A STUDY OF HIGH-DOSE-RATE BRACHYTHERAPY

IN THE TREATMENT OF

CARCINOMA OF THE UTERINE CERVIX

BEING DISSERTATION SUBMITTED BY

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SUMMARY

AIM:

To study the acute side effects associated with HDR brachytherapy and compare it with those of LDR.

MATERIALS AND METHODS:

Sixty two (62) patients treated with HDR studied. Seven (7) had had previous surgery. Thirty one (31) had HDR intracavitary insertion concomitant with EBT and twenty four (24) after. A total of 104 patients treated with LDR evaluated for comparison.

RESULTS:

Diarrhoea was the most frequent acute side effect noticed, mostly of low Grade - I & II - recorded in $^{18}/_{31}$ (58%) of concomitant arm and $^{10}/_{24}$ (42%) of after-EBT arm. Dysuria was uncommon in HDR patients. Diarrhoea was less frequent in LDR patients - $^{28}/_{104}$ (26%) - while dysuria was more frequent - $^{30}/_{104}$ (29%) - than in HDR patients. These symptoms in LDR patients were mostly of low-grade nature. Previous surgery was associated with a higher incidence of acute side effects - $^{6}/_{7}$ (85%) patients had low grade diarrhoea and $^{2}/_{7}$ (28%) patients had dysuria.

CONCLUSION:

Acute side effects associated with two insertions of 7 Gy HDR were low grade and tolerable. Literature review showed that larger numbers of insertions are better tolerated with reduced late complications comparable to those of LDR. Most late complications were associated with fraction sizes greater than 7 or 8 Gy. It is recommended that HDR afterloading treatment continues in Bulawayo using three fractions each of 6 Gy given at weekly intervals, the first two during the course of EBT and the third following completion of EBT, keeping overall time under seven weeks. Further work is indicated to assess the frequency of late complications.

1. INTRODUCTION

1.1 IMPORTANCE OF CARCINOMA OF THE CERVIX IN ZIMBABWE

Carcinoma of the cervix is the commonest cancer in females in Zimbabwe. According to the Cancer Registry in Harare, between January and December 1991, 600 cases of cancer of the cervix were recorded. This formed 25% of all cancers reported in females during same period. A breakdown of this figure showed that:

44 cases (7%) occurred in the 20 - 30 year age group;
134 cases (22%) occurred in the 30 - 40 year age group;
151 cases (25%) occurred in the 40 - 50 year age group;
149 cases (25%) occurred in the 50 - 60 year age group; and
74 cases (12%) occurred in the 60 - 70 year age group, as shown below in Figure I:

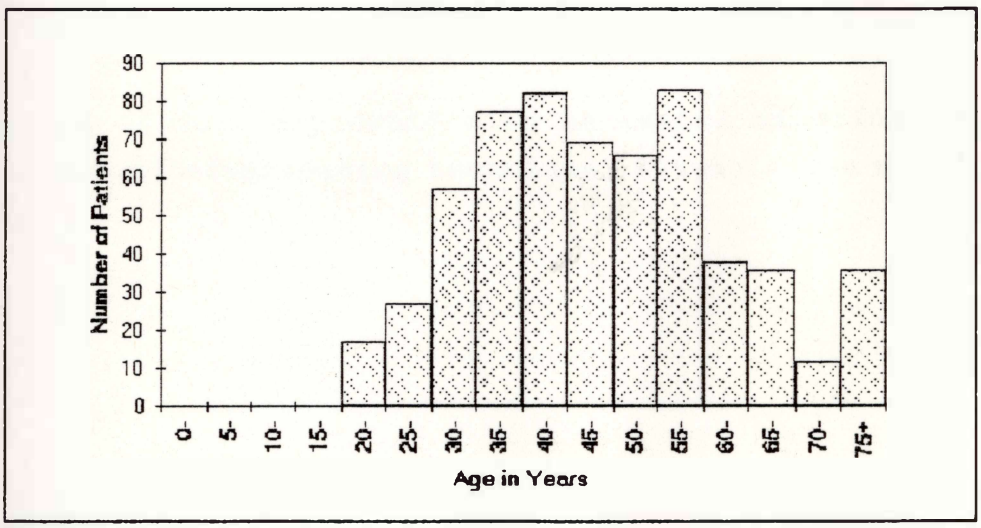


FIGURE I:
HISTOGRAM SHOWING THE DISTRIBUTION BY AGE GROUP

For 1992, cervical cancer formed 24% of the total cases of cancer recorded in females; it formed 38% in 1990, 33% in 1989, 28% in 1988 and 35% in 1987.

1.2 USE OF RADIOTHERAPY IN THE TREATMENT OF CARCINOMA OF THE CERVIX

Radiotherapy plays a major role in the treatment of Carcinoma of the uterine cervix. Most patients with this disease will require radiotherapy, either as definitive treatment or as an adjuvant. Over 90 percent of our patients in Zimbabwe fall in the former category, i.e. over 90 percent will require radiotherapy as the definitive form of treatment, because most of them present with advanced disease not amenable to surgery. There are two modalities of administering radiotherapy, the external beam therapy, involving the use of megavoltage machines such as ^{60}Co machines and the linear accelerator - treatment given in fractionated doses over a period of several weeks. The second involves the use of intracavitary brachytherapy (see 1.3 below).

1.3 USE OF INTRACAVITARY IRRADIATION IN THE TREATMENT OF CARCINOMA OF THE CERVIX

Intracavitary brachytherapy is an essential component in the treatment of cervical cancer. It involves the insertion of radioactive sources through applicators into the uterus and vagina to deliver high doses of irradiation to the immediately surrounding tissues. According to the International Commission on Radiation Units (ICRU) Report 38 on dose and dose specification for reporting intracavitary brachytherapy in gynaecology,

- Dose Rates in the range of 0.4 - 2.0 Gy/hour are referred to as low dose rates.
- Dose Rates in the range of 2 - 12 Gy/hour are referred to as medium dose rates.
- Dose Rates greater than 12 Gy/hour are high dose rates.

The method of delivery could also be manual afterloading or by remote control afterloading technique, which is the method being studied.

