RESEARCH COMMUNICATION

# Treatment of Cervical Carcinoma with High-Dose Rate Intracavitary Brachytherapy: Two Years Follow-Up Study

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## Abstract

**Aims: This study focused on pelvic recurrence rate and late complications following treatment with high dose rate brachytherapy with a three fractionation scheme. Setting and design: This retrospective observational study was conducted from 1st November 2003 to 31st March 2005 at a tertiary care centre. Methods and materials: Women were treated with external beam radiotherapy and three fractions of high dose rate brachytherapy, divided into two broad groups IIB+ IIIA and IIIB+IVA. Duration of follow-up was 2 years and main outcome measures were recurrence and rectal and urinary bladder complications. Results were assessed with the Chi square test and P-values using an alpha level of 0.05 for Type I error. Results: Of the total of 286 women, 72 (25.4%) developed central-regional recurrence. Overall two year pelvic control rate was 74.6%, with values of 78.1% and 72.8% for stages IIB+ IIIA, IIIB+IVA, respectively. Five women developed distant metastasis and 21.5% suffered low grade rectal complications. After two years the prevalence of bladder complications was only 5.4%. Conclusion: Using a three fraction scheme, high dose rate brachytherapy is safe and effective in the management of cervix cancer.**

**Keywords:** Cervical carcinoma - high-dose rate intracavitary brachytherapy - radiation proctitis - complications

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## Introduction

Radiation therapy alone is considered as the standard treatment of most stages of cervix cancer. It can be delivered through the combination of external beam radiotherapy (EBRT) and intracavitary brachytherapy. The function of brachytherapy is to deliver a high radiation dose directly to the tumor while sparing the adjacent normal tissues. High-dose-rate (HDR) brachytherapy was developed to overcome some potential disadvantages of low-dose rate (LDR) brachytherapy, such as radiation exposure of the professional staff, prolonged treatment time, need of hospitalization, risk of anesthesia, bed immobilization that can lead to thromboembolism, discomfort of vaginal packing and displacement of the applicators (Orton et al,1991).

The HDR brachytherapy unit was installed in 2003 at our institution and the HDR brachytherapy unit began on November 2003. Until March 2009, more than 10000 procedures were performed, and the most frequent application was in the treatment of uterine cervical cancer. India has a high incidence of cervical carcinoma, representing the most frequent malignant neoplasm and cancer-related cause of death among women. In the year 2004, national estimate was 112,609 new cases cancer cervix, corresponding to an incidence of 26.1% new cases among all cases of cancer among women ( Krshnan et al ,2005). Furthermore, due to the problem of the waiting list for hospitalization, many patients with cervix cancer have their wait for treatment with LDR brachytherapy excessively prolonged. The advent of HDR brachytherapy in our Institution, which has the advantage of rigid immobilization, outpatient treatment, patient convenience, and potential cost savings, (Bastin et al.,1993; Petereit and Pearcey, 1999) brought a convenient treatment option for patients with cervix cancer. As a result, a large number of women are treated in short period and thereby lessening the social problem arising out of the disease process.

Although many decades of experience and literature reports on the use of HDR brachytherapy for treatment of cervix cancer are available in world literature, not many contributed from Indian scenario. More over, a wide range of fractionation schedules exists and the optimum treatment scheme still remains unclear. This retrospective analysis aimed to report our experience with HDR brachytherapy in the treatment of patients with cervical cancer, analyzing the dose effectiveness and incidence of late complications with the fractionation schedule used.

## Materials and Methods

This was a cross sectional observational study with

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retrospective data obtained from patient medical records. Study was conducted during the period of 1st November 2003 to 31st March 2005 in a tertiary care centre to evaluate the pelvic recurrence rate and late complications for high dose rate intracavitary (HDR-IC) brachytherapy in the treatment of cervical carcinoma using a three fraction scheme. Women were included in the study if they were registered for treatment of carcinoma cervix with external beam radiotherapy and three fractions of high dose rate brachytherapy. Women were excluded from the study if (a) they did not complete treatment protocol (b) they had prior surgical treatment (c) presented with distant metastasis and were treated with palliative intent. Analysis was undertaken with prior approval of Ethics Committee of our Institution.

Staging of cancer cervix was done according to the International Federation of Gynecology and Obstetrics (FIGO) criteria. Staging was performed in all patients through chest radiograph, i.v. pyelography (IVP), blood chemistries, cystoscopy, and rectosigmoidoscopy.

All patients were treated initially with external beam irradiation. Whole pelvic irradiation was administered with Co60 $\gamma$ ray through anterior-posterior parallel opposing ports (AP/PA) with a field size of 14-16 to 16-17 cm. The dose to the central cervix was 40 Gy. An additional boost of 10-20 Gy in 5 to 10 fractions was given to the bilateral pelvic wall through AP/PA ports with a 5cm midline block to shield the central structure.

