Original article

# Biological effective doses in the intracavitary high dose rate brachytherapy of cervical cancer

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## Abstract

**Purpose:** The aim of this study is to evaluate the decrease of biological equivalent dose and its correlation with local/loco-regional control of tumour in the treatment of cervical cancer when the strength of the Ir-192 high dose rate (HDR) brachytherapy (BT) source is reduced to single, double and triple half life in relation to original strength of 10 Ci (~ 4.081 cGy x $m^2$ x $h^{-1}$).

**Material and methods:** A retrospective study was carried out on 52 cervical cancer patients with stage II and III treated with fractionated HDR-BT following external beam radiation therapy (EBRT). International Commission on Radiation Units and Measurement (ICRU) points were defined according to ICRU Report 38, using two orthogonal radiograph images taken by Simulator (Simulix HQ). Biologically effective dose (BED) was calculated at point A for different Ir-192 source strength and its possible correlation with local/loco-regional tumour control was discussed.

**Result:** The increase of treatment time per fraction of dose due to the fall of dose rate especially in HDR-BT of cervical cancer results in reduction in BED of 2.59%, 7.02% and 13.68% with single, double and triple half life reduction of source strength, respectively. The probabilities of disease recurrence (local/loco-regional) within 26 months are expected as 0.12, 0.12, 0.16, 0.39 and 0.80 for source strength of 4.081, 2.041, 1.020, 0.510 and 0.347 cGy x $m^2$ x $h^{-1}$, respectively. The percentages of dose increase required to maintain the same BED with respect to initial BED were estimated as 1.71, 5.00, 11.00 and 15.86 for the dose rate of 24.7, 12.4, 6.2 and 4.2 Gy/hr at point A, respectively.

**Conclusions:** This retrospective study of cervical cancer patients treated with HDR-BT at different Ir-192 source strength shows reduction in disease free survival according to the increase in treatment time duration per fraction. The probable result could be associated with the decrease of biological equivalent dose to point A. Clinical end point of this study is more significant from double half life reduction of original source strength.

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**Key words:** HDR brachytherapy, cervical cancer, biological effective dose, dose rate.

## Purpose

Among the therapeutic modalities available for the treatment of cervical cancer, irradiation is regarded to be the standard treatment for all tumour stages [1-4], which includes external beam radiation therapy and brachytherapy, or a combination of these two. The curative potential of radiation therapy in the management of cervical cancer is greatly enhanced by the use of intracavitary brachytherapy (ICBT) [1-4]. Brachytherapy is normally used either alone or, more commonly, as a part of a multi-modality approach with EBRT, surgery, and/or chemotherapy. In a typical radiotherapy department, about 10-20% of all radiotherapy patients are treated with brachytherapy [5]. Commonly, brachytherapy is used with EBRT to locally increase the dose to an area at greatest risk for tumor recurrence, such as the original distribution of gross tumor or to the tumor bed at a surgical resection site. High dose escalation is possible with ICBT at the site with greater therapeutic ratio, which may not be possible even with EBRT using intensity modulated radiotherapy or image guided radiotherapy. The American Brachytherapy Society (ABS) strongly recommends that radiation treatment for carcinoma of cervix (with or without chemotherapy) should include brachytherapy as a component of treatment [6]. There is a good relationship between the total dose delivered to the tumour and local tumour control [3, 4, 7, 8]. At the same time, the complication rate of the surrounding healthy tissue/critical organs also has a positive correlation with the radiation dose received [9-12]. Inadequate dose delivery to the treated volume is frequently identified as a possible cause for local failure [7, 8]. Radiotherapy plans based on physical dose distributions do not necessarily reflect on the biological effects under various fractionation schemes. Traditionally, the BED method has been used to assess the biological effectiveness following irradiation of tissues. The linear-quadratic (LQ) model is used by radiologists as a convenient tool to quantify biological effects of radiotherapy [13-16]. The two radiobiological parameters namely the '$\alpha/\beta$' ratio and the half life ($T_{1/2}$) of repair of the relevant tissues together with other possible

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factors are also employed in the determination of biological dose reduction when changing from low dose rate (LDR) to medium dose rate (MDR) or HDR [14, 16]. Cervical cancer patients treated with Ir-192 HDR brachytherapy source with an initial strength of about 10 Curie need to change the radiation source for every 3-4 months to maintain appropriate dose rate. However, in resource crunch areas using the Ir-192 HDR source strength down up to triple or even fourth half life decay has been frequently observed. In this study we evaluated biological effective dose of the prescribed dose to point A of the Manchester system in the treatment of cervical cancer, when the strength of Ir-192 HDR brachytherapy source has been decreased to double, triple and fourth half life. It is also further discussed critically the need to maintain BED for local/loco-regional control of the cervical cancer.

