HIGH-DOSE RATE BRACHYTHERAPY IN CARCINOMA CERVIX STAGE IIIB

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ABSTRACT

INTRODUCTION

Radiotherapy is the standard treatment in locally advanced (IIB-IVA) and early inoperable cases. The current standard of practice with curable intent is concurrent chemoradiation in which intracavitary brachytherapy is an integral component of radiotherapy. This study aims at assessing the efficacy of HDR ICBT (High-dose rate intracavitary brachytherapy) in terms local response, normal tissue reactions, and feasibility.

METHODS AND MATERIALS

A total of 20 patients of stage IIIB cancer of the uterine cervix were enrolled in the study and were planned to receive concurrent chemotherapy weekly along with EBRT (external beam radiotherapy) to a dose of 50 Gy/25 Fr. Suitability for ICBT was assessed at 40 Gy/20 Fr. 6/20 patients were suitable at 40 Gy and received HDR ICBT with a dose of 5.5 Gy to point A in 4 sessions (5.5 Gy/4 Fr). The remaining 14/20 patients completed 50 Gy and received HDR ICBT with a dose of 6 Gy to point A in 3 sessions (6 Gy/3 Fr).

RESULTS

A total of 66 intracavitary applications were done and only one application required dose modification due to high bladder dose, the pelvic control rate was 85% (17/20). 10% (2/20) had stable disease and 5% (1/20) had progressive disease at one year of follow up. When toxicity was considered only 15% developed grade I and grade II rectal complications. Patient compliance and acceptability was 100%. Patients were very comfortable with the short treatment time as compared with patients on LDR ICBT (low-dose rate intracavitary brachytherapy) treatment interviewed during the same period.

CONCLUSION

This study proves that HDR brachytherapy is efficacious and feasible in carcinoma of cervix stage IIIB. It also proves that good dose distribution can be achieved with HDR intracavitary facility by the use of dose optimization. The short treatment time in HDR ICBT makes it possible to maintain this optimised dose distribution throughout the treatment providing a gain in the therapeutic ratio and ensuring zero radiation hazards to the medical personnel.

KEYWORDS

Cancer cervix, Brachytherapy, High-dose rate, Low-dose rate.

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INTRODUCTION: Cervical cancer is the fifth most common cancer in humans, the second most common cancer in women worldwide, and the most common cancer cause of death in the developing countries.(1) The worldwide incidence of cervical cancer is approximately 510,000 new cases annually with approximately 288,000 deaths worldwide.(2) Unlike many other cancers, cervical cancer occurs early and strikes at the productive period of a woman's life. The incidence rises in 30-34 years of age and peaks at 55-65 years with a median age of 38 years (age 21-67 years).(3)

Every year in India, 122,844 women are diagnosed with cervical cancer and 67,477 die from the disease. India also has the highest age standardised incidence of cervical cancer in South Asia at 22, compared to 19.2 in Bangladesh, 13 in Sri Lanka.(4)

Radiotherapy is the standard treatment in locally advanced (IIB-IVA) and early inoperable cases. The current standard of practice with curable intent is concurrent chemoradiation in which intracavitary brachytherapy (ICBT) is an integral component of radiotherapy.(5) Incorporation of brachytherapy along with external beam radiotherapy (EBRT) has shown significant survival improvement 67% vs 37% (1973 Patterns of care study) and it is also the single most important prognostic treatment factor in a multivariate analysis for stage IIIB cancer cervix in terms of pelvic control and survival. There was a significant improvement in disease free survival rates 36% vs 29% at 5 yrs.; however, this improvement was not significant at 10 yrs. 27% vs 27.(6)

Brachytherapy application is unique in cancer cervix as it is based on the nature of spread of the tumour, which influences the arrangement of applicators chosen. The probability of parametrial spread demands that the full advantage be taken of the distensibility of the vagina to arrange the source so as to throw the radiation as far

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laterally as possible and at the same time the dose be kept low as possible on the dose limiting structures i.e. the bladder and the rectum. This combination of circumstances calls for the creation of a field of radiation of a flattened pear shape, maximal along the three natural lines of spread, and minimal in the direction of bladder and rectum.[7] Thus, there exists a large number of available technological and biological options, which produce a wide variation of dose distribution and effects. The various dose rates and schedules in Intracavitary Brachytherapy (ICBT) as defined by International Commission on Radiological Units 38 (ICRU).[8]

- Low-Dose Rate (LDR) dose delivered at <2 Gy/hr.
- Medium-Dose Rate (MDR) dose delivered at 2-12 Gy/hr.
- High-Dose Rate (HDR) dose delivered at >12 Gy/hr.

