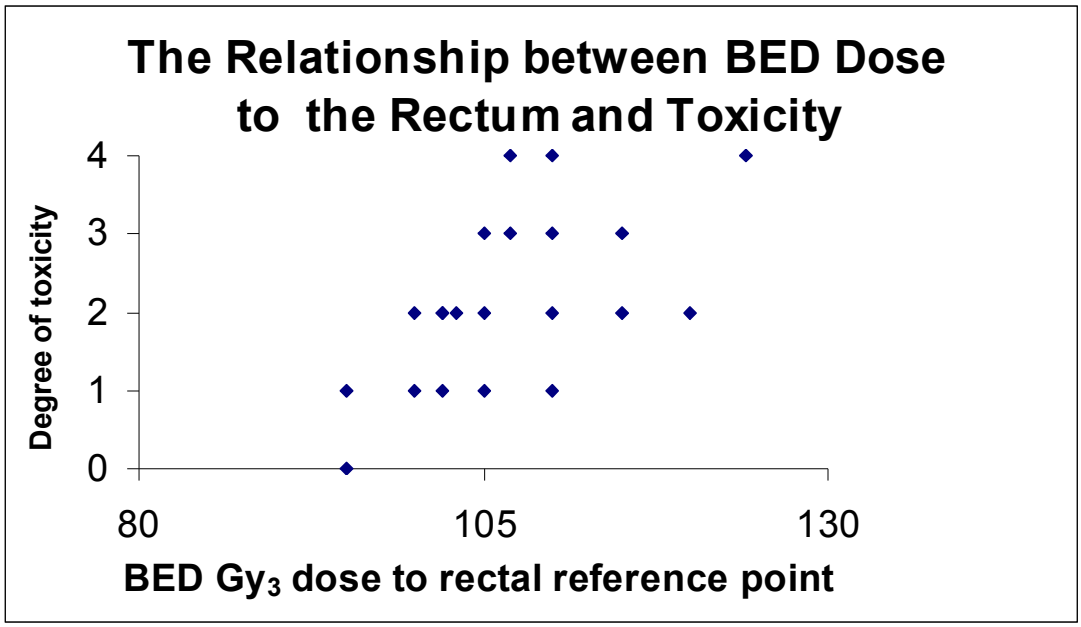


Figure 17. Relationship between the rectal dose and degree of toxicity

Radiation induced bladder toxicity increased when the dose to the bladder reference point increased.

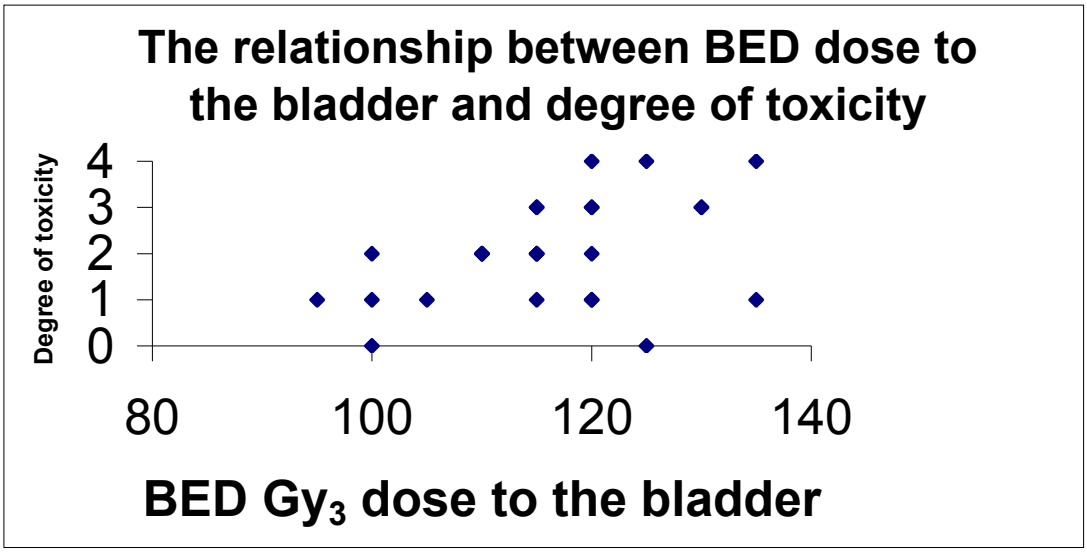


Figure 18. Relationship between the bladder dose and degree of toxicity

In this study, the Gy_3 BED dose to the organ at risk that induced grade 3 & 4 of toxicity were different in each Arm. The range of BED dose either to bladder or to the rectum was high in arm I and low in arm III. Almost all patients who did receive the threshold dose mentioned in table 3 developed grade 3 or 4 radiation induced toxicity.