## Material and methods

### *Patient selection*

Fifty two patients with squamous cell carcinoma of cervix (stages II – 38 patients and III – 14 patients) were selected for this retrospective study. All patients were treated from June 2009 to January 2011 in the Department of Radiotherapy, Regional Cancer Centre, Regional Institute of Medical Sciences, Imphal, India.

### *ICBT applicator placement and brachytherapy treatment planning*

Fletcher-Suit applicators (Nucletron) were used with appropriate ovoid's: half ovoid (15 mm and 20 mm – diameters) and full ovoid (20 mm – diameter) both with tandem angle of 15°, 30° or 45°. Combination of ovoid size and tandem angle were chosen according to patient's anatomy. Packing was done to avoid any shifting or changes in the geometry of the applicators placement and to prevent the relocation of the rectum and bladder. Brachytherapy treatment planning was done using Simulix Simulator (Nucletron) and Plato Sunrise Treatment Planning System (Nucletron). Dose prescription was done at point A of Manchester System using standard source loading pattern without optimization. In the planning process, rectal and bladder doses were planned to be kept below 80% of dose to point A for each planned fraction.

### *Treatment*

For external radiotherapy, telecobalt (Theratron 780C) was used by box technique and dose given was 44-50 Gy/22-25 fractions. Following a rest period of one week for the tissues to recover and to control any associated local infection (80% of the patients), but within 2 weeks for all patients HDR brachytherapy (Micro Selectron HDR) treatment was started delivering a dose of 7 Gy per fraction in 3-4 session. The whole treatment (external and brachytherapy) was completed within 8 weeks, except for 8 patients who completed within 9 weeks for which the BED lost due to additional few days in the overall treatment time were not considered in this study.

### *Clinical details*

Out of 38 patients of stage II, 37 patients (97.4%) and 12 patients of 14 patients of stage III (85.7%) achieved complete response, and partial response was seen in 1 patient (2.6%) of stage II and 2 patients (14.3%) of stage III at the end of the treatment. The follow up at 6 months/12 months post treatment showed 3/3 patients of stage II and 3/2 patients of stage III having local/loco-regional disease as seen clinically and by imaging modalities used. The median follow up of patients was 16 months (6-26 months).

### *Biological effective dose evaluation*

Biological effects (E) following to irradiation of tissues is determined by the surviving fraction of target cells [17, 18] as:

$$\begin{aligned} E &= -\log(\text{surviving fraction}) \\ &= -\log[\exp\{-(\alpha d + \beta d^2)\}] \\ &= \alpha d + \beta d^2 \end{aligned} \quad (1)$$

where $\alpha$, $\beta$ are the constants for linear and quadratic component of the surviving equation ($\alpha$ and $\beta$ are normally expressed in the units of $Gy^{-1}$ and $Gy^{-2}$, respectively) and $d$ is the radiation dose delivered to the tissue.
Eqn. (1) may be rewritten as:

$$E/\alpha = d[1 + d(\alpha/\beta)] \quad (2)$$

This $E/\alpha$ is term as biological effective dose (BED). One factor $g$ is introduced to compensate the incomplete repair during continues exposures in $\beta$ damage component, then

$$BED = d + g\{d^2/(\alpha/\beta)\} \quad (3)$$

where $g = \{2/(\mu T)^2\}\{\mu T - 1 + e^{(-\mu T)}\}$, $\mu = 0.693/T_{1/2}$, $T_{1/2}$ is half life time for repairing of tissues. $T_{1/2}$ is of crucial importance. As Thames *et al*. [19] suggest, the early reactions are characterized by a shorter repair half-life between 0.3 and 0.9 hours. Then the number of half-times of repair will give an approximate guide as to the completeness of sub lethal damage repair. The assumption of half life as 0.5 hour [20] and $\alpha/\beta = 10$ Gy for rapidly proliferating tumours (e.g. squamous cell cancer) [15, 20, 21] were used in this study. This value of $\alpha/\beta = 10$ Gy is in agreement with GEC-ESTRO recommendation [22]. GEC-ESTRO [22] also suggested that for the whole treatment, the total dose values should be reported as physical dose, indicating the fractionation and dose rate and, in addition, as biologically weighted dose ($EQD_2$, biologically equivalent dose in 2 Gy fraction). $EQD_2$ is logistically and conceptually equivalent to BED, but has numerical values which can be related directly to clinical experience as the method converts all treatments and partial treatments into isoeffective schedules of 2 Gy fractions [27].

