Original article

Positional variation of applicators during low dose rate intracavitary brachytherapy for cervical cancer: a prospective study

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Abstract

Purpose: In order to know the effect of variation in position of applicators to the dose received by the tumor volume, critical organs such as rectum and bladder and the correlation of variation on the clinical outcome.

Material and methods: 36 patients with histologically proven cervical cancer, undergoing intracavitary brachytherapy (ICBT) from October 2005 to December 2006 were the subjects of the study. Two pairs of orthogonal X-ray films were taken: one prior to loading of sources and the other after removal of sources. These patients were followed up as per the RTOG criteria.

Results: The median duration of insertion was 25 hours with a median follow up period of 6.7 months. The translational variation of the applicator position for all patients was 3 mm and 1 mm (2 SD), respectively, in the patient's lateral and antero-posterior direction. The rotational variation was 3 and 4 degrees (2 SD) in the patient's transverse and sagittal planes. Detailed analysis of source movement showed following changes in median dose: point A: 14%, point B: 2%, point P: 1%, Rectum 1: 3.5%, Rectum 2: 4% and Bladder: 9.1%. The incidence of rectal toxicity was 6/36 (16.7%) and that of bladder was 1/36 (2.8%). When the variables were grouped to evaluate the relationship, our study showed statistically significant relationship between: R2 and rectal toxicity (*p* value: 0.002), point A and rectal toxicity (Pearson: 0.792), lateral displacement/anteroposterior displacement and rectal toxicity (*p* value: 0.012/0.003), beta angle and R2 (*p* value: 0.002).

Conclusions: The geometric relationships between the ICBT applicators and the critical structures vary during the course of low dose rate brachytherapy. Source movement does result in significant dose alterations in terms of increased rate of complications, but its impact on cure rates needs to be studied in the future.

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Key words: cervical cancer, LDR brachytherapy, positional variation.

Purpose

As per the ICMR data, the incidence of cervical cancer in Bangalore is 21.7/100 000 population [1]. Currently chemoirradiation (CT + EBRT) is the standard procedure. Radiotherapy includes both external beam radiation therapy and brachytherapy. Since brachytherapy is based on the principles of both radiotherapy and surgery it has evolved independently with many different techniques, treatment regimens and planning methods. Intracavitary brachytherapy (ICBT) forms an integral part of radiotherapy, which is employed in the treatment of carcinoma cervix patients combined with EBRT. ICBT was first performed by Margaret Cleaves in 1903 which involves placement of uterine tandem and vaginal ovoids. It can be delivered either as low dose rate (LDR) or high dose rate (HDR) based system with the help of manual or remote after loading of Cesium 137 and Iridium 192 sources. In our institute we employ the manual after loading LDR brachytherapy (LDR BT) method with Cesium 137 sources. LDR BT involves delivery of radiation at a continuous rate of 0.4-2 Gy/hr and this means that the delivery of required dose will need around 24 to 30 hours. The ICBT procedure is done under aseptic precautions with epidural anesthesia in the operation theatre (OT). The applicators are placed in the uterine and the vaginal cavity. Then the patient is shifted to the brachytherapy department for simulation and after loading of Cesium 137 source, where the patient lies down in the same supine position for the prescribed duration of 20-30 hours. Due to long treatment time, soakage of vaginal packing and patient movement can result variation in the position of applicators. However, it must be remembered that the dose gradients around the applicators are very steep and small alterations in position of applicators relative to pelvic organs can have a consider-

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able effect on dose received by these organs. The purpose of this study was to evaluate the geometric movement of the fixed reference points in LDR brachytherapy patients and to determine the actual dose difference, in turn to critical structures and the clinical outcome.

Material and methods

Estimation of sample size

The estimation of sample size is based on the study "Positional stability of sources during low dose rate brachytherapy for carcinoma cervix". The sample size is estimated based on 5% significance level, with an error of 0.3 and 36 as the sample size. The subjects enrolled in this study are not involved in any other study in our department. Statistical analysis was done using ANOVA, univariate analysis and Pearson correlation technique. The formula used:

$$F = \frac{MS_{\text{between groups}}}{MS_{\text{within groups}}}$$

where *MS* – mean sum of square. Data analysis was carried out using statistical package for social science (SPSS, V 10.5).

