Original article

A proposed protocol on HDR cylinder treatments: proof of avoidance of re-planning of CT based fractionated treatment, using a critical, statistical and graphical analysis of clinical data

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Abstract

Purpose: An evaluation of CT plan data, using cylinder applicators, in fractionated HDR treatments of cervical cancers has been investigated in this clinical study. Critical and statistical analysis of the data, for each patient and fraction, for plan dose, doses for bladder and rectum have been enumerated and reported. Plans were done for each patient, following CT scans after insertion of the applicator in the respective cases. This process involved time for CT-scan and re-plan, in each fraction, adding cost of treatments for the poor patients.

Material and methods: This study on HDR brachytherapy for cervical cancer patients has applied the Co-60 BEBIG Multisource Unit. Cylinder applicators have been applied for treatments. A selection of twenty nine patients, out of a few hundred representative female patients, in the age group of 40-70 years, has been analyzed and presented in this paper. Radiation oncologists inserted the applicator and fixed it in more than 600 treatments. This study, therefore, aimed at their insertion technique, CT-planning by radiation oncology physicists and the delivery of the treatments. Details of set up and technique has been explained, where bladder and rectum doses has been assessed within the tolerance limit [1].

Results: Statistical analysis of data from the treatment plans, substantiates the conclusion of the argument that there is no need to do CT-plans for each subsequently prescribed number of fractions as the doses in plan, bladder and rectum are restricted within the limits of tolerance. Data in Table 1 are analyzed in various graphs. This utilized the Empirical Null Distribution of Group Differences. A graphic study of dose distribution is reported to assure the expected variation of dose from the central tandem. This analysis proves to substantiate a protocol that no re-plan for fractionated delivery is essential following the approval of the first plan.

Conclusions: The goal of this study was to critically evaluate the outcome of fractionated cylinder treatments of cervical cancers. This resulted in the set up technique for insertion of applicators and treatment plan, following a CT-scan and the assertion of the argument that re-plans are not necessary for multiple HDR cylinder treatments for the same patient [2,3].

J Contemp Brachyther 2012; 4, 3: 146-151
DOI: 10.5114/jcb.2012.30681

Key words: HDR, cervical cancer, cylinder plan, null distribution.

Purpose

Brachytherapy plays an important role in obtaining substantial cure rate with minimum complications. A good and consistent insertion delivers a very high radiation dose to the cervix, upper vagina and medial parametrium without exceeding the tolerance doses to rectum and bladder. HDR is now being increasingly used as the control rates are comparable and the toxicity is slightly less. Brachytherapy, therefore, is used in management of tumors in one of the two settings: 1) post hysterectomy for most non-bulky stage I, IIA tumors of cervix where radical surgery is performed with the removal of parametrical tissue, a vaginal cuff and pelvic lymphadectomy; 2) for some advanced bulky tumors of uterus, having stages IB, II, III and IV, primary radiotherapy and brachytherapy will be the treatment of choice.

Selection of patients for treatments with cylinder applicators, for this study, was carefully chosen based on criteria such as stage of disease, age, background and general conditions. The need for treatments of cervical cancer is

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Received: 20.02.2012
Accepted: 08.09.2012
Published: 27.09.2012

increasing each day as there is better knowledge about the disease among women and understanding for check up and detection at hospitals. Applicators such as cylinder, tandem and ovoid have been applied in most patients. Treatment modalities, in such cases are applied in two ways: volume of PTV is drawn and disease is treated as per prescription. Dosimetric method relies on the distribution of isodoses, encompassing the tumor volume at certain length and as per prescription. A data was collected in these treatment using the cylinder applicator where CT based HDR plans were done for each fraction for each patient. This clinical study directs analysis from set up, insertion of applicator to the delivery of HDR treatments. Critical review of each step and the collection of data included the doses to bladder and rectum. This report, therefore, summarizes the analysis of the data with a conclusive remark on the treatment using a cylindrical applicator [4].