1.4 ADVANTAGES OF HIGH-DOSE-RATE REMOTE AFTERLOADING INTRACAVITARY BRACHYTHERAPY

Recently, there has been increased interest in HDR remote-control afterloading intracavitary brachytherapy for carcinoma of the cervix. This emanated from certain advantages of this mode of treatment over the LDR which include:

1) Low personnel exposure;

2) Short treatment time, therefore, a greater number of patients per week could be treated;

3) More convenient and more comfortable treatment given on an out-patient basis, thus minimizing cost in terms of stay in the hospital, avoidance of catheter complications, reduced chance of thrombophlebitis and pulmonary emboli and skin breakdown in buttock crease;

4) Greater stability of the applicators during treatment because of short treatment time.

5) Constant and reproducible geometry of source positioning, therefore treatment planning and dosimetry are more exact (Speiser).

Besides these advantages, HDR and LDR have been found by different authors to have comparable local control rates and five-year survival rates. For example, in the series by Akine et al (1990) local control rate was 71% in the HDR group and 83% in the LDR group for stage II^B disease and 64% and 61% respectively for stage III^B diseases. The 5-year survival rate for both methods according to the FIGO annual report 1987(2) is as shown below:

HDR VS LDR INTRACAVITARY BRACHYTHERAPY FOR CARCINOMA OF THE CERVIX

(1979-1981) - FIGO ANNUAL REPORT 1987(2)

Stage	No of Patients HDR/LDR	5-year Survival (%)	
		HDR	LDR
I	160/422	76.9	71.6
II	358/796	58.1	54.4
III	386/588	38.1	38.4
IV	66/50	15.2	10.1

1.5 DISADVANTAGES OF HDR BRACHYTHERAPY

The history of brachytherapy evolved empirically to dose rates of +/- 10 Gy/day. Many efforts at high-dose teletherapy all revealed severe delayed complications and daily doses of 150 - 300 cGy are generally accepted for radical courses of treatment (although higher doses may be used in the treatment of pain and bleeding in palliative situations). HDR is very similar to a large external-beam-therapy fraction, however desirable it is to treat with few fractions, from a logistic point of view, brachytherapy is still under the same constraints biologically as teletherapy. Chen et al, 1991, compare the late complication rates in stage II^B and III^B diseases treated with LDR and HDR after external beam therapy. Analysis of their result showed slightly higher late-complication rates for HDR, though not statistically significant as shown in the table below.

TABLE I

	II^B		III^B	
	HDR	LDR	HDR	LDR
Late Complications				
Rectal Bleeding	34%	20%	31%	26%
Rectal Stenosis	2%	0%	4%	4%
Haematuria	9%	5%	3%	4%
Fistula	2%	0%	3%	4%

Choi et al, 1992, showed an unexpectedly high complication rate in patients treated with HDR brachytherapy which they found significant and unacceptable. In their study, late complications developed in 47% ($^{65}/_{137}$) of their patients. Grade 3 or above

complications occurred in the bladder, small bowel and sigmoid colon/rectum. Apart from Choi et al, most other studies showed slightly higher late complication rates with HDR, but were not statistically significant. Certain issues also remained unresolved for now regarding the use of HDR brachytherapy. For example:

1) What dose of HDR is equivalent to the standard dose of LDR?

2) Optimal treatment regimen schedule, including dose prescriptions, number of insertions and the interval between them and pelvic irradiation doses - these are all as yet unresolved.

Most of the studies that have examined these problems to date are largely retrospective and are all non-randomized. Broad-based prospective randomized studies will be required to resolve these issues and this will take some time.

In the meantime, however, what are the guidelines to be used as regards HDR brachytherapy in our situation for now?

1.6 FRACTIONATION - NUMBER, TIMING, SIZE

There is as yet no consensus of opinion on the optimal fractionation schedules to be used in HDR brachytherapy. Several authors have used different fraction numbers and sizes and have achieved fairly comparable results. Orton (1991) prefers conventional Low-Dose-Rate brachytherapy and multiple fractionation to allow for repair of normal tissues. He likened HDR to teletherapy with fewer big fractions and associated more late complications. Therefore, he feels it is important to use increased number of fractions in order to reduce late complications. He used 3.8 Gy per fraction and gave a total of 12 fractions. In his view, this fractionation will keep the dose to the bladder and rectum per fraction to 2 Gy - 2.5 Gy and that, with good application, rectum and bladder dose will be about 60% of the point A dose. His intracavitary fraction size of 3.8 Gy HDR is much less than that used by most other authors.

Chen et al, 1991, treated 365 patients with HDR. They gave external beam therapy with 10 MeV Linac Anterior and Posterior fields using field size 16 x 18 cm^3 at isocentre initially giving 44 Gy/22 fractions/4½ weeks, then 14 Gy/7 fractions side-wall boost for some II^B and III^B. This was followed by intracavitary insertion in three fractions. EBT for 2 weeks, 1^{st} intracavitary (IC), then 2 weeks later 2^{nd} IC, and 3^{rd} IC 2 weeks after, totalling 11 weeks of treatment time. The intracavitary dose was 770 - 850 cGy per fraction initially and was later reduced to 720 cGy per fraction to minimize dose to the rectum. Their complication rate in 20 cases of II^B and 23 cases of III^B who completed 3 insertions after follow-up period of 2 - 9 years was 13%, which was slightly above the usual LDR figures, but their local recurrence rate was 12% for stage II^B and 17% for stage III^B cancer.

Roman et al, 1991, in their treatment of 87 patients with stages II^A , II^B and III^B after a median follow-up of 40 months, used external beam therapy with 4 - 10 MeV Linac and 4 fields (Box) technique to 46 Gy at 2 Gy/fraction, and then intracavitary insertion giving 800 cGy - 1000 cGy to point A per insertion. They gave IC once weekly, with the number of insertions varying from 1 - 3. Six patients had one insertion only (either because of inability to find the cervical canal at the time of insertion or bulky residual disease), 51 had two insertions and 30 patients had three insertions performed. They obtained a survival rate of:

- 88% for stage II^A patients
- 64% for stage II^B patients
- 32% for stage III^B patients.