LDR brachytherapy was the most commonly practiced and accepted technique and was considered the gold standard as it had evolved over years of clinical experience producing consistent results. HDR was introduced in the 1960s to mainly overcome radiation hazard to medical personnel and reduce discomfort to patients. It is now well established that HDR has other advantages like OPD treatment, decreased anaesthetic risks, fixed applicator placement, decreased risk of thromboembolism, dose optimization, reduction in overall treatment time by integrating brachytherapy along with external beam therapy, which improves the local control.[9] The disadvantage of HDR brachytherapy is that it represents a therapeutic compromise with greater probability of late normal tissue reactions. This can be overcome by adequately fractionating the dose. Using different repair constants (μ) for early and late reacting tissues (i.e. tumour and normal tissues) in the Linear Quadratic (LQ) equation, it is seen that a minimum of 3 fractions at a dose of 12.2 Gy/fraction provides a therapeutic equivalent of LDR brachytherapy and any schedule, which has more than 3 fractions provides an additional benefit.[10]

The ultimate test comes from clinical studies and several randomised and non-randomised studies have shown equal results in terms of local control, survival, and complications. This study was to assess the efficacy in terms of tumour response (WHO), normal tissue reactions (RTOG), patient compliance, and the feasibility of HDR intracavitary brachytherapy in carcinoma cervix stage IIIB.

METHODS AND MATERIALS: A total of 20 consecutive patients of stage IIIB cancer of the uterine cervix were enrolled in the study. The study period was for one year starting from December 2011 to December 2012. The inclusion criteria were informed consent, age ≤65 years, KPS ≥70, normal liver and renal functions, haemoglobin ≥11 gm/dL, and histology - squamous cell carcinoma. The exclusion criteria were uncontrolled diabetes and hypertension, previous oncological treatment, HIV, and HBsAG positivity.

Pretreatment evaluation consisted of complete history, physical examination, biopsy of the tumour, complete blood count, biochemistry, chest x-ray, ultrasound of the abdomen and pelvis, proctoscopy/cystoscopy as and when indicated. EBRT-All patients were treated on telecobalt at 80 cm SSD in prone position. Two field parallel opposed or four field box techniques was used depending on the patient's separation. Target volume included tumour and lymphatic drainage areas as localised by bony landmarks and clinical examination as per standard treatment guidelines. The dose prescribed was 50 Gy/25 fractions, 5 fractions/wk calculated at the midpoint on the beam axis using central axis depth dose tables. EBRT or chemotherapy was not given on the day of ICBT. Chemotherapy – Cisplatin 40 mg/m2 was given on a weekly schedule for 4-6 cycles in a 2 hr infusion (capping the total dose at 70 mg). Chemotherapy was given 1 hr prior to radiotherapy. Myelosuppression and renal toxicity was evaluated on a weekly basis. Brachytherapy - After obtaining informed consent and necessary preoperative preparations the procedure was carried out under sedation (ketamine) on day care basis. The brachytherapy dose prescribed was 5.5 Gy in 4 sessions or 6 Gy in 3 sessions to point A using GammaMedPlus HDR Brachytherapy machine. The entire HDR ICBT treatment was completed in approximately 2 hours' time. EBRT and chemotherapy was not given on the day of HDR ICBT.

Pt. Characteristics	Mean±SD	Range	%
Age	42.50±9.85	25-65 yrs.	
KPS		>70	
Hb gm/dL	12.20±0.52	11-13	80-20%
Histology (SCC)			100%
Tumour size	4.80±1.15		
≤4 cm			40%
≥4 cm			60%
Parametrial Involvement			
Unilateral			75%
Bilateral			25%

Table 1: Patient Characteristics and Treatment Parameters

Radiotherapy	Mean (Gy)	Range	%
EBRT (pelvis)	50±0		
40 Gy			30% (6/20)
50 Gy			70% (14/20)
Dose to Θ A*	19.35±2.01		
17 Gy			5% (1/20)
18 Gy			60% (12/20)
22 Gy			35% (7/20)
Dose rectum	8.30±1.42		
Dose bladder	10.63±1.93		
LDR Eq** Θ A	31.10±2		
LDR Eq** rectum	10.78±1.98	28-35 Gy	
LDR Eq** bladder	13.95±2.72	8-15 Gy	

Total dose Ʊ A*	78.10±2.79	74-80 Gy	
Total dose rectum	57.15±3.51	52-61 Gy	
Total dose bladder	60.54±4.55	52-67 Gy	
BED† Ʊ A		71.1-82.3 Gy_{10}	
BED† Rectum		75-91 $Gy_{3\cdot87}$	
BED† Bladder		75.2-97.3 Gy_{4}	

* Ʊ A = Point A dose, ** Eq = Equivalent dose, and † BED = biological equivalent dose.