Table 13 Threshold BED Gy_3 Dose which Induced Grade 3 & 4 Toxicity in each Arm

Arm	BED Gy_3 to bladder range	mean dose to bladder	Threshold Dose induced grade 3&4 toxicity in Gy_3 to bladder	BED Gy_3 to rectum range	Mean dose to rectum	Threshold Dose induced grade 3&4 toxicity in Gy_3 to rectum
I	107-137	119	120	97-120	108	107
II	101-130	118	111	101-123	111	110
III	95-123	110	114	95-123	106	105

In our study the incidence of grade 3& 4 rectum and bladder radiation induced toxicity were observed on the patients who had above BED Gy_3 dose of 105 and 120 respectively to the rectal and bladder referral points.

Table 14. Incidence of grade 3 & 4 toxicity to the rectum and bladder depending on BED Gy_3 dose in Arm during six months

Site	Variable	Category Gy_3	Incidence of grade 3&4 toxicity
Rectum	Total BED at rectal point	< 105	5%
		> 105	10.2%
Bladder	Total BED at bladder point	< 120	7%
		>120	15%

DISCUSSION

Despite screening programs, cervical carcinoma remains a major health problem throughout the world. Until recently, pelvic radiation has been the standard therapy for advanced disease with overall five-year survival rates of 50%. Recently, 5 randomized trials demonstrated a significant survival advantage for the concomitant administration of radiotherapy and cisplatin-based chemotherapy[7].

Radiation therapy to cancer of the cervix is delivered with EBRT and BT. It is an alternative to surgery in stage I, IIA, and IVA and comparable survival and tumour control with either modality have been reported[37]. Several prognostic factors, including tumour stage, volume, age of patient, performance status, and presence of metastatic pelvic, para-aortic lymph nodes, have been shown to affect the therapeutic outcome[20].

A variety of technical factors has been found to influence the morbidity of radiation therapy in patients treated for carcinoma of the uterine cervix. Among these are the dose of irradiation, quality of the intracavitary insertion, type of application used and proportion of external beam or brachytherapy dose delivered. Host-related factors, such as the age of the patient, the presence of diabetes mellitus, hypertension, pelvic inflammatory disease and a history of prior surgery have also been reported to affect the incidence of complications[9], [29], [38].

Patients with extensive loco regional disease have a high rate of local relapse if treated surgically. For this reason, patients with stage IIB, III, and IVA tumours are treated with radiotherapy, which results in five-year survival rate of 65, 40, and less than 20 percent, respectively[37] .

In studies[23], tumour stage was a marginally significant factor for five-year actuarial local control with p value of 0.09. The treatment of FIGO stage IIIB carcinoma of the cervix poses special problems for the radiation oncologist[28]. The tumour volume is usually large, and the likelihood of regional metastasis is high. As a result, clinicians

tend to emphasize the role of EBRT more than they would for earlier stage diseases, arguing that an emphasis on ICRT results in relative under treatment of the tumour extending toward or involving the pelvic sidewall. However, the results of a study done by Mark D. Logsdon and colleges[28] provides convincing evidence that ICRT is a critical component of successful treatment of stage IIIB disease. In the literature, the survival and local control rate of stage II patients was better than that of stage III patients. In the current study, 59 patients were analyzed 57.6% of whom were stage IIB (distal) and the remainder (42.4%) were stage IIIB (early). The response to treatment at 6months was 91% vs. 86% for stage IIB and IIIB (early) respectively which was statistically not significant ($p = 0.328$).