These results are comparable with other results in the literature. Their acute complications are similar to those obtained with LDR, and their total complication rate was 11.5%. Some of the late complications they reported included proctitis - 2%; fistula - 3.5%; and small bowel obstruction - 6%.

1.7 DOSE OF HDR EQUIVALENT TO LDR

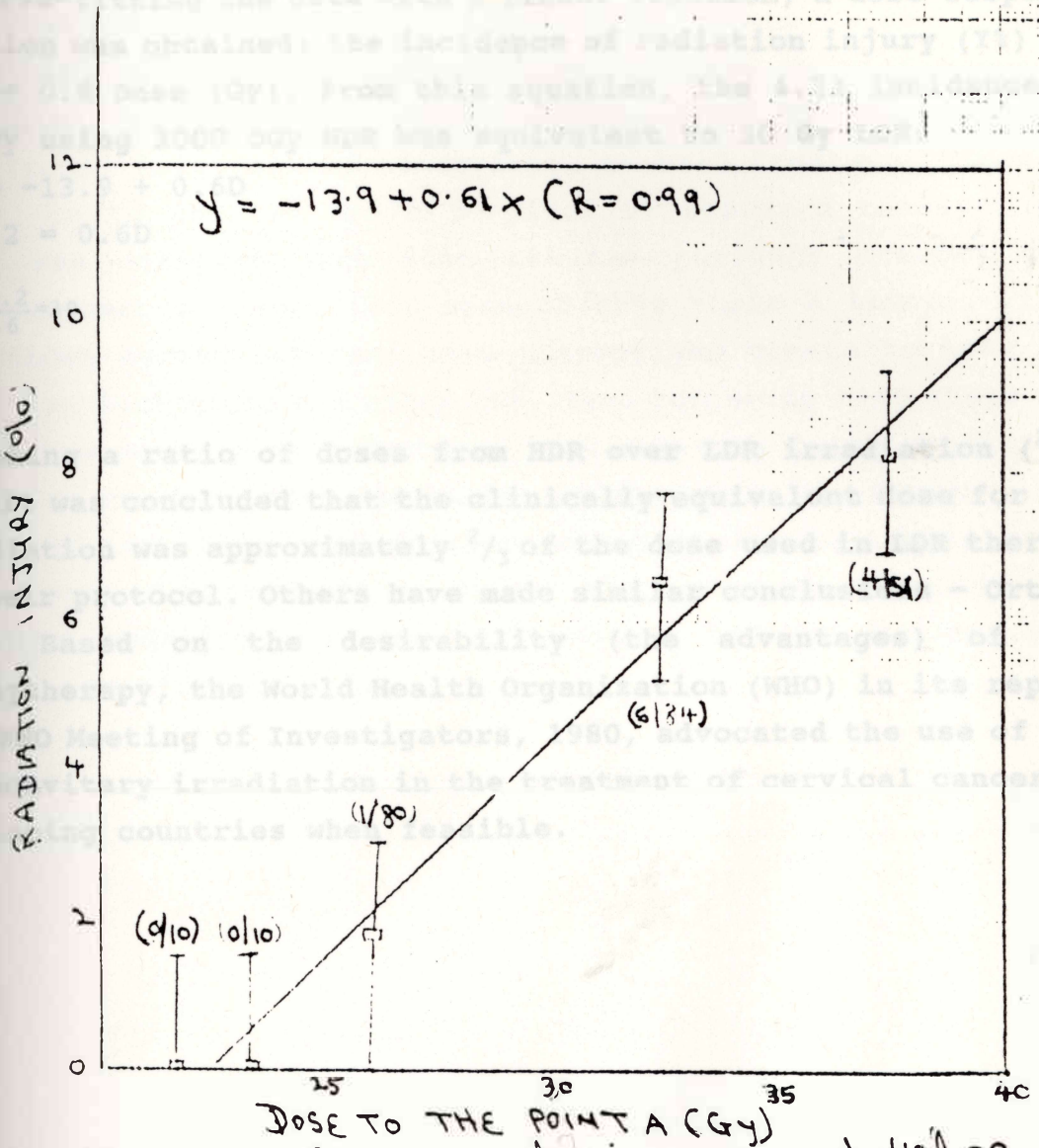
To estimate what dose of HDR is equivalent to LDR, Akine et al (1990) in a non-randomized retrospective study treated 370 patients with external beam therapy (EBT), then with either LDR or HDR brachytherapy. EBT was with 6 MeV Linac using anterior and posterior fields and field size 16 x 16 - 17.5 x 17.5 cm^3. They gave 50 Gy in 25 fractions over five weeks. This was followed by intracavitary insertions two weeks later, either as one or two applications of LDR doses, or four applications of 5 Gy HDR. Their local control rates and survival rates revealed no statistically significant difference.

Complication rates - they compared major complications only in stages II^B (69 patients) and III^B (184 patients) who had conventional LDR, with those who had HDR (16 stage II^B and 31 stage III^B; excluded were 46 patients who had less than 48 Gy or more than 52 Gy EBT, and 23 patients not treated according to the HDR protocol). Since both groups had the same external beam dose, it was the comparison of :

HDR - 2000 cGy/4 fractions with

LDR - 20 - 30 Gy, or 30 - 40 Gy to point A.

Then they plotted the incidence of major radiation injury as a function of the point A dose, as shown below in Figure II:



Incidence of Major radiation injury plotted as a function of the Point A dose. Bars correspond to the Standard Error. Numbers in parenthesis correspond to number of patients with major radiation injury over the total number of patients

Fig II

By curve-fitting the data with a linear function, a dose-response equation was obtained: the incidence of radiation injury (Y%) = -13.9 + 0.6 Dose (Gy). From this equation, the 4.3% incidence of injury using 2000 cGy HDR was equivalent to 30 Gy LDR.

$4.3 = -13.9 + 0.6D$

$\therefore 18.2 = 0.6D$

$$D = \frac{18.2}{0.6} = 30$$

By taking a ratio of doses from HDR over LDR irradiation ($^{20}/_{30}$ Gy), it was concluded that the clinically equivalent dose for HDR irradiation was approximately $^{2}/_{3}$ of the dose used in LDR therapy in their protocol. Others have made similar conclusions - Orton, 1991. Based on the desirability (the advantages) of HDR brachytherapy, the World Health Organization (WHO) in its report of a WHO Meeting of Investigators, 1980, advocated the use of HDR intracavitary irradiation in the treatment of cervical cancer in developing countries when feasible.