The extent of the disease is the most important factor for the treatment decision. After radical surgery, there is about 25% of chance of developing recurrent disease in the pelvis, so adjuvant external radiotherapy and brachytherapy are indicated. Deciding factors for external radiotherapy and brachytherapy to the vault of vagina in early stage of cervical cancer are poorly differentiated carcinoma, deep stoma, parametrical infiltration, nodal positivity, cut margin positivity, tumor size and inadequate surgery [1,4,5].

This study analyzed the dose data of HDR treatments using cylinder applicators, where a confirmation is reached and proved in delivering the same plan in subsequent fractions for the same patient.

Material and methods

Brachytherapy: cylinder cases

HDR intravaginal brachytherapy are given to those invasive cervical cancer patients who have high grade histological varieties, positive or closed surgical margins. It is also applied to the patients having vault recurrence when they are susceptible to vault recurrence i.e. endometrial carcinoma. External radiotherapy to pelvis for 50 Gy/25 fractions/5 weeks is followed by HDR-CVS (cylindrical vaginal source). The dose in this procedure is usually calculated at 0.5 cm from the cylinder surface where organs at risk (OAR) are very close. A prescription for 5 Gy/2 fractions at 0.5 cm from cylinder surface (i.e. cylinder radius, r, +0.5 cm). This is delivered weekly to the upper third of the vagina. Brachytherapy usually starts 1-2 weeks after EBRT. Patients with positive cut margin are given higher doses, 7 Gy × 2 fractions. Intrauterine applicator and vaginal cylinder are being used for patients who are in inoperable stage and whose vagina are stenored or narrow and unsuitable for vaginal ovoid's placement. Dose is calculated at 1cm from the central axis of intrauterine applicator and 0.5 cm from the surface of vaginal applicator [6].

Management of gynecologic malignancies, insertion of radioactive source with dwelling times into the body cavities adjacent to tumors allows delivery of large doses in the tumors while minimizing the adverse effects on regional normal tissues. Intracavitary apparatus used in treatment of gynecologic malignancies is fairly standardized. Tandems are curved to conform the anatomy where uterus is tilted anteriorly, causing an angle between the vagina and uterus. Patients are usually treated as out-patients. Before starting brachytherapy treatment, all patients are given enema to clear the lower gut. Insertions of cylinder are done without anesthesia. A Foley's catheter is introduced to the bladder and 7-10 cc air is pumped to inflate its bulb. No packing is usually required if correct size of cylinder is selected. If necessary, gauge soaked in normal saline is used for packing. Rectal marker is used for positioning of rectum and dose calculation. Cylinder is secured in position with stand holder or gauge bandage [4,5]. CT scan is done for all patients for verification and planning. Bladder and rectal dose calculations are limited in planning as per ICRU guidelines [1]. Plan is reviewed and approved by the relevant experts on HDR brachytherapy [6,7].

Results

Clinical data as tabulated in Table 1 represents a selection of patients varying in age, health, disease and anatomical differences, where fractionated HDR treatments have been delivered using cylindrical applicators. CT-based plan is created for the first fraction of a patient where a cylindrical applicator is inserted. Bladder and rectum doses are then tabulated. Data from a large number of patients are given in Table 1. In order to test the differences a statistical method is applied; in the prescription, bladder and rectum doses in all individual CT-plans, for different fractions are delivered to the same patient and to all the patients. The method of such an analysis is enunciated as follows:

The study seeks to test whether the difference in sample fractions between patients is significantly different from zero. A resort to non-parametric testing approaches using the permutation test is applied. The test utilized is a non-parametric re-sampling-based version of the matched-pairs t-test described in [8] and implemented in the R- programming language. The permutation procedure can be described as follows: 1) compute the observed matched pair's *t*-test statistics as the mean patient fractional group difference/square root (variance of the patient fractional group difference/n); 2) randomly change the sign of the difference between the two groups for each patient and then recalculate the matched-pairs *t*-test statistics; 3) repeat 10 000 times and then calculate the proportion of times that the test statistics based on the randomly permuted data, exceed the observed test statistics. This value is the permutation *p*-value.