In previous years, different studies have shown that HDR brachytherapy with concomitant chemo-radiotherapy is safe and effective in management of locally advanced cervical cancer. Patel et al (1992)[10] studied 412 patients diagnosed with stage III cancer of the cervix treated with EBRT. Patients were randomized to receive either 18 Gy in two fraction of nine Gy each or 35 Gy by continued low dose rate BT. the 5 years survival, local control and distant failure were not significantly different and there was no evidence of increased toxicity in HDR group. More recently at the end of 2001 a study done in Albert Einstein College of Medicine[16] showed that 2 fraction of HDR brachytherapy of 9 Gy each with concomitant EBRT to the pelvis provided similar local control with out increasing toxicity. In the current study, the local control rate based on 6 months clinical finding and Pap-smear result did not show any statistically significant differences when comparing the 3 brachytherapy fractionation regimens.

According to a univariate analysis done in Brazil, the overall treatment time with cohort value of 50 days was a statistically significant factor for five years actuarial local control rate (84% versus 53%, $p = 0.008$)[23]. The over-all treatment duration has been reported by several authors to be of prognostic significance in patients with cervical cancer treated by radiation therapy[12][39]. The American Brachytherapy Society (ABS)[21][22] recommends keeping the total treatment duration to less than 8

weeks, because prolongation of total treatment duration can adversely affect local control and survival[12], [39], [40]. In this study, the duration of treatment did not influence significantly on local control, but the follow up time is too short to assess definitively the local control as only response was assessed at 6 months.

In a study done by Robson Ferrigno and collages shows that patient's age with cohort value of fifty years did not influence the actuarial local control (p = 0.99)[23]. In addition to that, this study has shown that local control did not have any dependency on age group of the patient, duration of treatment or by using two (AP-PA) or four fields (AP-PA and 2 Lat). The main reason why this study differs from others may be small number of patients and very short follow up period.

A retrospective study done in Japan showed[37] that concurrent chemo-radiotherapy using HDR-ICBT is feasible and efficacious for patients with loco regionally advanced uterine cervical cancer. They demonstrated that those patients who received a cumulative rectal BED of more than 100 Gy_3 had significantly higher incidences of proctitis than those who received less than 100 Gy_3 (p = 0.013). The median BED values at the ICRU 38 rectal reference point was 94.1 Gy_3 (range: 78.3 – 116.1 Gy_3). The low rectal BED value may have favourably affected the incidence of severe rectal complications[16].

Similarly, a study done in Brazil[23] as shown in Table 15 found that the 5 years actuarial incidence of late complication depends on total BED dose to the organ at risk.

Table 15. Five years actuarial incidence of late complication based on BED dose to bladder and rectum[23]

Site	Variable	Category Gy_3	Incidence in %
Rectum	Total BED at rectal point	≤ 110	12
		>110	18
Bladder	Total BED at bladder point	≤ 125	9
		> 125	17

The significant correlation was found between the dose calculated and measured at the rectal point defined by the ICRU and the incidence of late rectal complications. Using the linear quadratic model, they established a threshold value for the possibility of developing late rectal complication of 125 Gy_3, which is unrelated to the number of HDR fractions but rather to the total dose delivered to the rectal point by the combination of EBRT and HDR brachytherapy. Thus, keeping the biologically effective dose below 125 Gy_3 at the defined ICRU rectal point will minimize the risk of late rectal toxicity. The late rectal damage is a function of total biological effective dose to ICRU rectal point and not of the number of HDR BRT fractions[23].

In our study, as shown in Table 14, the biological effective dose, which causes grade 3 and 4 bladder and rectum toxicity appears to be lower than the previous study done in Brazil[23]. The follow up of this cohort of patients is too short to comment on the incidence of rectal complication and more follow up is required.

In general, there is more variability in the rectal dose reports. As in some series, the point for calculation of the rectal dose is pre-determined and others take into account several points along the anterior rectal wall. Nevertheless, the different series do show a correlation between rectal dose and complications[20]. In spite of the variations in the way the rectal doses are calculated, a cumulative dose of 75 Gy can result in a

10% incidence of proctosigmoiditis. With higher rectal doses, the incidence of proctosigmoiditis also increases[36][41].

Esche et al[42][36] showed that the frequency and severity of proctitis increases with cumulative rectal doses and volume treated. The majority of the recto-sigmoid complications occurred with cumulative rectal dose in excess of 70 Gy. Perez et al, has reported on the correlation of the dose with genitourinary and recto-sigmoid complications. In this study, the frequency of the grade II and III irradiation induced complications with bladder and rectal doses of 80 Gy is 5% but rises steeply with doses above this level.