1.8 AIM OF THE STUDY

Study aimed basically at identifying acute side effects associated with HDR brachytherapy and compare it with those of LDR. Also the study was to define the dose of intracavitary insertions, intervals of insertions, overall treatment times in weeks, to be used at Mpilo Hospital as standard therapy. The study was designed such that all the patients started with external beam therapy, then some to have their 2 intracavitary insertions during external beam therapy and others to have one insertion during and one after EBT. Then comparing them stage for stage, the acute side effects of each arm were to be studied to determine which regimen was better tolerated in the patient. The number of insertions was deliberately kept low initially until the outcome of this study was known, since when introducing a new treatment modality, one does not want to have an unacceptable initial complication rate.

2 MATERIALS AND METHODS

The Curietron - which is a high-dose-rate remote after-loading machine became functional at Mpilo Hospital in Bulawayo in July 1992. Since then, to date, most patients with carcinoma of the cervix seen at the centre were treated with a combination of External Beam Therapy (EBT) and two intracavitary insertions. Between July 1992 and March 1993, 70 patients had one or two intracavitary insertions with the Curietron. As of March 1993, 62 patients had completed external beam treatment and two intracavitary insertions. It is these 62 patients that were studied in this non-randomized prospective exploratory study.

In all, 198 patients were studied:

BULAWAYO - 62 patients comprising of

GROUP A - 31 patients had EBT and first insertion 3rd week of EBT and 2nd insertion one or two days after n of EBT.

GROUP B - 24 patients had EBT and first insertion 3rd week of EBT and the 2nd insertion within two weeks of completion of EBT.

GROUP C - 7 patients had previous surgery, then EBT and 2 insertions of HDR intracavitary brachytherapy (dose: 7 Gy/fraction in 20 minutes to 0.5cm depth).

HARARE - 104 patients

GROUP D - had EBT and one insertion of LDR intracavitary brachytherapy (dose: 25-28 Gy over 60-65 hours to point A).

GROUP E - palliated cases - 32 patients.

Of the 62 patients at Mpilo Hospital, Bulawayo, seven had previous surgery and subsequent vault caesium. Therefore, 55 patients had two courses of intracavitary insertions - 31 of them during EBT, i.e. first insertion in third week of EBT and second insertion one or two days after (GROUP A) and therefore completed their treatment within five weeks of commencement. Twenty four had first insertion during EBT and the second within two weeks of completion of EBT (GROUP B), thus completing within six to seven weeks after commencement of EBT.

2.1 PATIENTS' CHARACTERISTICS

All patients included in the study had histologically proven carcinoma of the cervix. All the patients were staged clinically by gynaecologists and radiotherapists, 2 patients had intravenous urogram done as part of the staging procedure. Patients studied included those with stages I^B to III^B carcinoma of the cervix. Excluded from the study were patients treated palliatively and were as such offered only EBT. Reasons for exclusion, number of patients and treatment outcome were as shown in Table II. They were reviewed at the completion of treatment to monitor response to treatment.

TABLE II

Patients Treated Palliatively with only EBT - E

REASON	NUMBER	OUTCOME
Fistula - VVF, RVF	7	No treatment
I^A - Referral for Surgery	1	
Stage II Bulky	2	1 NED after treatment; 1 persistent disease
III $^{A+B}$	11	3 NED; 8 persistent disease
IV^A	3	1 NED; 2 persistent disease
III^B Bulky	8	1 NED; 7 persistent disease
TOTAL	32	

(NED = No Evidence of Disease)

2.2 TREATMENT TECHNIQUES

2.2.1 EXTERNAL BEAM THERAPY

All the Patients who received external beam radiotherapy were treated on ^{60}Co machine, using 80 cm SSD. They were treated in two phases. In phase I, they received parallel opposed anteroposterior field to 40 Gy/20 fractions in four weeks. In phase II, they received two lateral fields to treat the parametrium taking the dose to the pelvis to 50 Gy. The rectum was shielded posteriorly at 46 Gy in all patients to reduce dose to the rectum except when the posterior vaginal walls were involved in III^{A} or III^{A+B} cases. When using anteroposterior fields, the treatment volumes were as follows:

1) Superior border at the junction of L4/L5 level
2) Lateral border 1 - 2 cm clear of the pelvic brim
3) Lower border usually at the lower margin of the obturator foramen, except where lower $^{1}/_{3}$ of the vagina is involved, when the inferior margin was extended to the level of the ischial tuberosity using an anal marker.

Check films were taken in all cases and corrections made on the fields where necessary. The dose delivered ranged from 42 - 50 Gy at 2 Gy per fraction, using 5 fractions per week. All fields were treated each day. The patients were treated in both prone and supine positions to prevent buttock crease ulcerations.

2.2.2 INTRACAVITARY BRACHYTHERAPY

The Curietron remote after-loading machine in use in Bulawayo consists of 4 sources. These include:

1) 6 cm long with source strength of 2466 mCi-^{137}Cs; active length is 6 cm, labelled TU08.
2) 8 cm active length with source strength of 3315 mCi-^{137}Cs.

Appropriate uterine tandems were used depending on the length of the uterine cavity as determined by uterine sound. Either of the two uterine sources was used such that not more than 1 cm of the active length lay within the vagina.

The other two sources are the vaginal colpostats:

1) 2 cm active length of 830 mCi- labelled TA65.
2) 2 cm active length of 835 mCi- labelled TA64.