HDR- ICRT was given one week after external beam irradiation.. In operation theatre, tumor regression was evaluated and endocervical canal was dilated. A urinary catheter with 7cc. urograffin filled balloon was installed to outline the posterior bladder wall. Length of uterine cavity was measured with uterine sound and an applicator inserted. Ovoids were separated, according to the patient's vaginal anatomy. At the end of the procedure, rectal separator inserted, vagina was tightly packed with contrast soaked gauges. A flexible lead bead wire was inserted in the rectum to indicate the anterior rectal wall. Orthogonal films were then taken for therapy planning and dose calculation done. The entire procedure, including application, simulation, dose calculation, and treatment delivery, can be accomplished within 50-70 minutes.
The HDR-ICRT facility was a micro-Selectron system ( Nucletron co., Holland ) employing Ir-192 sources. This unit is a computer controlled remote after loading device equipped with 18 source channels, a single hopping source for central tandem and two ovoids. Mechanically, this unit allowed for a stepwise fine adjustment, for source dwell in central tandem and ovoids. The applicator was modified Fletcher Suit type, consisting of one curved central tandem and two shielded ovoids.

The standard dose per fraction in patients (97%) was 7Gy. In total 21Gy in 3 fractions was given to point 'A' with each fraction spaced 1-2 weeks apart. Minor modifications of dose per fraction to 6.5 Gy were justified in, senile patients associated with chronic comorbid conditions (3%).

Our programme of quality assurance, source calibration, and brachytherapy planning were done. The basis of optimization has been empirical and partly extended from the Low Dose Rate-Intracavitary technique. The concept of differential loading in tandem was generally applied to our treatment. This was achieved by modulating the weight of the dwell time. On the orthogonal films, brachytherapy planning was performed with PLATO (Nucletron co., Holland) computer treatment planning system.

After the completion of treatment, patients were regularly followed-up at the department of radiation oncology and gynaecological oncology for up to two years. Follow-up was performed every 3 months following completion of treatment. Clinical examination was done and cervical cytology was taken at each follow-up. Chest radiograph and abdomino pelvic CT were done every 6 months or when clinically required. Local recurrent disease was histologically confirmed in all women. Local recurrence was considered if disease was detected centrally or in the parametrium within the true pelvis. Recurrences were defined as distant if they occurred in the para-aortic lymph nodes or elsewhere outside the pelvis. Follow-up time was defined by the interval between the first day of radiotherapy and the last information about the patient. Patients considered lost to follow-up who did not return after initial appointments. Patients with rectal or bladder complications were evaluated and managed by proctologist or urologists. Toxicity was graded according to the Common Toxicity criteria by RTOG ( Cox et al 1995). For a meaningful analysis, the small number of patients with stages IIA, IIIA, IVA were merged with stages IB, IIB and IIIB respectively and subsequently women were divided in two broad groups IIB+ IIIA and IIIB+IVA . Rectal and bladder complications were expressed as prevalence rate. The data were analyzed with SPSS software and Microsoft excels software. Results were calculated applying Chi square test and calculating the P-value using an alpha level of 0.05 for Type I error.

## Results

Between November 2003 and March 2005, 488 women were registered for treatment of carcinoma cervix. Three hundred six women were treated with external beam radiotherapy and three fractions of high dose rate brachytherapy and included in the study. One hundred eighty two women were excluded from study .Reasons were (a) 75 women did not complete treatment protocol amongst which 58 patients had only external irradiation without brachytherapy, (b)69 women were post operative and (c)38 women presented with distant metastasis and were treated with palliative intent. Out of 306 patients 20 patients of IB and IIA were again excluded from final analysis as they were lost to follow up. Therefore 286 women were evaluated who had maximum two years follow-up.

Table 1 shows the clinical presentation, tumor characteristics and type of treatment provided to the women. Pretreatment evaluation revealed the distribution of squamous cell carcinoma, adenocarcinoma and adenosquamous cell carcinoma between the two groups IIB+IIIA and IIIB+IVA were not statistically significant. An analysis of symptom and sign at presentation like