A total of 20 consecutive patients of stage IIIB cervical cancer of the uterine cervix were recruited. All patients were treated with concurrent chemoradiation and were assessed for suitability for ICBT from fourth week of EBRT. Patients who were suitable at 40 Gy of EBRT received four sessions of HDR ICBT (dose 5.5 Gy/Fr to point A, total point A dose =22 Gy). The remaining 10 Gy was delivered with a 4 cm central shield, which was placed after the first ICBT application. Patients not suitable at 40 Gy were taken for ICBT after completion 50 Gy of EBRT and three sessions of HDR ICBT (dose 6 Gy/Fr to point A, total point A dose = 18 Gy). The interfraction interval was 3 days to 1 week. All patients received the planned treatment. There were no treatment delays or treatment breaks. ICBT dose modification was required in one patient due to high bladder dose and she received 17 Gy to point A instead of 18 Gy. 19/20 patients received 4-6 cycles of chemotherapy and one received only three cycles due to prolonged leucopenia. All patients completed the planned treatment with an overall treatment time (OTT) of 51 days (mean OTT of 46.4±3.6 days). Response assessment was done at the last ICBT application and 4 weeks later follow up procedures included history, general physical examination, and pelvic examination. When central or parametrial recurrence was suspected on clinical examination a pap smear/biopsy was taken for confirmation. Chest x-ray, ultrasound of the pelvis and abdomen done at 6 months and one year. Patients with symptoms relating to complications were evaluated with proctoscopy, cystoscopy, and sigmoidoscopy.

STATISTICS: Statistical analysis was performed using computer software SPSS epi info version 5. Tumour response was assessed based on WHO criteria and normal tissue toxicity as per RTOG criteria. All patients were assessed at the end of treatment and 4 weeks later and every 2 months for the first 6 months and every 3 months for the next one year.

RESULTS: The local control rate at follow up of one year was 85% (17/20), partial response rate was 10% (2/20), local recurrence 5% (1/20). This patient developed a nodular lesion on the anterior lip of cervix, which was confirmed on biopsy.

Univariate analysis was performed with respect to initial response of the tumour and prognostic factors like age, KPS, tumour size, ICBT dose, overall treatment time, and chemotherapy. When age factor was considered this study included patient's age ranging from 25 to 65 years. At the end of treatment, there were 7 complete responses of which patients ≤40 years of age had a complete response rate of 43% (3/7) as compared to 57% (4/7) patients ≥40 years of age. The age factor did not show any significance (p=0.42). Size of the tumour had a significant influence on the tumour response. Patients with tumour size less than 4 cm had a response rate of 71% as compared to 28% for tumours more than 4 cm (p=0.025, chi sq 4.43), this finding is similar to other studies.[11,12] The significance of parametrial involvement has not been confirmed in this study. With respect to point A dose, a higher response rate of 57% vs 23% p=0.27 was observed when the ICBT dose was 22 Gy as against 18 Gy. Though the p value did not reach statistical significance, a trend towards the same was observed. 95% of the patients received a minimum of 4 cycles of chemotherapy and the effect of chemotherapy on initial response was not significant. The overall treatment time failed to show any relationship to tumour response, which may be due to the very small variation in the study group.

The treatment was well tolerated by all patients in the study group; none of the patients had grade 3 or 4 reactions. 2/20 (10%) patients developed grade I proctitis, which responded to dietary changes, 1/20 (5%) developed grade 2 proctitis at 5th month of follow up, the effect of rectal dose in this case was studied and there was no correlation. She responded to steroid retention enema. None of the patients developed bladder or upper GI reactions. 3/20 (15%) had grade 1 and 4/20 (25%) had grade 2 haematological reactions attributed to chemotherapy. One patient had prolonged leucopenia and she received only 3 cycles of chemotherapy. 16/20 (80%) had grade 1 and 2/20 (10%) had grade 2 skin reactions. 8/20 (40%) had grade 1 mucous membrane reactions.

Univariate analysis of prognostic factors (table 2).