Explanation of the test is explained as follows: by analysis, the *p*-value is significant when it is < 0.05 and the limits are 0 (most significant) and 1 (least significant). The *p*-value is generated empirically using a randomization approach. This approach has become popular in recent decades and is assumption free. Hence, it does not assume that the differences between the groups are distributed normally. The data in Table 1 shows fractions # 1 and # 2 measurements for each of the patients. If one subtracts the values of the two as given above for each patient, one can call this as "observed differences" in the sample. If a sum these differences and the total in fraction 1 and fraction 2 between

Table 1. Master data used in the analysis of clinical evaluation

S/L	Age	Length	Dia	Rx#1	Rx#2	Fx	TD (Gy)	Bladder Dose		Average Bladder Dose	Rectum Dose		Average Rectum Dose
								#1	#2		#1	#2	
1	55	4	25	5	5	2	10	3.36	3.18	2.38	3.36	3.18	3.27
2	40	5	25	5	5	2	10	1.22	1.50	1.58	1.22	1.50	1.36
3	45	4	25	5	5	2	10	1.98	2.62	2.69	1.98	2.62	2.30
4	70	4	25	5	5	2	10	2.67	1.04	1.50	2.67	1.04	1.86
5	40	4	30	5	5	2	10	2.05	2.44	2.07	2.05	2.44	2.25
6	40	4	25	5	5	2	10	1.99	1.58	2.28	1.99	1.58	1.79
7	45	5	30	5	5	2	10	2.17	2.44	3.20	2.17	2.44	2.31
8	55	4	25	5	5	2	10	2.22	1.27	2.89	2.22	1.27	1.75
9	50	4	25	5	5	2	10	2.21	2.03	2.20	2.21	2.03	2.12
10	60	5	30	5	5	2	10	2.20	3.12	3.51	2.20	3.12	2.66
11	50	4	25	5	5	2	10	2.39	2.18	2.70	2.39	2.18	2.29
12	57	6	25	5	5	2	10	1.73	2.32	3.14	1.73	2.32	2.03
13	56	4	25	5	5	2	10	2.05	3.71	3.70	2.05	3.71	2.88
14	57	5	30	5	5	2	10	2.75	2.14	2.39	2.75	2.14	2.45
15	55	5	25	5	5	2	10	3.14	3.38	3.95	3.14	3.38	3.26
16	65	5	30	5	5	2	10	2.77	2.68	4.17	2.77	2.68	2.73
17	45	4	25	5	5	2	10	3.03	3.58	2.50	3.03	3.58	3.31
18	45	4	25	5	5	2	10	2.73	3.26	3.61	2.73	3.26	3.00
19	58	4	30	5	5	2	10	3.36	3.54	3.86	3.36	3.54	3.45
20	42	4	30	5	5	2	10	3.50	3.59	4.84	3.50	3.59	3.55
21	55	4&5	25	5	5	2	10	3.31	2.36	2.34	3.31	2.36	2.84
22	60	4&5	25	5	5	2	10	5.45	3.03	3.49	5.45	3.03	4.24
23	40	5&6	20&30	5	5	2	10	3.15	3.66	3.49	3.15	3.66	3.41
24	65	4	25&30	5	5	2	10	2.10	1.91	2.84	2.10	1.91	2.01
25	70	5	30&25	5	5	2	10	1.54	1.33	1.84	1.54	1.33	1.44
26	42	4	30	7	7	2	14	3.50	3.59	4.59	3.50	3.59	3.55
27	55	5	25	7	7	2	14	3.14	3.38	3.95	3.14	3.38	3.26
28	39	4	30	7	7	2	14	4.87	4.87	3.81	4.87	4.87	4.87
29	55	5	30	5	7	2	12	4.02	5.63	4.69	4.02	5.63	4.83

all patients is close to zero. This implies that in overall there is not too much difference in the two fractions for all patients.