## Results

The reduction factor of BED to single, double and triple half life decayed of original source strength and their respective percentage of fall in fractionation are given in Table 1.

**Table 1.** HDR-BT dose rate at point A, inter-fractional variation of BED for various treatment time (prescribed dose = 7.00 Gy)

| Source strength ($cGy \times m^2 \times h^{-1}$) | Dose rate at point A (Gy/hr) (Appx.) | Treatment time per fraction (min) | Inter-fractional variation (%) in BED w.r.t. 1st# | | | Average BED (4#) ± SD | BED change w.r.t. $BED_1$ (%) |
|---|---|---|---|---|---|---|---|
| | | | 2nd # | 3rd # | 4th # | | |
| 4.081 | 49.4 | 8.5 | 0.09 | 0.26 | 0.43 | 11.57 ± 0.02 | 0.00 |
| 2.041 | 24.7 | 17 | 0.35 | 0.62 | 0.88 | 11.27 ± 0.04 | 2.59 |
| 1.020 | 12.4 | 34 | 0.46 | 0.92 | 1.39 | 10.76 ± 0.06 | 7.02 |
| 0.510 | 6.2 | 68 | 0.69 | 1.39 | 2.08 | 9.99 ± 0.09 | 13.68 |
| 0.347 | 4.2 | 100 | 0.94 | 1.67 | 2.40 | 9.47 ± 0.10 | 18.13 |

*# – fraction, SD – standard deviation, $BED_1$ – biological effective dose corresponding to initial source strength (i.e. treatment time/# of 8.5 min)*

**Table 2.** Recurrence of disease in different treatment time schedule of cervical cancer

| Stage of cervical cancer | | Disease recurrence (total number of radiotherapy patients) for different treatment time schedule | | | |
|---|---|---|---|---|---|
| | | < 20 minutes | 20-40 minutes | 40-60 minutes | > 60 minutes |
| II | | 1 (15) | 2 (11) | 1 (6) | 2 (6) |
| III | | 1 (4) | 1 (3) | 1 (4) | 2 (3) |
| Observed total | | 2 (19) | 3 (14) | 2 (10) | 4 (9) |
| Recurrence | | | | | |
| | Probability from data | 0.10 | 0.21 | 0.20 | 0.44 |
| | Expected probability | 0.12 | 0.15 | 0.28 | 0.43 |
| Expected total | | 2 (19) | 2 (14) | 3 (10) | 4 (9) |

**Table 3.** Extra dose required to maintain BED in respective treatment time schedule

| Treatment time per fraction (min) | Prescribed dose per fraction D (Gy) | Reduction in BED w.r.t. $BED_1$ | Required dose to maintain same BED (Gy) | Extra dose required (%) to maintain same BED |
|---|---|---|---|---|
| 8.5 | 7.00 | 0.00 | 7.00 | 0.00 |
| 17 | 7.00 | 0.29 | 7.12 | 1.71 |
| 34 | 7.00 | 0.80 | 7.35 | 5.00 |
| 68 | 7.00 | 1.56 | 7.77 | 11.00 |
| 100 | 7.00 | 2.07 | 8.11 | 15.86 |