With the uterine tandem in place and the two vaginal colpostats in the lateral fornices and with adequate packing (anteriorly and posteriorly to separate the anterior rectal wall and posterior bladder wall from the sources as much as possible) the most superior edge of the 2 colpostats lies at the lowest active point of the uterine tandem. The point A dose was taken as 2 cm lateral to and superior to the lateral fornix along the long axis of the uterus. The arrangement of the sources was as shown below in Figure III:

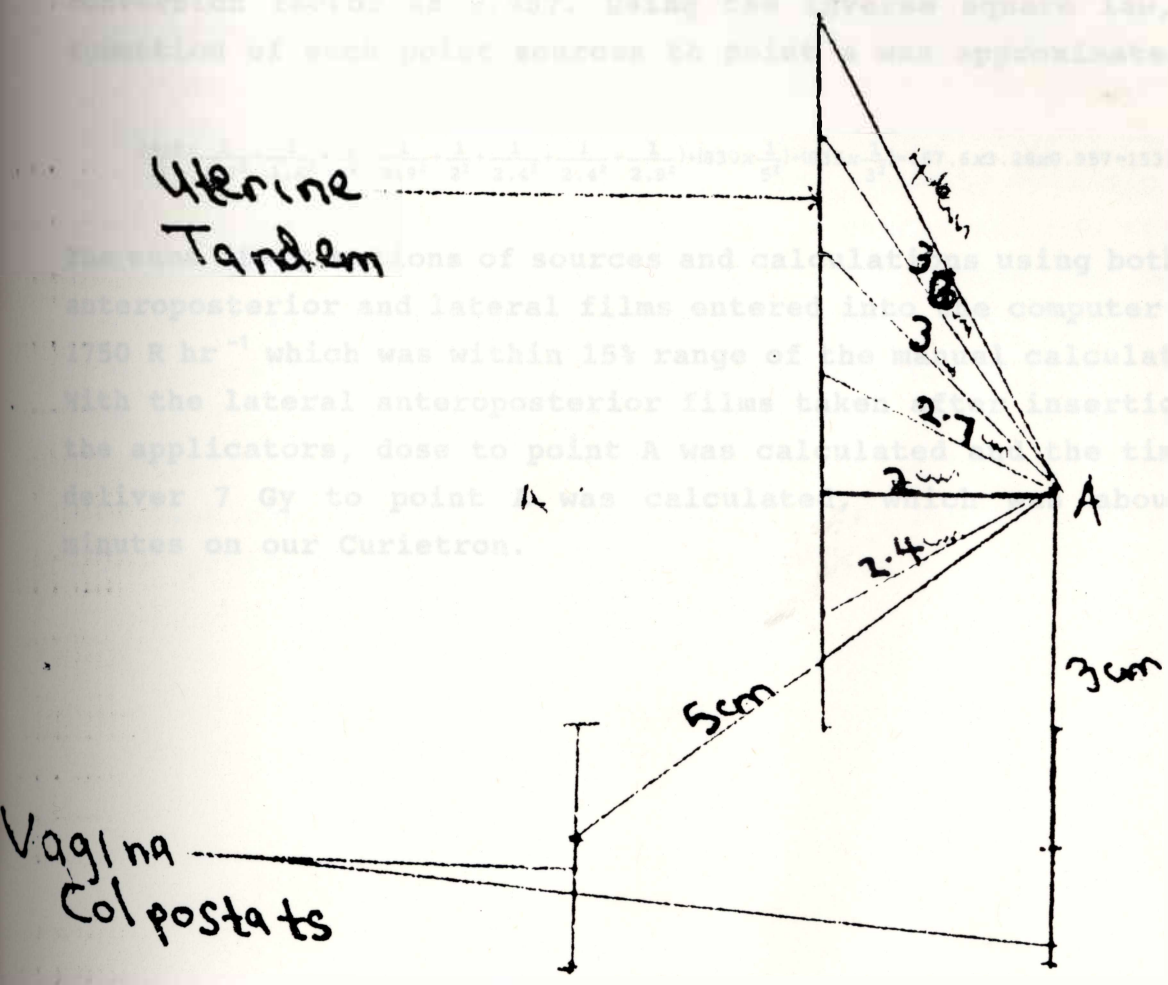


Fig III

2.3 DOSAGE CALCULATION

Clipping the colpostats together after insertion leaves a distance of about 4 cm between them. Considering the two colpostats as point sources and each centimetre of the 6 cm long tandem as six separate point sources, the contribution from all the three sources to point A was calculated. The K-factor of ^{137}Cs was taken as 3.28 R-hr mCi-1 at 1 cm. The Roentgen to Rads conversion factor as 0.957. Using the inverse square law, the summation of each point sources to point a was approximately:

$$\frac{2446}{6}\left(\frac{1}{4.6^2}+\frac{1}{3.8^2}+\frac{1}{3^2}+\frac{1}{2.9^2}+\frac{1}{2^2}+\frac{1}{2.4^2}+\frac{1}{2.4^2}+\frac{1}{2.9^2}\right)+\left(830x\frac{1}{5^2}\right)+\left(835x\frac{1}{3^2}\right)=487.6x3.28x0.957=1531Rhr^{-1}$$

The same distributions of sources and calculations using both the anteroposterior and lateral films entered into the computer gave 1750 R hr^{-1} which was within 15% range of the manual calculation. With the lateral anteroposterior films taken after insertion of the applicators, dose to point A was calculated and the time to deliver 7 Gy to point A was calculated, which was about 21 minutes on our Curietron.

2.4 LDR INTRACAVITARY BRACHYTHERAPY IN HARARE PATIENTS

The 104 Harare patients all had EBT on 6 MeV linear accelerator in two phases, and the total dose ranged from 42 - 50 Gy at 2 Gy/fraction, five days a week. Following the completion of EBT, intracavitary insertions were done within two weeks. These patients were treated with the conventional low-dose-rate manual afterloading ^{137}Cs sources. Patients were admitted on the day of the procedure, shaved and catheterised on the ward. Pre-medication was given 30 minutes before the procedure - IM Pethidine 100 mg and IM Valium 10 mg stat. They were cleaned and draped in the theatre, vaginal examination done to assess disease status and uterus sounded with the uterine sound to determine the depth. Amersham applicators - one uterine tandem and two vaginal colpostats of appropriate size were then inserted and packed adequately anteriorly and posteriorly. Manual afterloading done in a separate room on the ward designed for the purpose. Doses from IC insertion ranged from 25 - 28 Gy to point A in single insertions of between 60 - 67 hours, during which the patients were cautioned against active movements that could displace the source positioning.