In order to evaluate whether the total before (fraction 1) and after (fraction 2) differences in the sample are statistically significant, i.e. is this difference statistically different from zero? This would imply that before and after measurements are truly different from each other, rather than not different. To determine this, a re-sampling approach is utilized. For this, the values has been taken from before measurements for each patient and randomly assign to other patients before measurements from the treatment plans. Also, for each patient the after measurements has been taken and randomly assign to other patients after measurements. Then another computation is done of the total difference between the before and after measurements for each patient. This is done 1000 times until we have 1000 total overall differences from the randomized datasets. These observations consist of the "empirical null distribution" of the data and we can use these randomized quantities to determine what the observed total overall difference compares to the randomized ones.

Based on this randomization scheme, the empirical probability that we would see, a total overall difference in the sample as extreme or greater than the observed difference is 0.44, that is 44% of the randomized differences, greater than the observed difference. At the *p*-value cut off of 0.05 - this is not significant (because it is greater than 0.05). Therefore, we conclude that not statistically significant difference between measurements, thus a follow up measurement is unnecessary for the patients tabulated in Table 1.

These permuted differences and the test-statistics generated from them, represent the distribution of the patient

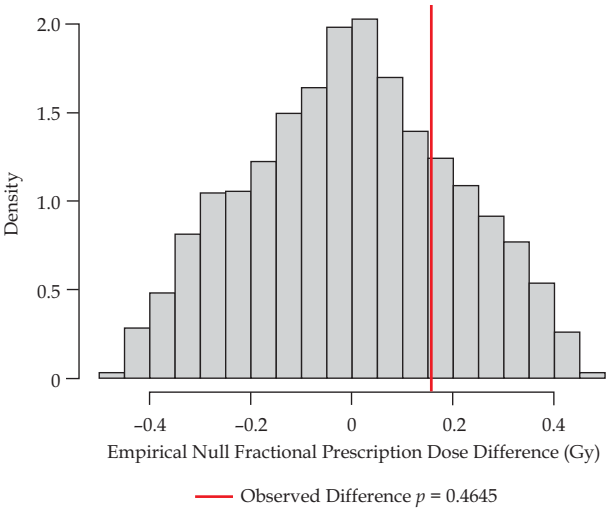

Fig. 1. Empirical null distribution of group differences versus observed sample difference for two prescription dosing fractions

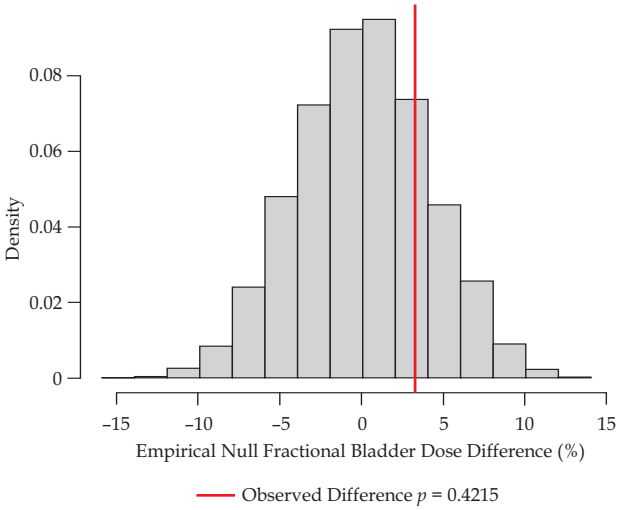

Fig. 2. Empirical null distribution of group differences versus observed sample difference for two bladder dosage percentage fractions

fractional differences that we would expect to see by random chance. If the matched-pairs test statistic based on the observed is much greater or much less than the majority of the 10 000 test statistics based on the permuted values (in our case 95% of them for an alpha level of 0.05), then we would declare the observed value as statistically significant. Otherwise, we fail to reject the null hypothesis that there is no difference in groups means between fractions [8]. Figure 1 is based on the empirical null distribution of group differences versus observed sample difference for two prescription dosing fractions. Figures 2 and 3 represent similar distributions in bladder and rectal dosage fractions. The analysis is based on the clinical data as presented in Table 1.