**Table 1. Patients, Tumour and Treatment Characteristics**

| Variables | Total | IIB +IIIA | IIIB+IVA |
|---|---|---|---|
| Number | 286 (100%) | 98 (34.0%) | 188 (65.7%) |
| Pathology | | | |
| Squamous cell | 258 (90.2%) | 90 (91.8%) | 168 (89.4%) |
| Adenocarcinoma | 15 (5.2%) | 4 (4.1%) | 11 (5.9%) |
| Adenosquamous | 3 (4.5%) | 4 (4.1%) | 9 (4.8%) |
| Tumour type | | | |
| Proliferative | 158 (55.2%) | 59 (60.8%) | 99 (52.7%) |
| Ulcerative | 93 (32.5%) | 22(22.7%) | 71 (37.8%) |
| Infiltrative | 34 (11.9%) | 16(16.5%) | 18 (9.6%) |
| Symptoms and signs at presentation: | | | |
| Bleeding P/V | 286 (100%) | 98 (100%) | 188 (100%) |
| Back pain | 282 (98.9%) | 98 (100%) | 184 (98.4%) |
| Pain abdomen | 202 (70.6%) | 62 (63.3%) | 140 (74.5%) |
| Karnofsky performance score | | | |
| 70-80 | 10 (3.5%) | 3 (3.1%) | 7 (3.7%) |
| 81-90 | 53 (18.5%) | 15 (15.3%) | 38 (20.2%) |
| >90 | 223 (78.0%) | 80 (81.6%) | 143 (76.1%) |
| External beam irradiation, EBRT dose: | | | |
| 40-45Gy | 20 (7.0%) | 6 (6.1%) | 14 (7.5%) |
| 46-50 Gy | 28 (9.8%) | 10 (10.25) | 18 (9.6%) |
| 51-55Gy | 82 (28.3%) | 23 (23.5%) | 58 (31.0%) |
| 56-60Gy | 156 (54.5%) | 59 (60.2%) | 97 (51.9%) |

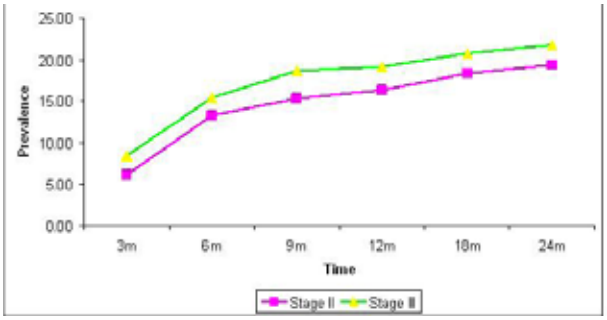


**Figure 1. Failure Rates in the Two Groups over Time**

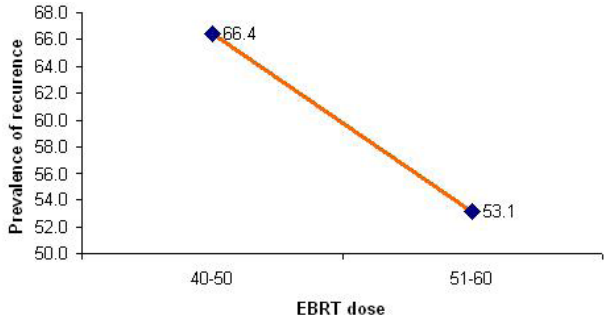


**Figure 2. Relation of EBRT Dose to the Prevalence of Recurrence**

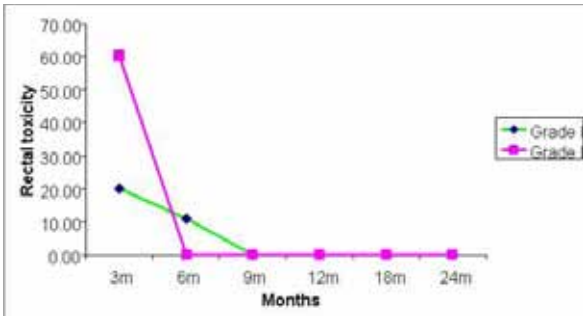


**Figure 3. Prevalence of Rectal Toxicity**

**Table 2. EBRT dose, Pelvic Recurrence and Distant Metastasis by Stage of Disease**

| Stage | IIB +IIIA | IIIB+IVA | Total |
|---|---|---|---|
| Recurrence | 21(21.9%) | 49 (27.2%) | 70 (25.4%) |
| Distant metastasis | 2 (2.1%) | 3 (1.7%) | 5 (1.9%) |

bleeding p/v, back pain and pain abdomen, among the therapeutic groups failed to indicate any statistically significant difference. Karnofsky performance status was evaluated throughout the study and revealed no statistically significant difference between two groups . The distribution of tumour type i.e. Proliferative, ulcerative and infiltrative and differentiation have no statistical difference between abovementioned two groups. Seventy three patients (25.4 %) had central and/or regional recurrence at 3 to 24 months (median 13).The two years pelvic control rate was 74.6%. Five patients (1.9%) developed distant metastasis at 3 to 24 months (median 19 months). Patterns of pelvic recurrence and distant metastasis by stage are listed in Table 2.