In this study, grade 3 and 4 rectal complications increased when the dose to the rectal reference points was beyond 105 Gy_3. The chance of grade 3 and 4 bladder irradiation induced toxicity increased when the dose to the bladder reference point was above 120 Gy_3. The rate of radiation induced grade 3 and 4 bladder and rectal toxicity increased in those patients received prescribed EBRT in two fields than four fields. Among 12 patients who developed grade 3 and 4 radiation induced toxicity, seven of them were stage IIIB and the remaining five patients were stage IIB.

There are usually limitation factors in most of the studies with the respect of to the analysis and data may affect the accuracy of the results. Limitation of this study (limited frame time, limited number of patients, 2-D treatment planning and inaccurate orthogonal films) are the possible causes of some of the results differing to the other studied that are done previously.

CONCLUSION

Careful attention to normal tissue doses such as the rectum, bladder, and small bowel is important when brachytherapy is combined with concomitant chemo-radiotherapy regimen in the treatment of locally advanced cervical cancer.

Limiting the number of HDR brachytherapy application from 4 or 3 to 2 may improve patient comfort and compliance. Two insertions of 9 Gy each HDR application was feasible with an acceptable complication rates and equivalent local control rates when compared with 6.5 Gy for 4 fractions and 8 Gy for 3 fractions. Decreasing the number of fractions of brachytherapy is likely to be cost effective and will lead to shorter waiting list of patients and avoiding hospitalization.

Careful attention to radiotherapy technique and planning, such as patient positioning and number of portals will minimize both acute and long term toxicity.

ETHICAL CLEARANCE

Ethical approval was obtained from the committee for research on Human Subjects of the University of the Witwatersrand – Johannesburg. A copy of the clearance certificate number M03-10-36 is attached herewith.

The faculty of the Health Sciences Postgraduate Committee formally approved the protocol (please see attached herewith a copy of letter of approval).

APPENDIX A

Example:-

If a patient with stage IIB (distal) cancer of the cervix receives 9 Gy X 2 HDR and 50 Gy EBRT in 25 fractions – 2 Gy per fraction. The total rectal BED dose will be:

$= 25 \times 2\ [1 + 2/10] + 9 \times 2\ [1 + 9/10]$

$= 60\ Gy_{10} + 34.2\ Gy_{10}$

$= 94.2\ Gy_{10}$ for early responding tissues

$= 25 \times 2\ [1 + 2/3] + 9 \times 2\ [1 + 9/3]$

$= 83.3\ Gy_{3} + 72\ Gy_{3}$

$= 155.3\ Gy_{3}$ for late responding tissues

However, assuming that the ICRU rectum reference point does not receive the full brachytherapy dose, as the isodose curve is flattened posterior, and the rectal point receives only 80% of the prescribed dose. 80% of 9 Gy is 7.2 Gy and that is the dose to the rectum per fx; $7.2 \times 2\ (1 + 7.2/3) = 48.9\ Gy_{3}$ and will receive a total BED dose of $83.3\ Gy_{3}$ from EBRT + $48.9\ Gy_{3}$ from HDR = $132.2\ Gy_{3}$

APPENDIX B

- Grade 1 represents the most minor symptoms that require no treatment,
- Grade 2 represents moderate symptoms, requiring only conservative treatment,
- Grade 3 represents sever symptoms, which have a significant negative impact on daily activity, and which require more aggressive treatment.
- Grade 4 represents irreversible functional damage, necessitating major therapeutic intervention.

Bladder toxicity

Grade

0 No complaints

1. Mild dysuria
2. Moderate dysuria
3. Severe dysuria, gross haematuria
4. Deep ulcer, fistula

Rectum toxicity

Grade

0 No complaint

1. Tenesmus
2. Moderate diarrhoea
3. Pain less rectal bleeding
4. Deep ulceration, fistula

APPENDIX C

Total BED = BED (EBRT) + BED (HDR)

Total BED =nd[1+(d/α/β)] + Br [1+(d/α/β)]

$$Total(BED) = nd\left[1 + \frac{d}{\alpha/\beta}\right]$$ [16]

Where n = number of fractions in EBRT

d = dose per fraction

Br = total dose of brachytherapy

α/β = 10 for early responding tissues and 3 for late responding tissues (See Appendix A).

APPENDIX D

FIGO staging of carcinoma of uterine cervix[33][34].

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.

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