2.5 CLINICAL PROCEDURE USED FOR INTRACAVITARY BRACHYTHERAPY FOR MPILO PATIENTS

Patients who had intracavitary insertions were admitted on the morning of the procedure. The external beam treatments were omitted that day. They were pre-medicated with Tabs Diazepam 10 mg and IM Pethidine 100 mg 30 minutes before the procedure. After cleaning and draping the patient, pelvic examination was done on all of them to assess the degree of tumour regression. Uterus was then sounded using uterine sound to determine the appropriate length of uterine tandem to be used. The appropriate length of the tandem and the two vaginal colpostats were then inserted and clipped together. This was followed by packing anterior and posteriorly as much as possible. The applicators were then connected to the source.

In the first few patients, AP and lateral films were taken after insertion of the applicators to ensure the positioning of the applicators and to assist the physicist in calculating the dose to point A. This was however discontinued due to poor quality picture obtainable from the old machine available in the Curietron room. Since the treatment time was quite short and patients' movement minimal (all patients were advised to stay still during treatment and were also monitored outside the Curietron room through the remote television camera installed in the room). It was assumed that position of the applicators if placed properly in the first instance, would not have changed enough to affect the dosimetry significantly during the short treatment time. Most of the patients had 7 Gy delivered to point A on two occasions this way. Thirty one had their two doses while on EBT, twenty four had one during and one after EBT, and seven had vault caesium, also during EBT. Two had 8 Gy at the initial stage and some patients with vaginal stenosis had their dose reduced to 5 - 6 Gy to prevent overdosing the rectum. Those who had had previous surgery had only the vaginal colpostat inserted and packed adequately. A dose of 20 Gy to 0.5 cm depth was delivered to the vaginal mucosa in this way. After the procedure, applicators were removed and patients moved to the ward attached to the Curietron room to rest for the day.

2.6 ACUTE SIDE EFFECT SCORING

Since the study was aimed at monitoring the acute side effects the patients suffer from during treatment, they were all seen at least once weekly in the on-treatment clinic to assess their progress, elicit any complaints and treat as appropriate. Similar information was retrospectively analyzed from the case files of the Harare patients treated with LDR. The main symptoms sought for were diarrhoea, dysuria, nausea and vomiting, skin reaction, any vault narrowing or vagina stenosis during examination, and haematuria. Acute side effect was defined as side effects noticed or treated within 90 days after the commencement of treatment. Late side effect was regarded as those noticed 90 days or more after completion of treatment - though late side effect was not assessed in this study. The side effects were graded according to RTOG/EORTC acute radiation morbidity scoring criteria for bladder and small/large bowel since these were the major symptoms most patients complained of. This is shown in Table III.

TABLE III - RTOG/EORTC ACUTE RADIATION MORBIDITY SCORING CRITERIA

Grade 1 -	Minor symptoms requiring no treatment.
Grade 2 -	Symptoms responding to simple out-patient management. Life style (performance status) not affected.
Grade 3 -	Distressing symptoms altering life style (performance status). Requiring stoppage of treatment, hospitalization for diagnosis, or requiring minor surgical intervention.
Grade 4 -	Major surgical intervention or prolonged hospitalization or prolonged stoppage of treatment required.
Grade 5 -	Fatal complications.

2.7 FOLLOW-UP STUDIES

Following completion of treatment, patients were seen six weekly for three months, two monthly for six months and thereafter two to three monthly for two years. Patients were questioned for complaints and were examined for tumour status, skin reactions, vaginal or vault stenosis or rectal problems. Follow-up period in this study ranged from six months for those treated early in the study to a few weeks for those treated only recently.

3 STATISTICAL ANALYSIS

Using a statistical package called NANOSTAT (developed by Professor Healy of the then London School of Tropical Medicine and Hygiene) the Chi-squared (X^2) values were used to find out whether there were any associations between the treatment and the side effects observed.

4. RESULTS

The Tumour characteristics are shown in Tables IV and V.

TABLE IV

Stage	Nº of Patients
TOTAL	62

TABLE V

Histology	Nº of Patients
Squamous Cell Carcinoma	59
Adenocarcinoma	2
Clear Cell Carcinoma	1
TOTAL	62

The radiation doses are shown in Tables VI and VII.

TABLE VI

EBT Dose to the Pelvis (Gy)	Nº of Patients
50	51
48	3
42	2
40	4
46	2
TOTAL	62

TABLE VII

Dose per Fraction to Point A (Gy)	Nº of Patients	
	1st Insertion	2nd Insertion
4 – 5	3	3
5 – 6	1	2
6 – 6.5	5	4
7	42	41
7 – 7.5	3	4
8	1	1
TOTAL	55	55

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4.1 ACUTE SIDE EFFECTS

Diarrhoea

As shown in Table VIII, 18/31 patients in group A (those had two IC during EBT) and 10/24 in group B (those who had one IC insertion during EBT and the other after) had grades I and II diarrhoea. P=0.35 and X^2 = 0.87- no statistically significant difference observed. In the LDR-Group-D, 28/104 patients had diarrhoea Grades 1 and 2.

Comparing the incidence of diarrhoea in HDR (groups A and B) and LDR Group D - Table IX - P = 0.0048 and X^2 (with two degree of freedom) = 10.67 showed a highly statistically significant; difference. Comparing the different arms of HDR with LDR (A vs D), P = 0.003 and X^2 = 8.97 - the difference is highly statistically significant, in contrast comparing B vs D, P= 0.24 and X^2 = 1.39 - no statistically significant difference observed.

Dysuria and Frequency

As shown in Table IX, 30/104 (29%) patients in the LDR group had dysuria and frequency during treatment, as compared to 3/55 (5.5%) patients (Table VIII) in the HDR group (P = 0.0011 and X^2 = 10.59, which is a highly statistically significant difference).