Method of collection of data

From October 2005 to January 2007, 36 consecutive cervical cancer patients who underwent LDR BT were the subjects of the study. Post treatment localization radiographs were obtained for comparative analysis. These patients had received EBRT with a dose of 46 Gy to the pelvis with or without midline shielding 30 and were followed with ICBT within a gap of 2 weeks. The dose delivered by brachytherapy ranged from 30 Gy to 32 Gy to Point A. ICBT procedure was done in the operation theatre with all the precautions under combined spinal and epidural analgesia. After this the patient was transferred to a stretcher with the help of a lift board and shifted to the recovery room and then to the brachytherapy simulator room. Orthogonal X-rays were taken and different measurements necessary for calculation of magnification were recorded. The center of the cross wires was marked on the patient skin and the patient was shifted to the brachytherapy treatment room where manual after loading of cesium sources were done with patient reclining in supine position for 24 to 26 hours. Once the treatment was completed, as previously decided after going through the dose distribution on the TPS (Treatment Planning System), the patient was shifted back to the simulation room for post treatment X-rays. Care was taken to make sure that orthogonality was maintained and the skin marks along with measurements matched to those of pretreatment recordings in order to avoid any kind of error. Finally, the applicators were removed and patient was shifted to the ward for observation and discharged with the advice of reviewing after 2 weeks. Localization images were a set of orthogonal antero-posterior and lateral radiographs. Reference planes (x, y, z) were defined for each set of images by using patients bone landmarks to evaluate changes in positioning of applicators relative to fixed bony landmarks of the patient. The x reference plane was defined as a line passing through the symphysis pubis on the antero-posterior radiograph. The y reference plane was described as a line passing through the centre of pubic symphysis and the vertebra. The z reference plane was define as a line passing parallel to the table and the anterior most point of vertebra or the pubic symphysis. All these reference planes were maintained in both the radiographs i.e. one taken before and after the treatment. Measurement of the values of all the variables in all the planes were taken and reproduced into the after X-ray (i.e. X-ray taken after completion of treatment) in order to calculate the precise positioning and potential dose variations. The reference points or variables used to evaluate the effect of applicator movement on doses were Point A, Point B, and Point P, ovoid right and left, flange, bladder and rectal points. All these points were recorded as per the ICRU 38 and ABS guidelines. Patients were followed up and they rectal and bladder reactions were evaluated as per the RTOG gradation criteria.

Results

Correlation between displacement and rectal toxicity

Lateral displacement of applicators whilst tabulated against rectal toxicity *p* value was 0.012 which demonstrates significant and positive correlation. In the same way, the *p* value for anteroposterior displacement and rectal toxicity was 0.003, which proves that rectal toxicity depends on the magnitude of displacement (Table 1).

Correlation between alfa angle and dose variation

Alfa angle was measured in the study to substantiate the observation that even in the absence of the variation in position of applicators, several discrepancy in dose can occur. Furthermore, it demonstrates that applicators not only vary in position, but the presence of rotation of applicators is also substantial. Although variation in dose at point A, B, P was recorded, it was not statistically significant whenever correlated with the alfa angle as shown in Table 2.

Correlation between beta angle and dose variation

In the present study the relation between beta angle with dose variation at R2 was statistically significant with a *p* value of 0.002 (Table 3).

Correlation between toxicity and point A, B, P dose variation

Figure 1 shows that the variation at point A dose and development of rectal toxicity has a *p* value of 0.083.

Discussion

In the present era of technology and advancement management of cervical cancer involves multimodality approach. For improving local control, treatment and quality of life (QoL) it mandates every specialty to deliver the

Table 1. Correlation between displacement and rectal toxicity

	Rectal toxicity	*N*	Mean	Standard deviation	Min	Max	*t* value	*p* value
Lateral displacement	No	30	2.667	1.634	0	5.0	7.117	0.012
	Yes	6	4.817	2.569	2.0	7.8		
Antero posterior displacement	No	30	0.80	0.96	0	3	10.481	0.003
	Yes	6	2.33	1.51	0	4		

