Original Article

Prospective randomised study comparing three-fraction regimens of High Dose Rate Brachytherapy for cancer of the cervix stage IIB and IIIB

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ABSTRACT

AIM Limiting the number of high-dose-rate brachytherapy (HDR-BT) applications from 4 or 3 to 2 fractions has the potential benefit of improving patient compliance. Two HDR-BT applications of 9 Gy each is most cost effective and resource sparing compared to 3 or 4 insertions. The aim of this study was to compare the treatment results and incidence of bladder and rectal complications following radical treatment of carcinoma of cervix with 2, 3 or 4 fractions of (HDR-BT) and standard external beam radiotherapy (EBRT).

METHODS Sixty-six patients with biopsy proven stage IIB and stage IIIB cancer of the cervix received EBRT 50 Gy in 25 fractions and concomitant Cisplatin 80 mg/m^2 once every 3 weeks. The patients were then randomized into one of three-fractionation arms of HDR-BT: (I) 6.5 Gy x 4; (II) 8 Gy x 3; and (III) 9 Gy x 2. The biologic effective dose (BED) to organs at risk was used to assess the complication rates of treatment. Patients were evaluated using SOMA/LENT (subjective, objective, management and analytic/ late effects in normal tissues) scales during treatment, at 6 weeks and finally at 6 months. Pap-smears were performed at 6 months to assess local control.

RESULTS Fifty-nine patients completed chemo-radiotherapy and attended follow up for evaluations at 6 weeks and 6 months. 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 influence of the following prognostic factors on local control was not statistically 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 to organs at risk and 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 This study showed that 9 Gy x 2 fractionations HDR-BT with concomitant chemo-radiotherapy was equally effective in short term local control and had similar incidence of treatment related complications compared to 6.5 Gy x 4 and 8 Gy x 3 regimens during 6 months of follow up.

Keywords: Cancer of cervix; Implant radiotherapy; Brachytherapy; Dose fractionation; Radiotherapy

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 among African and European-African females in South Africa with a lifetime (1-74 years) risk of 1 in 41 [2] and the 2nd and 5th most common cancer in Asian and Caucasian 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) is the cornerstone and the treatment of choice for Fédération International de Gynécologique et Obstétrique (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 disease. [4-5] RT for primary cervical cancer consists of a combination of external beam radiotherapy (EBRT) and intracavitory brachytherapy (ICRT), except in stage IA disease where brachytherapy alone may be used. [5]

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] The use of high dose rate (HDR) brachytherapy is the result of technological developments in the manufacture of high-intensity radioactive sources, sophisticated computerised 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, individualised treatment with source optimisation 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.

In order to maximise the benefits of HDR-BT while improving patient compliance and resource sparing, various fractionation regimens have been studied in different countries and centres. [7-10] Five-year survival, local control, and recurrence rates have not been significantly different and there has been no evidence of increased toxicity in the HDR brachytherapy groups.

Limiting the number of high-dose-rate brachytherapy (HDR-BT) applications from 4 or 3 to 2 fractions has the main potential benefit of improving patient compliance. Two HDR-BT applications of 9 Gy each is most cost effective and resource sparing compared to 3 or 4 insertions. The aim of this study was to compare the treatment results and incidence of bladder and rectal complications following radical treatment of carcinoma of cervix with 2, 3 or 4 fractions of (HDR-BT) and standard external beam radiotherapy (EBRT).

METHODS

Sixty-six patients with biopsy proven cancer of cervix and FIGO stage IIB (distal) or stage IIIB (early) disease were recruited if they met the following additional criteria: age above 20 and below 75, performance status ECOG 0 up to 2 and HIV negative. Patients were excluded if they were unavailable for follow up, had previous hysterectomy or pelvic radiotherapy, had active systemic disease, or had other malignancy other than skin cancer not controlled for five or more years. Ethical approval was obtained from the committee for research on Human Subjects of the University of the Witwatersrand – Johannesburg.