A histogram of sample fractional prescription dose differences obtained by random chance (via sample permutation) are shown as overlain (red line) with the actual group difference. A difference of 0 signifies no difference between group and larger positive/negative values indicate a greater difference between groups. The *p*-value testing the null hypothesis that the observed prescription dose difference between groups is not different from zero is evaluated via permutation tests (see methods) and it comes to 0.4691. This demonstrates that there is no evidence to suggest a difference between dosing fractions and second fraction being not necessary to plan again in order to deliver the treatment.

A histogram of fractional bladder dosage percentage difference obtained by random chance (via sample permutation) is shown as overlain (red line) with the actual group difference. A difference of 0 signifies no difference between group and larger positive/negative values indicate a greater difference between groups. The *p*-value testing the null hypothesis that the observed prescription dose difference between groups is not different from zero is evaluated via permutation tests (see methods) and it comes to 04277. This shows that there is no evidence to suggest a difference between fractions and second fraction being not necessary.

A histogram of fractional rectal dosage percentage difference obtained by random chance (via sample permutation) as overlain (red line) shown with the actual group difference. A difference of 0 signifies no difference between group and larger positive/negative values indicate a greater difference between groups. The *p*-value testing the null hypothesis that the observed prescription dose difference between groups is not different from zero is evaluated via permutation test (see methods) and comes to 0.8797. This confirm that there is no evidence to suggest a difference between fractions and a second fraction being not necessary.

Figures 4 and 5 depict the variations of bladder and rectum doses for a number of patients when HDR plans were delivered. Radiation oncologists inserted the applicator and CT-scan was performed followed by individual planning for the patients in all fractions for treatments. It should be mentioned that, after the first treatments, patients re-

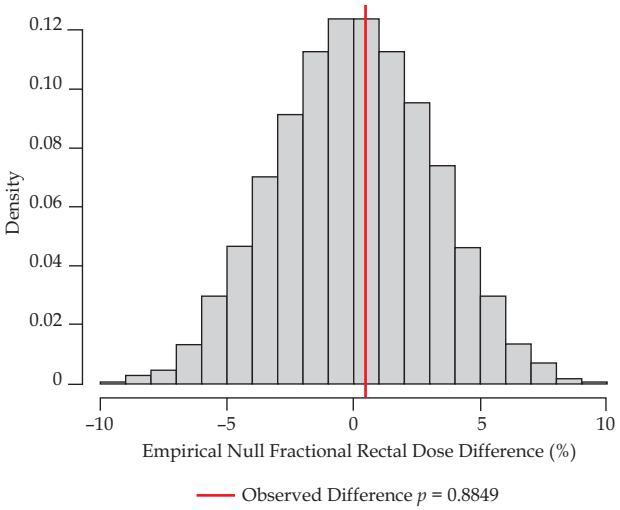

Fig. 3. Empirical null distribution of group differences versus observed sample difference for two rectal dosage percentage fractions

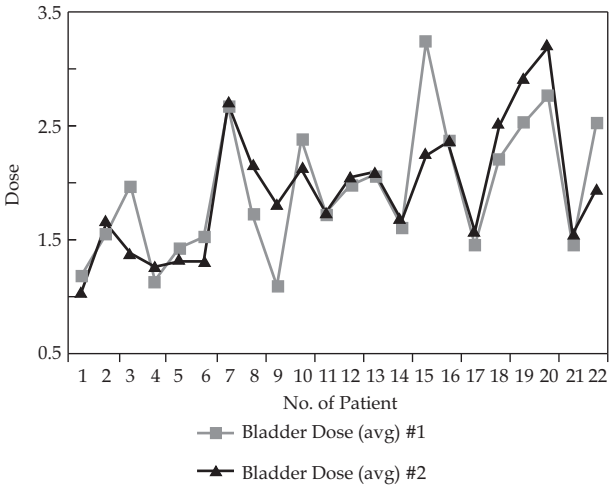

Fig. 4. Average dose differences between fractions for bladder are depicted here for a prescription dose (Rx) = 5 Gy