There is a continuous fall of BED in the inter-fraction that ranges from 0.43% between the first and the last fraction of initial stage of the source (i.e. treatment time per fraction of 8.5 min) to 2.08% of the triple half life decayed of source strength. The calculated treatment time to deliver 7 Gy at point A from the source strength of 4.081, 2.041, 1.020, 0.510 and 0.347 cGy x $m^2$ x $h^{-1}$ are 8.5, 17, 34, 68 and 100 minutes, respectively. Then the reduction in BED w.r.t. initial source strength (i.e. 4.081 cGy x $m^2$ x $h^{-1}$) are observed as 2.59, 7.02, 13.68 and 18.13% for the source strength of 2.041, 1.020, 0.510 and 0.347 cGy x $m^2$ x $h^{-1}$, respectively. The recurrence of disease for the patients both for stage II and III ($P$ = 0.471) treated with HDR-BT (following to EBRT) within classes of treatment time schedule is given in Table 2. The ratio of the outcome of event i.e. recurrence of disease and total number of events for respective classes of treatment time (per fraction), provides the probability of the event corresponding to the class of treatment time (per fraction). Uncertainties (error) involved in obtaining the observed data (e.g. during the treatment procedure, small sample size etc.) can be minimized by fitting a mathematical model using least square technique to the observed data. The degree of goodness of fit is normally evaluated by the co-efficient of determination $R^2$. The best fit mathematical model (i.e. expected data) of this observed data is a quadratic equation ($Y = 9E - 0.5x^2 - 0.0024x + 0.1361$) with $R^2$ value 0.843. The expected probabilities of recurrence of disease within 26 months (June 2009 – August 2011) are evaluated as 0.12, 0.12, 0.16, 0.39 and 0.80 for treatment time per fraction of 8.5, 17, 34, 68 and 100 minutes, respectively. This expected probability is not significantly different from the observed data at 5 percent level of probability (as per $\chi^2$ distribution). It is also observed that percentage of recurrence of disease for stage II patients as 15.8 ($P$ = 0.647) and stage III patients as 35.7 ($P$ = 0.875). Prescribed dose and required dose to maintain the same level of biological effect with respect to initial source strength based on the equation (3) is given in Table 3. The physical doses required to maintain the same

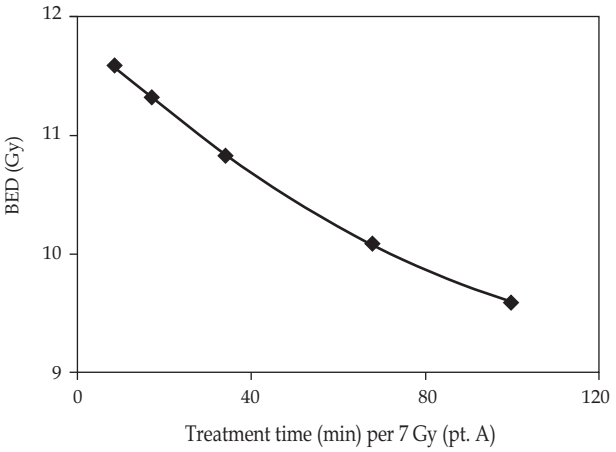


Fig. 1. Graph showing BED in respect to varying treatment time per fraction (7 Gy). N.B. It follows a well defined quadratic equation, Y = 1.20E-04X$^2$ – 3.54E-02X + 1.19E+01 with $R^2$ = 1.00

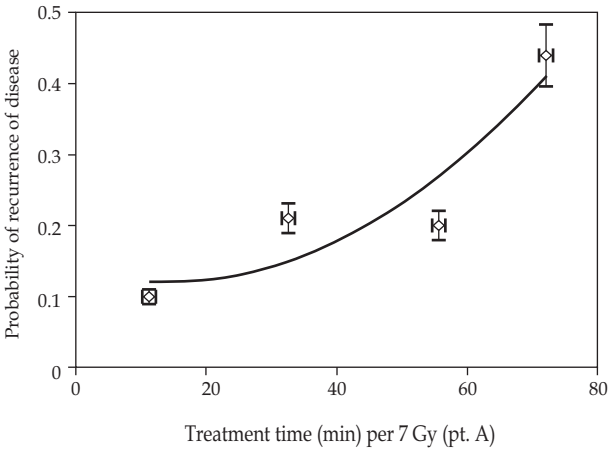


Fig. 2. Graph showing probability of disease recurrence in relation to varying treatment time. N.B. It follows a well defined quadratic equation, Y = 9E-05X$^2$ – 0.0024X + 0.1361 with $R^2$ = 0.843

biological effect with respect to initial dose rate (49.41 Gy/hr at point A) are estimated as 7.12 Gy, 7.35 Gy, 7.77 Gy and 8.11 Gy for dose rate of 24.7, 12.4, 6.2 and 4.2 Gy/hr, respectively.