Table 2. Correlation between alfa angle and dose variation

	Alfa angle	*N*	Mean	Standard deviation	Min	Max	*F* value	*p* value
Point A dose variation (%)	0-2	17	15.65	7.60	6	30	0.254	0.777
	3-5	15	14.27	7.13	5	28		
	6-8	4	13.25	4.43	9	18		
Point B (%)	0-2	17	2.32	1.27	1	5	0.528	0.595
	3-5	15	1.93	1.00	1	4		
	6-8	4	2.38	1.38	1	4		
Point P (%)	0-2	17	1.38	0.85	0	3	0.555	0.580
	3-5	15	1.10	0.72	0	3		
	6-8	4	1.38	0.75	1	2		
Rectum 1 (%)	0-2	17	4.12	1.76	2	8	0.856	0.434
	3-5	15	3.40	1.64	1	7		
	6-8	4	4.25	1.50	3	6		
Rectum 2 (%)	0-2	17	4.647	2.760	1.0	10.0	0.562	0.576
	3-5	15	3.900	2.140	1.0	9.0		
	6-8	4	3.500	1.915	2.0	6.0		

Table 3. Correlation between beta angle and dose variation

	Beta angle	*N*	Mean	Standard deviation	Min	Max	*F* value	*p* value
Point A dose variation (%)	0-2	3	14.00	5.29	10	20	1.000	0.379
	3-5	24	13.83	6.82	6	30		
	6-8	9	17.67	7.86	5	30		
Point B (%)	0-2	3	2.00	0.87	2	3	2.060	0.143
	3-5	24	1.94	1.03	1	4		
	6-8	9	2.82	1.41	1	5		
Point P (%)	0-2	3	1.27	0.64	1	2	2.708	0.081
	3-5	24	1.08	0.65	0	3		
	6-8	9	1.76	0.97	1	3		
Rectum 1 (%)	0-2	3	3.33	0.58	3	4	1.157	0.327
	3-5	24	3.63	1.56	1	6		
	6-8	9	4.56	2.13	2	8		
Rectum 2 (%)	0-2	3	2.333	0.577	2.0	3.0	7.613	0.002
	3-5	24	3.604	1.961	1.0	9.0		
	6-8	9	6.444	2.506	2.0	10.0		

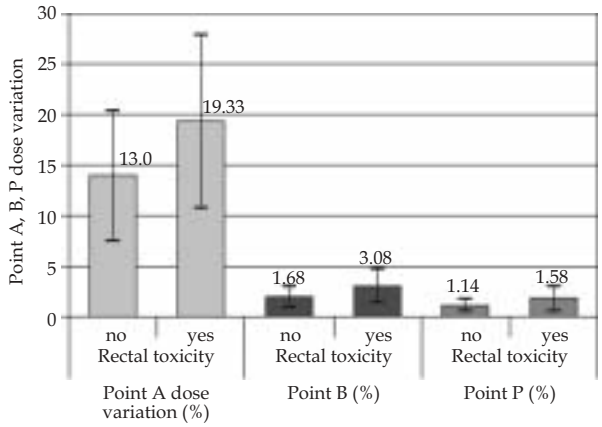

Fig. 1. Distribution of toxicity and point A, B, P dose variation

best attention. It is a known fact that adequate loco regional control prevents metastatic microscopic spread of tumor cells and by delivering adequate radiation to loco regional disease it is possible to improve local control, treatment and QoL. Therefore, the radiation therapy is an inseparable specialty in the management of cervical cancer. In the current radiotherapeutic practice it is compulsory to deliver lethal dose for achieving complete tumor control which is directly proportional to radiation dose delivered. Brachytherapy forms the ideal tool to achieve this objective and also respects the tolerance of healthy tissues. Our study included 36 consecutive patients of cervical cancer undergoing ICBT and 72 pairs of orthogonal films pre and post ICBT were studied. Quantification of the data was as per ICRU 38 [2] and ABS [3] guidelines. Variation was assessed in terms of displacement at point A, point B, point P, rectal points and bladder points with respect to the bony pelvis. In addition to the above mentioned points, variation in terms of angles Alfa and beta were analyzed to further validate the results. Of the 36 patients, the mean age was 54 years with a range of 32-76. Most of these patients were of stage III B i.e. 52% of all cases, with median follow up of 6.75 months. As per the treatment protocol followed at our institute which is in cognizance to the world data, these patients received 46 Gy of external bean radiotherapy to the pelvis. After a gap of 2 weeks they underwent ICBT procedure with a dose of 30-32 Gy to point A, subject to condition whether a patient received midline shielding at the end of 40 Gy.