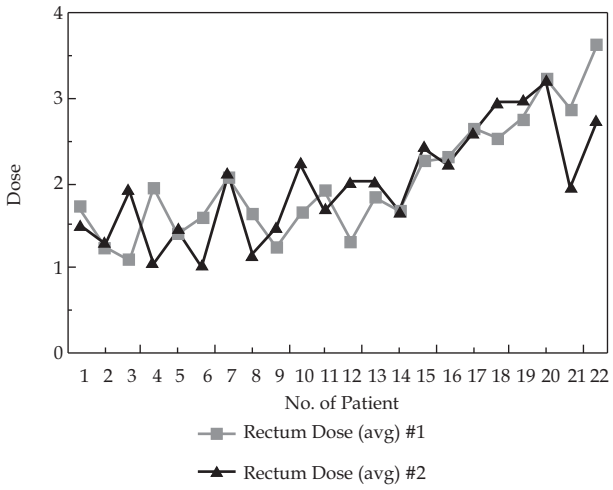

Fig. 5. Average dose differences between fractions for rectum are depicted here for a prescription dose (Rx) = 5 Gy

ceived the second or subsequent fractions at some interval of days, determined by the oncologists. The insertion technique, set up and choice of applicators remained reproducible by the oncologists and, therefore, variation of doses in those anatomy were shown marginal and within the limits as referenced by [1]. Dose variations in bladder and rectum for a prescription dose of 7 Gy also testifies the fact that CT-scan for the first fraction in HDR treatments, using cylindrical applicators, is essential and this first plan can be used for the subsequent fractions, for the same patient, with no notable dose distribution in critical structures. These patients in Table 1 were clinically judged by the oncologists in applicator diameters, point of interest choices and even in prescribed doses. Dose delivery is symmetrical as ascertained in treatment plans using the source installed in the HDR unit.

Figure 6 also highlights the fact that the dose distributions in the anatomical cross section of coronal plane testifies the expected dose values from the center of the applicator to pelvic wall. The doses to pelvic wall in two or three fractions are within the acceptable limits of the radiation oncologists. The study, therefore, analyzed and enumerated and, above all, graphically ascertained that the Co-60 Multisource unit provided the delivery of treatments as per the expected prognosis and outcome for cervical cancer patients. It may be mentioned here that there is a symmetrical delivery of the dose as shown in Figure 6.

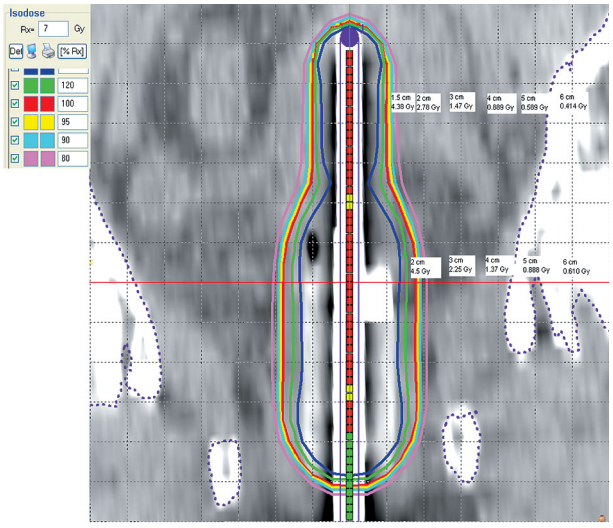

Fig. 6. Tandem-cylinder dose distributions are shown in an anatomical cross-section. Both sides have similar doses as has been expected observed