## Discussion

Initially, the presence of a dose rate effect was not supported by a randomized study for patients with cervical cancer that showed no difference in overall survival or local control for a dose rate of 0.4 Gy versus 0.8 Gy per hour [24, 25]. However, the dose rate is one of the principal factors in determining the biological effects of radiotherapy. In general, the effects of radiotherapy decrease as the dose rate decreases, predominantly due to increase in repairing of tissues. During the study period, BED lost in EBRT (Cobalt-60) was found much less than 1% whereas BED lost was significant in HDR-BT as shown in Table 1. Moreover, two Ir-192 radioactive sources were used during the study period. This fast decay of dose rate causes the BED change within fractionation of HDR-BT as shown in Table 1. It shows an increase of variation of BED with half life decay. The BED change becomes more significant from double half life decayed of Ir-192 source strength. The lowest recommended source strength of Ir-192 is 1.02 cGy x m$^2$ x h$^{-1}$ i.e., double half life decayed of its original strength (4.081 cGy x m$^2$ x h$^{-1}$) which corresponds to about 12 Gy/hr in this study. Brachytherapy schedule of 7 Gy per fraction 3-4 times weekly is assumed as standard in this study, i.e it gives almost similar clinical response to LDR 30-40 Gy single dose. The graph between BED and treatment time per fraction is shown in Fig. 1. It is well fitted to a quadratic equation (Y = 1.20E-04X$^2$ – 3.54E-02X + 1.19E+01) with coefficient of determination ($R^2$) equal to 1.00. It is also observed that BED is decreased with increasing treatment time per fraction. The BED reduction following to dose rate reduction were compared with initial condition of the source (i.e. corresponding to treatment time per fraction of 8.5 min, which is the maximum treatment time per fraction experienced at our hospital for HDR-BT of cervical carcinoma when the source is new, approximately 3.673 cGy x m$^2$ x h$^{-1}$). The recurrence of disease within classes of treatment time schedule for delivering same dose fraction (i.e. 7 Gy) of cervical cancer patients (stage II and III) is given in Table 2. The expected total number of patients having recurrence of disease for respective classes are evaluated by multiplying corresponding expected probabilities with total number of patients within the classes of treatment time schedule. Figure 2 shows graph between probabilities of recurrence of disease (stage II and III) with median value of treatment time within classes of treatment time schedule. This graph shows that cervical cancer treated (HDR-BT) without any correction of BED at different treatment time per fraction due to the variation of dose rate indicates declining of disease free survival with increasing treatment time per fraction, especially from double half life reduction of source strength. Thus, from Figs. 1 and 2 reduction in BED may be correlated with the increasing disease recurrence. This is in agreement with earlier work on local control in image guided brachytherapy in patients of cervical cancer with dose delivery (expressed in EQD2) [7, 8]. The sample size of this retrospective study is small, however it may be fitted to a polynomial of degree 2 with $R^2$ value 0.84 for any statistical conclusion. The expected probabilities of disease free survival of this study of 26 months are estimated by subtraction of expected probability of recurrence of disease from total probability (i.e. 1.00) as 0.88, 0.88, 0.84, 0.61 and 0.20 for source strength of 4.081, 2.041, 1.020, 0.510 and 0.347 cGy x m$^2$ x h$^{-1}$ , respectively. These disease free survival probabilities are almost comparable up to double half life reduction of source strength. This disease free survival evaluation method may not be appropriate in the event of lost to follow up of patients. During this study period of 26 months, there were no cases of lost to follow up. Appropriate Kaplan-Meier survival analysis suggested that in the event of lost to follow up as it is based on estimating conditional probabilities at each time point when an event occurs, and taking the product limit of those probabilities to estimate the survival rate at each point in time.

If it is required to maintain a relatively constant BED, the study suggest a need to deliver an extra dose to compensate for an overloading treatment time of HDR-BT that allows significantly more sub lethal damage repair and a higher surviving fraction during exposure. The extra dose requires to maintain the same BED, when initial one increases more significantly from double half life reduction of source strength onwards, as shown in Table 3. There is also a suggestion that 1% change in BED may produce 1% change in tumor control probability [16]. This suggestion is in agreement with our finding of recurrence of disease with lowering BED.

## Conclusions

This retrospective study of cervical cancer patients treated with HDR-BT (following to EBRT) at different stages of Ir-192 source strength shows: 1. Linear Quadratic model based analysis of biological effective dose reveals fall of BED with decrease in dose rate due to the decay of Ir-192 source strength. The possible reason could be the increase of sub lethal damage repairing in long time treatment; 2. The reduction in disease free survival with an increase in treatment time duration due to the source decay may be associated with the decrease of biological equivalent dose to point A; 3. Clinical end point of this study is more significant from double half life reduction of source strength onwards.

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