TABLE VIII

ACUTE SIDE EFFECTS IN HDR-TREATED PATIENTS ACCORDING TO STAGE:

DIARRHOEA GRADES I & II

A - 31		B - 24	
Stage	Diarrhoea Grades I & II	Stage	Diarrhoea Grades I & II
I	2/6	I	1/2
II	12/16	II	7/12
III^{B} Unilateral	2/4	III^{B} Unilateral	2/4
III^{B} Bilateral	1/3	III^{B}	0/3
III^{A+B}	1/2	III^{A+B}	0/3
TOTAL	18/31 (58%)	TOTAL	10/24 (42%)
A - DURING EBT No grade III and above diarrhoea seen in either group Skin - 6 patients: 3 Stage III, 1 Stage II, 2 Stage I Nausea & Vomiting - 4 patients *Dysuria - 2 patients		B - AFTER EBT Skin - 4 patients Vomiting - 3 patients Dysuria - 1 patient	

TABLE IX

ACUTE SIDE EFFECTS IN LDR-TREATED PATIENTS-ACCORDING TO STAGE-D-LDR-Total-104.

Stage	Diarrhoea	Dysuria & Frequency
I	2/5	2/5
II	11/29	6/29
IIIB Unilateral	3/17	5/17
IIIB Bilateral	8/24	6/24
IIIA+B	4/25	9/25
IVA	0/4	2/4
TOTAL	28/104 (26%)	30/104 (29%)

TABLE X

PATIENTS WHO RECEIVED HDR RADIOTHERAPY FOLLOWING SURGERY-C

Total - 7 patients
Dysuria - 2/7
Diarrhoea - 6/7

5 DISCUSSION

5.1 ACUTE SIDE EFFECTS

Diarrhoea was the most common acute side effect that was noticed in the patients treated with EBT plus two intracavitary insertions (C - 58%, A - 42%) and most were grades I and II. Only two of the patients had grade III diarrhoea. In one of them the diarrhoea persisted for the whole duration of the treatment time. One had persistent diarrhoea over 3 months after the completion of treatment and this patient turned out to be HIV positive, which explained the persistent nature of her diarrhoea. Fifty eight percent of those who had their insertion during EBT had grades I - II diarrhoea, as compared with 42% of those who had it after. Diarrhoea in LDR patients occurred also in 26% of patients.

That diarrhoea was more common in those who had their IC insertions during EbT than in those who had it after is not unexpected, since they had their irradiation to the large and small bowel within a shorter overall treatment time. Dysuria is generally a less common complaint amongst patients treated with HDR brachytherapy and occurred in only three patients. That dysuria was less common in these groups of patients compared to 29% in LDR patients may be explained. Since they did not require hospital admission, bed rest with catheterization, their chances of developing urinary tract infection was smaller.

Other side effects were less common. Six patients in group A had minor skin exfoliation/ulceration and four patients in group B.

Buttock crease ulceration was rare since most of the patients were treated in prone and supine positions, which reduce the chance of gluteal ulceration. Nausea and vomiting were also not common in both groups.

When the acute side effects in patients with HDR were compared with those treated with LDR in Harare, it was also observed that diarrhoea was commoner in HDR patients (A - 58%, B - 42%) as compared to 26% in LDR patients ($P = 0.0048$ and $X^2 = 0.67$). By contrast, LDR patients had a higher incidence of dysuria and frequency - 29%, as compared to three patients (5%) in the HDR-treated group ($P = 0.001$ and $X^2 = 10.59$. The incidence of diarrhoea was considerably lower in LDR patients, perhaps because these patients were apparently getting much lower dose rate to their bowel but the incidence of dysuria and frequency was greater , perhaps because all of them required catheterisation for their treatment with increased urinary-tract trauma and infection (while HDR patients were not catheterized and had their treatment completed within 30 minutes).

Six of seven patients who had had previous surgery had diarrhoea grade I and II, and 2/7 had dysuria. This was in keeping with the known fact that previous abdominal surgery is associated with higher complication rates in pelvic irradiation (Perez and Brady).

Post treatment, over 90% of the patient were without evidence of residual disease at first review and non of the patient has had recurrence following subsequent review.

5.2 PALLIATED CASES

Table II shows the breakdown of 32 patients not included in HDR group in Bulawayo during the same period. Twelve of them had no radiotherapy treatment, nine because they had had fistula already, their pain was controllable with morphine and they were bleeding actively. Those with bulky II^{B} disease, III^{A+B} disease and III^{B} bulky disease treated palliatively had a poor response to treatment despite high dose of palliation given - 3750 Gy/10 fractions, 40 Gy/15 fractions and 50Gy/20 fractions. 18/32 (56%) of these patients had persistent disease n follow up. They probably would not have done better on intracavitary insertions, because they were all assessed midway and towards the completion of EBT for fitness for intracavitary insertions. With residual disease on cervix ranging from 3-6 centimetres in diameter and parametrial residual disease, it was preferable not to give intracavitary treatment.

5.3 TIME SCHEDULE FOR HDR INTRACAVITARY TREATMENT

Overall treatment time is quite important in radiotherapy of carcinoma of the cervix, as in head and neck cancer. This was one of the reasons why some of the patients treated had their first IC insertion given before completion of EBT. The overall treatment time in most of these patients was less than 6 weeks. This was in keeping with the current Pattern of Care study in patients with carcinoma of the cervix (Lanciano et al, 1992). They evaluated 837 patients in a multivariate analysis of overall time, stage, Karnofsky status and dose of irradiation.

TABLE XI

OVERALL TREATMENT TIME (O.T.)

< 6 weeks	22%
6 - 8 weeks	41%
8 - 10 weeks	22%
> 10 weeks	15%

TABLE XII

RESULT AT 4 YEARS - LANCIANO ET AL

	<6/52	6 - 8/52	8 - 10/52	>10/52
Pelvic recurrence	6	12	15	20
Survival (%)	81	74	73	76
Major complications	15	11	12	17

They also showed that in field recurrence and survival were independent prognostic factors and paracentral doses > 75 Gy have greater complication rates as compared to doses less than 75 Gy. This study supported our practice of keeping our overall treatment time as reasonably low as possible, since the shorter the overall treatment time, the lower the pelvic recurrence rate the better the survival and complications are not significantly worse than for those treated with longer overall treatment time. Review of the literature showed that treating patients with EBT and concomitant IC is quite a common practice worldwide, as shown in Table XIII. External beam doses ranging from 29 to 67 Gy additional to intracavitary insertions, as many as 6, utilizing 6 - 7 Gy/fraction had been utilized by many authors