Discussion

Vaginal Cylinder treatment has proved to be best when the carcinoma of the endometrium is diagnosed. The main risk is thought to be sub-mucosal lymphatic infiltration. HDR treatment, with cylinder applicators, is chosen for the delivery of high dose at the volume of interest [9-11]. Image guided brachytherapy as reported here and CT-scan, provided a study of more than 500 cervical cancer treatments of various stages and extent of disease. This report has been modified later to correlate with the present results. Volumetric and point doses relied on the conformal dose distribution to treat the disease. A represented sample of patients has provided the study parameters viz. symmetry of dose distribution, dose variations in critical organs and, above all, the reproducibility of set up and insertion techniques. This study aimed at analyzing this procedure of treatment using applicators like cylinder and tandem, as the case may be. This study used various prescription doses, as deemed fit by the radiation oncologists and different diameters of cylinders, even a tandem only for anatomical constrictions. Table 1 exemplifies a selection of a large number of patients of almost similar background, age and prognosis. The study analyzes an application of repetitive procedure in using cylinder applicators and dose evaluation in critical structures like bladder and rectum. Figures 1-6 and dataset highlighted the facts that evolved and guided us in presenting the results to an effective conclusion as described below.

Conclusions

In ICRU Report 38 [1], the reference volume is defined as the volume encompassed by the reference isodose, mostly 100%, which is selected and specified in terms of dimensions and absolute volume to compare treatments delivered in different centers using similar techniques. Gynecologic brachytherapy correlation between radiation dose and the normal tissue effects, have been assessed using point doses. Since 1985, these points refer as standard specification points as outlined in the report of ICRU 38 [1]. Generally, a correlation between radiation point doses and dose volume effects has been observed to agree with each other. The statistical analysis in Table 1 has substantiated this agreement as it has been surveyed and reported by Pötter *et al.* [12].

In 2000 GEC-ESTRO established a Gynecological Working Group (CWG) with physicians and physicists from different centers using 3D image guided treatment and planning. The concept was developed to inter-comparison of the outcome of this technique, used by various groups in other clinical practices. The method relies on CT and/or MR imaging rather than 2D orthogonal radiographs. Doses are prescribed to volumes rather than reference points. The GEC-ESTRO has reported in the following years 2002, 2006, 2010 [13-15]. Recommendations by the GEC-ESTRO group on target volume concepts and plan evaluation using DVHs, GTV, high risk (HR), CTV and intermediate risk (IR). Intercavitary approach makes the technique adequate to treat cervical tumors from stage I – IV or in a scheme of multi-therapeutic scheme with surgery [14].

Analysis of data statistically, graphically and dose distribution, in using applicators like cylinder and tandem, have confirmed that for CT-imaged HDR plans, no CT-scan is to be done for the delivery of second and subsequent fractions for the same patient, provided the insertion technique that remained the same. CT-scan with the applicator will be done once only followed by the HDR plan of the first fraction. This plan, after reviewed and accepted, should be applied to all other subsequent fractions for the same patient, as the decay of the source and hence the time of treatment in HDR planning software. This conclusion, therefore, saves time, treatment expenses and avoids CT scan of the patient. The detailed analysis on the measurements of the fractional prescription doses, bladder and rectum doses suggest, very conclusively, that a follow up HDR planning for cylinder treatment is unnecessary. The avoidance of repeated plan has been recognized in this study, so a protocol in using a cylindrical applicator is established and a repeat procedure for planning and delivery is not necessary for the same patient. This approach of 3D image based adaptive gynecological brachytherapy treatments enabled individualized optimization of the dose distribution, resulting in encouraging clinical results. This approach allows for a meaningful assessment of the dose volume histogram parameters and their correlation with clinical outcome [16].

Acknowledgement

Our sincere thanks to Delta Hospital Ltd and Professor S. Mukarram Ali, FRC $_{Path}$, for his encouragement in providing the facilities to work on HDR treatment. Thanks for some clinical support of Dr. Lutfun Nahar, MD.

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