All patients were treated radically based on departmental protocol and received EBRT 50 Gy in 25 fractions at 2 Gy per fraction. Patients also received concomitant Cisplatin 80 mg/m^2 every three weeks. Patients were then randomized into one of the three-fractionation arms of HDR. In 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. In arm II, patients received HDR brachytherapy of 3 fractions of 8 Gy per fraction. The brachytherapy was given during the last 3 weeks

of EBRT with concomitant chemotherapy. In arm III, patients received HDR brachytherapy of 2 fractions of 9 Gy per fraction. The brachytherapy was given weekly during the last 2 weeks of external beam radiotherapy with concomitant chemotherapy.

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

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 individualised for each patient. Two radiographs anterior posterior (AP) and lateral with a dummy source in the applicator were taken (Figure 1).

Transparencies 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.

The pelvic sidewall reference point was visualised 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.

By using packing with each application, an attempt was made to increase the distance between the tandem and critical organs. The dose to critical organs was inversely proportional to the square distance away from the tandem (Figure 2). 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.

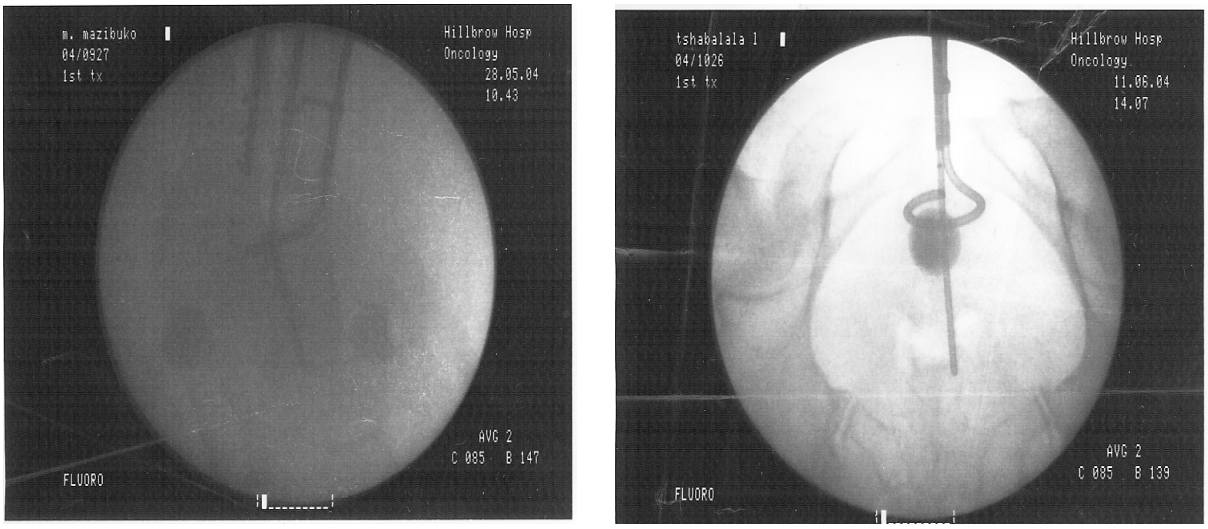