	CR%	**PR%**	**P value**
Age Years			
≤40	43%	61%	P=0.42
≥40	57%	38%	
Tumour Size			
≥4cm	71%	23%	P=0.025
≥4cm	28%	7.6%	
Parametrium			
Unilateral	85%	69%	P=0.41
Bilateral	14%	30%	
Central dose (Gy)			
External radiation dose			
40	57%	23%	P=0.27
50	43%	7.6%	

Brachytherapy dose (Gy)			
18	43%	7.6%	P=0.27
22	57%	23%	
Total ΘA* dose LDR Eq**			
74.4 Gy	42%	57%	P=0.67
80 Gy	30%	69%	
Chemotherapy (Cycles)			
≤4 cycles	57%	53%	P=0.88
≥4 cycles	43%	46%	
OTT† (days)			
≤45	57%	53%	P=0.88
≥45	43%	46%	
Table 2			

* Θ A = Point A dose, ** Eq = Equivalent dose, and † OTT = overall treatment time.

DISCUSSION: High-dose rate is defined as dose rate high enough such that the exposure time is short as compared to the repair time of sublethal damage i.e. <1hr. The dose delivered in this system is >12 Gy/hr or 0.2 Gy. High-dose rate intracavitary brachytherapy for cervical carcinoma is being widely used and is now an accepted form of treatment modality. Several randomised and non-randomised trials have equal results in terms of local control survival and toxicity.[13-19] The major advantage with HDR–ICBT is the short treatment time, which makes treatment on an outpatient basis possible, improving patient comfort, and increasing the cost effectiveness. Another important aspect of HDR brachytherapy is the ability to optimise the radiation dose to the target and critical organs providing a better therapeutic ratio with zero radiation hazards to the medical personnel.

However, there are still some problems surrounding HDR brachytherapy. HDR treatment is often considered as a therapeutic compromise. It involves a greater probability of late effects on normal tissues for a given tumour control. HDR ICBT can safely replace LDR ICBT and produce similar tumour and late tissue effects when sufficiently fractionated. The equivalent dose schedule for HDR brachytherapy can be obtained using the LQ model.[20] Several randomised and non-randomised trials comparing HDR ICBT and LDR ICBT have reported comparable 5 year local control, survival, and complication rates.[13-19] In this present study, a total of 66 intracavitary applications were done and only one application required dose modification. At one year of follow up, the pelvic control rate was 85%, which is comparable to the recent series reporting local control rates of 84-70%.[13-19] When toxicity was considered only 15% developed rectal complications, which is relatively low as compared to other studies.[20,21] The possible explanation could be due to the short follow up period and dose optimisation. Another important contributory factor for the low complication rates is the reduced rectal and bladder dose, which was possible with computerised planning and dose optimisation. Estimating the threshold dose for normal tissues using the LQ formula, the Biological Effective Dose (BED) causing complications to the bladder for 75 Gy, LDR is 125 Gy_3, and 70 Gy LDR for rectum is 120 Gy_3. In this study, the BED for bladder was 75.2-97.35 Gy and rectum was 75-91.7 Gy, which was much less than the predicted value that causes complications (table 3). Patient compliance and acceptability was 100%. Patients were very comfortable with the short-treatment time as compared with patients on LDR treatment during the same time period.

The outcomes for stage I and stage II cervical cancer has remained stable over the time of surveys while the results have improved for stage IIIB disease due to the higher paracentral dose, which has decreased the pelvic failures and improved survival, which has been demonstrated with point A doses above 85 Gy. The other treatment factors associated with improved outcome include reduction in overall treatment time and adequacy of intracavitary placement.[22]

In future, the therapeutic window will be increased by integration magnetic resonance imaging into the treatment planning thus allowing for a highly individualised approach with further adaptation of radiation dose and volume both to the target and to the individual topography of organs at risk.

CONCLUSION: This study proves that HDR brachytherapy is efficacious and feasible in carcinoma cervix stage IIIB. It also proves that good dose distribution can be achieved with HDR intracavitary facility by the use of dose optimisation. The short treatment time in HDR ICBT makes it possible to maintain this optimised dose distribution throughout the treatment providing a gain in the therapeutic ratio and ensuring zero radiation hazards to the medical personnel.

	Grade I (%)	**Grade II (%)**	**Grade III (%)**	**Grade IV (%)**
Skin	80	10	-	-
Mucous Membrane (Vagina)	40	-	-	-
Rectum	10	5	-	-
Bladder	-	-	-	-
Upper GI	-	-	-	-
Haematological	15	25	-	-
Table 3: Toxicity Profile				

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