Magnitude of displacements of applicators

The estimation of magnitude of variation of applicators was first studied by Corn in the 80's, showing various displacement of applicators in the lateral direction on an average of 3 mm [4]. This has been presented by other oncologists such as Pham *et al*. [5] and Bahena *et al*. [6] who found that the displacements were not only in lateral, but also in anteroposterior and superio inferior directions. In our study the average displacement in the lateral and anteroposterior directions were 3 mm and 1 mm respectively. It complies with the above mentioned studies. There has been paucity of data in terms of angular variation in LDR BT. In our study we could find an average angular variation of 3 degrees of alfa angle and 4 degrees of beta angle. This becomes significantly important due to observation of angular variation in the absence of applicator displacement in nearly 5 cases.

Magnitude of dose variations

Dose to point A variation has been studied by many radiation oncologists such as Corn *et al*. [4]. Those studies demonstrated dose variation of 2%, 35%, 8% and 20%. This is wide range for the fact that some of the studies were completed with radium source and several with iridium and cesium sources. In our study we found an average variation of 14% which is well within the data shown in the above mentioned studies. We also assessed the variation in dose at point B and point P in order to make out the differences at the lymph node areas. Corn *et al*. [4] showed this variation to be 1.7% and 0.9% respectively. In the present study we encountered a variation of 2% and 1% at point B and point P respectively. As per the guidelines there was only one rectal point, but in our study we have tried to include two rectal points in order to assess rectal morbidity. Studies done by Corn and Pham [4,6] have shown certain dissimilarity of 3% and 10% respectively. In our study we could find 3.5% variation in the dose to rectum. As far as bladder dose variation is considered, our study presented on an average 9.3% and the results of other studies by Corn and Pham 1.9% and18% respectively.

Magnitude of toxicity

As per the world literature, the incidence of toxicity after LDR BT is 20% (moderate) and 5.3% (severe) at the end of 5 years [8]. Combined rectal and bladder toxicity in our study is 16% with a maximum follow up of 18 months. It is necessary to analyze the incidence of rectal and bladder toxicity and its possible correlation to the positional variations. Despite of deficiency of data regarding analysis of correlation between dose variation and toxicity, there have been sufficient number of studies on critical organ dose and morbidity. Stryker *et al*. [9] have publicized that the dose to critical organ and toxicity is directly proportional in addition to the relation between the dose to critical organ and the measured dose at the respective points.

Correlation of toxicity and variation

There are no LDR brachytherapy data regarding this aspect of correlation in a prospective form due to insufficient period of follow up. The aim of our study was to emphasize this aspect with a reasonable follow up time to assess the satisfactory results.

Relation between lateral displacement and rectal toxicity was not statistically significant, but when attached to anteroposterior displacement, the relation became statistically significant with a p value of 0.003. There was a positive correlation between alfa angle and point A dose variation and also with rectal dose. The possibilities of rectal toxicity with point A dose variation were statistically significant. Among this two rectal points, the variation at R2

seems to be statistically significant in terms of resulting toxicity, according to the studies done by Stryker at TMH hospital [9]. However, the relation between the bulkiness of the disease and the resultant variations was not statistically significant as shown by some of the studies done by Eifel *et al*. [10], our study had shown some correlation involving these alterations in dose to the clinical outcome of the disease. Nevertheless, due to insufficient follow up period it was difficult to predict the exact figures in terms of overall survival.

This study was done taking into consideration alterations occurring just after the loading of the sources. With the present technology further analysis is needed in order to exactly evaluate at what stage of the treatment duration the variations occurred. Though HDR brachytherapy is being employed, LDR BT is practiced in the majority of centers in India. Additional studies with longer follow up period are necessary to confirm the relationship between variations in applicator position and clinical outcome.

Conclusions

The geometric relationships between intracavitary brachytherapy applicators and the critical structures vary significantly during the course of LDR BT. Source movement results in considerable dose alterations to the critical organs which can generate an increased rate of complications that can influence the cure rates and it needs to be studied in the future. In order to minimize the variation, the following indications ought to be considered: 1) it is essential to ensure adequate sedation used for patients comfort and to achieve better geometry of the applicators; 2) good level of awareness of possible occurrence of different geometric variations; 3) although our study showed significant dissimilarity in position of applicators, it is difficult to predict the exact time occurrence of variations; 4) since patient movement is one of the most important factors resulting in displacement of applicators which is attributed to long treatment time, HDR brachytherapy could be the right solution for a short treatment time.

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