Figure 1. Lateral and anterior posterior radiographs of applicator in situ

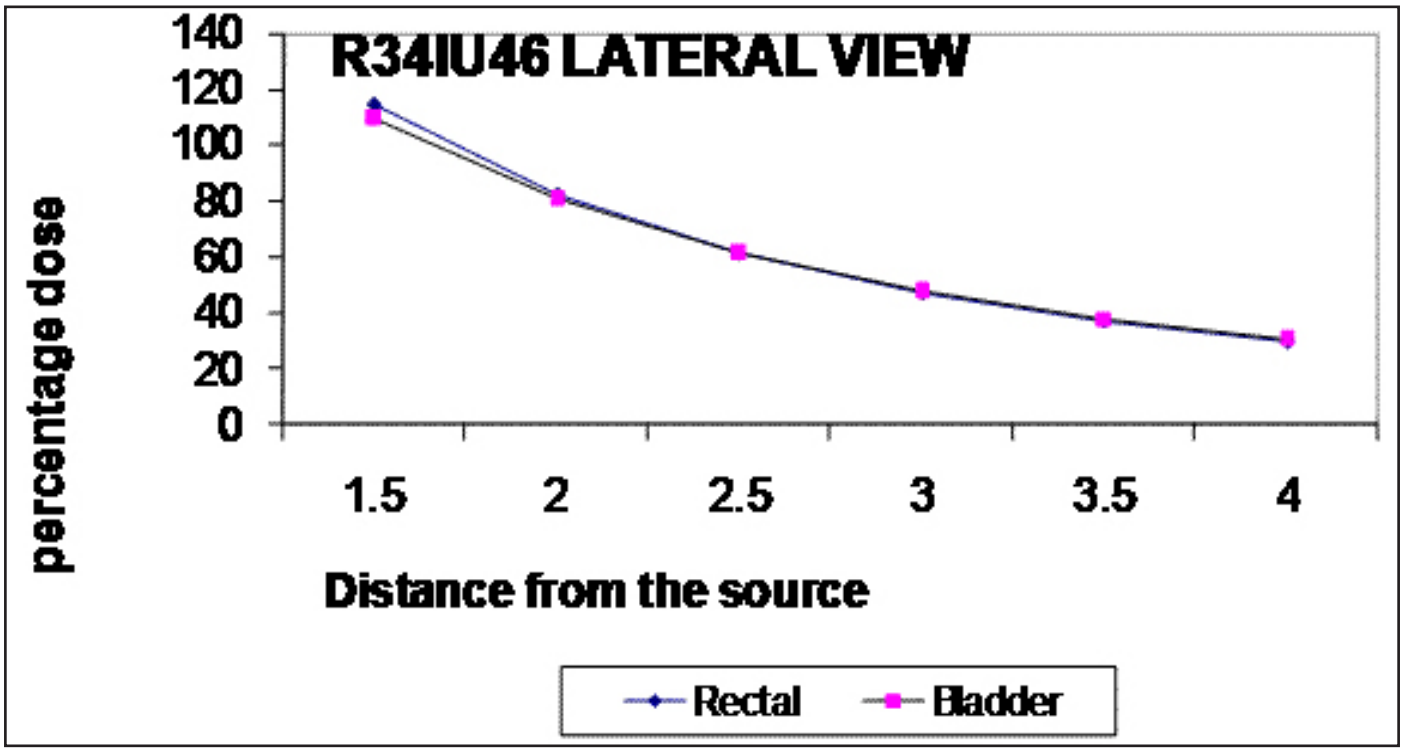

Figure 2. Relationship between the percentage dose prescribed to point A against distance from applicator, ring size 34 and tandem size 46 (R34IU46), to the ICRU rectum, bladder.

For each arm, the contribution of point A dose was calculated as per the linear quadratic model (LQM) from both external beam radiotherapy and intracavitary portions of the treatments. The total biologically effective dose (BED) to the tumor was calculated by using an α/β ratio = 10 (Gy10) [4,6] (Table 1). The BED Gy10 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). [11]

The median BED for late responding tissue for arm I patients was 165 Gy_3 at point A. With adequate packing and good application, the bladder and the rectum would usually receive 60 – 80% of the prescribed dose to point A. [4,6] If the normal tissues received 70% dose, then the 165 Gy_3 term would reduce to about 115 Gy_3. The LQED [6,11] 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 (Table 2).

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; (3) the effect of age and number of fields treated on radiation induced toxicity; and (4) the doses to the bladder and rectal reference points and their association with radiation induced toxicity. Radiation induced grade 3 and 4 bladder and rectum effects were assessed using Lent SOMA scale in each arm.