Pelvic recurrence rate of 27.2% at two years for IIIB+IVA group was always higher than that of IIB + IIIA (21.9%) and shows an upward trend than the later group (Figure 1). The patterns of failure were studied for all women. Out of 286 women, 73 women (25.4%) developed local failure in the pelvis, and 5 women (1.9%) developed both local failure in the pelvis and failure at distant sites. The most common site of distant metastasis was lung followed by bone. When the final result tabulation was done, 32 patients (11.1%) died. The cause of death in all the patients were due to distant metastasis to lung followed by bone and liver.

EBRT dose given were variable between 50 to 60Gy with midline shielding at 40Gy.Few patients also received 40 & 45 Gy.There is no significant difference in dose received between two groups. Pelvic recurrence rate falls, with increasing EBRT dose (Figure 2).

Sixty (60) patients (21.5%) developed grade 1-3 rectal complications. None had grade 4 complication and none of the patients developed rectovaginal fistula related to treatment. The prevalence of grade 1-3 rectal complication was 50 (17.9%); 5 (1.8%); 5 (1.8%) respective ( Fig -3 ). Peak onset was at 3 months. All these women responded well with conservative treatment. Proctitis and rectal discomfort can be alleviated by suppositories containing sucralfate and small enemas with hydrocortisone. A low residue diet with no spices and increased fibre in the stool help to decrease gastro intestinal symptom.

Fifteen patients (5.2%) developed cystoscopy proven radiation cystitis. None of the patients developed vesicovaginal fistula. The onset of radiation cystitis was relatively late and the range was (10-24 months). Bladder complication by grade was gr1-3 was 10 (3.6%); 3(1.1%) and 2 (0.7%).

## Discussion

Over the past twenty years, the clinical perspective to HDR intracavitary radiation therapy in the radical treatment of carcinoma cervix has changed significantly.

A meta-analysis of twenty published reports comparing HDR-IC and LDR-IC concluded that treatment results are comparable or slightly superior to LDR-IC( Orton 1993). Many non-randomised and major randomized trials by Shigematsu et al(1983) and Patel et al (1994) have demonstrated that HDR brachytherapy is an equal alternative to conventional LDR brachytherapy in the treatment of carcinoma cervix. Despite these randomized trials, routine HDR use has been questioned because of a narrow therapeutic window, and lack of consensus on fractionationation (Eifel, 1992).

The optimal fractionation scheme in HDR-IC is not well established (Fu and Phillips 1992).Although no clear consensus of the appropriate number of fractions or the dose per fraction has been reached, various fractionation schemes have been used experimentally in search of the optimal technique. Most institutions have restricted this range to between two and seven fractions and fraction size between 4 to 10 Gy. The current scheme, 7Gy for three fractions, in our institution has been based on the work of Chen et al ( 1991). Treatment results of two years and pelvic control rate of 74.6% in our 286 patients according to this schedule appeared to be comparable to the study conducted by Marcial et al (1983). In the study by Patel et al (1994), 24.3% had locoregional failure, 6.44% had distant failure only in locally advanced carcinoma cervix, receiving brachytherapy. Our results are also comparable and acceptable with existing results of LDR-IC (Teshima et al., 1987; Horiot et al., 1988).

The primary disadvantage of HDR brachytherapy is the potential late toxicity of large dose per fraction. Akine et al (1988) and Teshima et al (1988) reported a 27% rectal complication rate in patients treated with HDR-IC. Rectal complications were categorized as mild (low grade) and severe (high grade).Severe complication required intensive medical and surgical treatment and most reports presenting both HDR-IC and LDR-IC results observed a significant reduction of severe complication rate in HDR treated patients. In our study, estimated rectal complication rate, calculated by prevalence, the incidence of gr-3 was 1.8% (5 patients) and gr-4 complication were not found; at two years. The two years, prevalence rate for (gr1 and gr2) complications were 17.9% (50 patients) and 1.8% (5patients) respectively. The reason for the paradoxically increased low-grade rectal complications may be a clinical reflection of the biological disadvantage of HDR-IC with this fractionation. The therapeutic ratio of HDR-IC is known to be narrow. The window could be further widened by appropriately increasing the number of fractions.

Shigematsu et al (1983) has depicted 2% bladder toxicity at 3 years and 5% rectal toxicity at 3 years. Teshima et al (1987) also showed 4.2% bladder toxicity at 3 years & 6.4% rectal toxicity at 3 years, similar to our study. Considering our results of recurrence and late toxicities, HDR intracavitary brachytherapy using 7 Gy /fraction for 3 such along with EBRT is a quite feasible option in the management of locally advanced carcinoma of cervix uteri. The end point in any clinical trial is survival. Our results are not matured enough to comment on survival and incidence of late toxicities yet. Nevertheless, there was 88.9% survival in patients in our study. Further inclusion of patients and prolonged follow-up is required to arrive at more decisive results.

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