TABLE XIII

HDR BRACHYTHERAPY FOR CARCINOMA OF THE CERVIX: DOSE FRACTIONATION SCHEDULE

1st Author (Country)	Dose/Fx at Pt A (Gy)	No of Fx	No of Fx/Week	Dose (Gy)	Timing
Glaser (Germany)	6 - 7	5 - 6	1	40 - 50	A
Vahrson (Germany)	6 - 14*	3 - 7	.5 - 1	45 - 46	C
Cikaric (Yugoslavia)	9 - 10	4	1	35 - 46	C
Akine (Japan)	3 - 5	5 - 6	2 - 3	29 - 67	B
Himmelman	8.5+	5	1	40 - 50	A
Kuplers (Netherlands)	8.5	2	2	46	B
Sato (Japan)	6.1	5	1	50 - 60	B
Shigematsu (Japan)	8 - 10	3	1	40	C
Taina (Finland)	7.5 - 10	3 - 5	1	50	A
Aral (Japan)	3 - 7	4 - 13	1 - 3	45 - 65	A
Joslin (UK)	8.5	2 - 5	1	24 - 45	C, B
Mizae (Japan)	5.0	6 - 7	2	40 - 50	B
Ilic (Yugoslavia)	9 - 10.5	4	1	27	C
Teshima (Japan	7.5	3 - 6	1	14 - 40	C
Utley (USA)	5 - 6.6	6 - 10	2	20 - 50	C
Newman (UK)	7 - 8.5	2.5	1	22 - 63	C
Choi (Hong Kong)	7 - 8	3	1	40 - 58	C

A = After; B = Before; C = Concurrent with brachytherapy

* Dose - maximum on the A-line (or A-plane) 2 cm lateral from the central axis of the applicator

+ Dose at the surface of the target volume

The majority of centres worldwide utilize a schedule of three to six insertions of 7 - 8 Gy per week. The external beam dose was variable worldwide and dependent on the stage of disease. In most countries, the intracavitary brachytherapy was carried out concurrently with or after external beam irradiation. In three centres, it was given before external beam irradiation. Significantly better survival for HDR group, local control rate comparable, and in some cases, better than LDR group were recorded by most authors,. Most individual institutions also showed comparable late complication rates between LDR and HDR, except a few. Cikaric et al 1988 in their series showed a higher complication rate with the LDR technique. The rectal complication was significantly higher in the LDR group, in this series - 7.1% for HDR and 16.6% for LDR, with a $p < 0.01$. They also showed that the bladder complication rate was lower in the HDR group - 5.0% - than the LDR group - 9.6% with $p< 0.01$, which was quite significant; the reason for this unusual finding was not stated.

(Choi et al 1992) in Hong Kong in their studies showed an unexpectedly high and unacceptable high complication rate with their HDR technique. In their study, they gave EBT to the whole pelvis - 46 Gy/23 fractions and 3 weekly applications of HDR intracavitary brachytherapy of 7 or 8 Gy per fraction to point A. Their results showed good local control rate and survival rate comparable with other studies, but late complications developed in 47% (65/137) of their patients. Grade III or above complications occurred in the bladder, small bowel and sigmoid colon/rectum in 5%, 3% and 7% of patients respectively.

They found that patients aged above 60 years and stage III disease were adverse determinants for survival by multivariate analysis. The most significant determinants of severe rectal complications in this study were:

1) Addition of a lower vaginal tandem ($p < 0.01$) which increased the volume of the rectum receiving high dose;
2) Uterine source length greater than 5 cm;
3) A total biological effective dose to the rectum of more than 120 Gy;
4) Stage III disease.

Literature review showed that 7 Gy to point A in 2 doses is not only tolerable for most patients, but more on the side of being too little. This study did not show any higher acute side effect with this dose, neither did any study show this. Also, late effect from 7 Gy/fraction in 3 insertions did not show worse complication rates. It is however important to examine factors associated with higher complication rates in Choi et al's study:

1) They used lower vaginal tandem we feel the vault ovoids are adequate to prevent vault recurrence.
2) Our uterine sources length are both longer than 5 cm. A 4 cm source would be desirable.
3) Most of our patients come with stage III disease and we do not have influence over this, as early presentation might still take some time to be the norm in our environment.
4) We do not know or estimate the biologically effective dose to the rectum in our practice, because of lack of diagnostic equipment, e.g. TLD.

In order to minimise late complication rates, one option is to reduce our dose per fraction to 6 Gy and give at least three insertions. This may be difficult given the number of D & C sets at our disposal and the staff establishment, but these are surmountable problems.

In view of the fact that 7 Gy per fraction given to most of our patients now is tolerable in terms of acute side effect and most centres giving such doses reported acceptable late effects, it is my recommendation that we continue to give 6 Gy/ fraction and give three insertions at weekly intervals, preferably two insertions during EBT and one after, reducing our overall treatment time 6 to 7 weeks maximum.

This is an exploratory study with the aim of studying the acute side effects in HDR brachytherapy patients. While it was found that the acute side effects were tolerable and not significantly higher than LDR, it must be borne in mind that the disadvantage of HDR does not really lie in the acute side effects but in the late complications. This could not be studied at this time in our centre with our less than one-year experience in the sue of HDR brachytherapy. Most late complications in patients treated with HDR appear from one to four years after the completion of treatment. Further work is therefore suggested to analyze late complications that develop in our HDR patients and compare these with those of patients treated with LDR.

6 CONCLUSION

Acute side effects of HDR as given in our centre in Bulawayo - 7 Gy/fraction and two insertions (either both during EBT and one during and one after EBT) - are of low grade and tolerable. An increased number of insertions to three insertions (two during EBT - second and third week - and one immediately after completion of EBT) and dose reduction to 6 Gy/fraction is suggested. This however is a higher dose of irradiation which may require slight reduction in the EBT dose to 45 Gy or 46 gy maximum. It is therefore recommended that HDR remote control afterloading treating continue in Bulawayo using three insertions each of 6 Gy given at weekly intervals, the first two during the course of EBT dose, keeping overall treatment time under seven weeks. Further work is indicated to assess the frequency of late complications of HDR and compare these with those of LDR.

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