All statistical analysis was performed using the Epi Info program 2002. 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 factor 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.

Table 1: BED Gy_{10} dose to point A for the three HDR fractionation regimens

Arm	EBRT Dose Gray/ fraction	EBRT fractions	HDR Dose Gray/ fraction	HDR fractions	$Gray_{10}$ Point A	LQED $Gray_{10}$ to point A2 Gray/ fraction
I	2	25	6.5	4	103	86
II	2	25	8	3	103	86
III	2	25	9	2	94	78

LQED-Linear Quadratic Effective Dose

Table 2. BED Gy_3 dose and to late responding tissue for three fractionation regimens

Arm	Gy_3 dose to the 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

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 repeat 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 to 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 every three weeks. The reasons for not receiving chemotherapy (n=7) were low creatinine clearance in four patients, two could not receive chemotherapy for logistical reasons and one patient absconded. Of the seven patients, three were in arm I, two were in arm II and two were in arm III. The only chemotherapy-related side effect noted was mild to moderate nausea and vomiting. Further analysis included only those 59 patients who completed the prescribed dose of chemoradiotherapy and attended the six week and six month assessments and Pap smears.

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 three arms with p value of 0.995. There were no statistically significant differences between the three arms in terms of stage distribution and the number of chemotherapy cycles given (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 with p value of 0.651.

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

In terms of adverse effects of radiation, 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 ($p < 0.001$). The BED to the rectum and bladder ICRU reference point was calculated from both EBRT and intracavitory 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 ($p = 0.001$). 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.

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. [5]

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. [8] 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. [11]

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. [12]

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) [7] studied 412 patients diagnosed with stage III cancer of the cervix treated with EBRT. More recently at the end of 2001 a study done in Albert Einstein College of Medicine [10] showed that 2 fractions of HDR brachytherapy of 9 Gy each with concomitant EBRT to the pelvis provided similar local control without increasing toxicity. In the current study, the local control rate based on 6 month clinical findings 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%, $p = 0.008$). [11] 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. [12-13] The American Brachytherapy Society (ABS) [14-15] recommends keeping the total treatment duration to less than 8 weeks, because prolongation of total treatment duration can adversely affect local control and survival. [12-13] In this study, the duration of treatment did not influence local control, one possible reason is that the follow up time is too short to assess definitively the local control as only response was assessed at 6 months. A study done by Robson Ferrigno and colleagues showed that patient's age with cohort value of fifty years did not influence the actuarial local control ($p = 0.99$). [11] 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 number of fields whether two (AP-PA) or four fields (AP-PA and 2 Laterals). 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 that concurrent chemo-radiotherapy using HDR-ICBT is feasible and efficacious for patients with loco regionally advanced uterine cervical cancer. [8] 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. [11]

Similarly, a study done in Brazil [11] found that the 5 years actuarial incidence of late complications depends on total BED dose to the organ at risk.

A 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 110 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 110 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. [1]
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. 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. [16] The optimisation of HDR brachytherapy can be further improved with 3D imaging using CT or MRI to increase the dose delivery to the adjacent normal tissues. The rate of radiation induced grade 3 and 4 bladder and rectal toxicity increased in those patients who received EBRT in two fields versus 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.

CONCLUSION

HDR brachytherapy in combination with megavoltage teletherapy appears to be safe and effective treatment modality in the treatment of cervical carcinoma. In our current study, we have proven that EBRT with concurrent chemotherapy and two insertions of 9 Gy each HDR application was feasible with an acceptable complication rate and equivalent local control rate when compared with 6.5 Gy, 4 fractions and 8 Gy, 3 fractions. Careful attention to radiotherapy technique, planning, patient positioning, and number of portals will minimise both acute and long-term toxicity. Limitations of this study included limited time frame, limited number of patients, and 2-D treatment planning.

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FOOTNOTES

Conflicts of interest: The authors declare no competing conflicts of interest

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