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VOLUMETRIC DOSE CORRELATION WITH CLINICAL CONTROL AND TOXICITY IN PATIENTS OF CARCINOMA CERVIX UNDERGOING HDR INTRA CAVITARY BRACHYTHERAPY

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ABSTRACT **Conclusions:** Our analysis indicated that the ICRU bladder point dose was substantially lower than bladder D2cc & ICRU rectum point dose was higher than the rectum D2cc. No significant acute toxicities were observed, and late toxicities only rectum. The threshold EQD2 dose for rectal toxicity estimated with the curve coordinates was 89.15Gy for Rectum ICRU point (sensitivity 75%, specificity 77.8%). The rectal toxicity threshold dose V2cc EQD2 was 72.18Gy (sensitivity 75% & specificity of 59.3%). D2cc bladder was well within the tolerance limit for all patients. The bladder toxicities were not observed, probably because the bladder doses were overestimated & rectum toxicities were common, probably because the rectal doses were underestimated. With vaginal stricture (13%) common in the study, there is a definite need to evaluate the dose to vagina as a separate OAR as recommended by the ICRU 89. With 3% incidence of faecal incontinence, the rectal sphincter dosimetric evaluation is important for its prevention. This study also conclude that point-dose estimates to be viewed with caution, looking beyond simple reference doses to assess the position qualitatively and packing ICRT placements using diagnostic imaging studies, whenever possible, to improve understanding of the relationship between intra cavitary applications and the underlying anatomy.

KEYWORDS : ICRT (INTRACAVITARY), OAR (ORGAN AT RISK) DOSE, HDR (HIGH DOSE RATE) BRACHYTHERAPY, CARCINOMA UTERINE CERVIX

INTRODUCTION

The doses delivered to tumor and normal tissues (OARs) from intracavitary radiotherapy (ICRT) are difficult to quantify accurately. Traditionally, physicians used reference-point doses to report treatment intensity and to estimate the maximal dose to OARs. In the modern era of volumetric dosimetry, physicians have a strong desire to know exactly where the dose is being deposited during ICRT. Ling et al. [3] published the first report describing the volumetric dose distributions from ICRT in 1987. While the use of ICRU38 [4] reference points provides a useful standard practice for cervical brachytherapy, continuing to report dose to point A or ICRU Report 38 parameters, is fraught with uncertainty. The GEC-ESTRO [12] working group released a series of recommendations promote an adaptive brachytherapy strategy; that is, a volume-based treatment approach, whereby the target is modified with each brachytherapy fraction, based on response to treatment. Ideally, an MRI is obtained (with the applicator in place) with each fraction. Where logistic and financial challenges prohibit this approach, an alternative strategy is to obtain an MRI with the first fraction, and CT for subsequent fractions. CT-based determination of cervical volumes is known to be inferior to MRI-based determinations, and so using MRI as much as possible is thought to be best. For organs at risk, GEC-ESTRO [12] suggest reporting the dose for the most exposed 0.1 cc, 1.0 cc, and 2.0 cc (D0.1cc, D1cc, and D2cc), of the rectum, sigmoid, and bladder. As data regarding optimal treatment volumes evolve, recording the dose to point A (and taking care not to under dose point A) is still recommended. Internationally, prescription to point A remains the norm. But practice is rapidly shifting away from prescriptions based solely on ICRU reference points, to volume-based prescription. Katz et al [8] evaluated the outcomes for tumour control and bladder and rectal morbidity in 808 applications in 396 patients with respect to the dose at point A and also the ICRU Report 38 rectal and bladder points & reported a lack of correlation between them [7]. Shin et al [9] performed CT based intracavitary brachytherapy, compared them with conventional point A based treatment plans, the mean values of bladder and rectal point doses and volume fractions receiving 50%, 80% and 100% of the reference dose did not differ between the plans based on CT or point A. In a comparative study of radiography and CT-based treatment planning in cervix cancer with specific attention to some quality assurance aspects by Fellner et al [10], investigated 28 patients with 35 applications receiving HDR treatment with Ir-192 using PLATO (Nucletron), maximum dose to the rectum was found to be 1.5 times higher than the dose at the ICRU reference point, and for the bladder 1.4 times higher. Kim RY et al [11], evaluated the dose-volume histograms (DVHs) of bladder, rectum, sigmoid colon, and small bowel using image-based 3D treatment planning for intracavitary brachytherapy & found that from CT-based 3-D evaluation, the ICRU bladder point dose was substantially lower than bladder D (2) dose & that special attention be given to the areas of proximal rectum and sigmoid colon due to more frequent high D (2) dose in these areas. In a study by Jamema et al [5], ICRU rectal point dose correlated well with maximum rectal dose, while ICRU bladder point underestimated the maximum bladder dose. In a retrospective dosimetric analysis by Tyagi et al [13], they concluded that treatment planning based on semi-orthogonal films underestimated the bladder D2cc volume doses, but no significant difference was found for rectum & that CT/ MRI based 3D volume based planning is better in assessing the doses to OAR volumes than conventional film point based 2D planning. Study by Onal C et al [14], found that the CT-plan is superior to the conventional plan in target volume coverage and appropriate evaluation of OARs, as the conventional plan overestimates tumor doses and underestimates OAR doses. A comparative study by Pelloski et al. [15] suggested that the ICRU bladder reference point is unacceptable surrogate for the maximal radiation dose delivered to the bladder during ICRT for cervical cancer but, estimated dose to the ICRU rectal point may be a reasonable surrogate for the D_{RV2}. A study by Addeo et al. [16], concluded that ICRU point doses and DR2 DVH generated values were similar for rectum but differed significantly for bladder. In a retrospective study by Tan et al. [17], they concluded that Bladder ICRU was not representative of bladder D2cc and resulted in different total dose. However, Rectum ICRU was found to be similar to D2cc dose and was reliable in total dose computation. In a 3D CT-based volumetric dose assessment of 2D plans using GEC-ESTRO guidelines for cervical cancer brachytherapy by Gao M. et al. [19], they concluded that the 2D plans revealed a suboptimal coverage of CT-based cervix and a negative correlation between coverage and cervical size but Rectum dose to 2 cc weakly correlated with ICRU point dose suggesting that the constraint for bladder in 3D planning was tighter than ABS guidelines in past 2D planning. In a comparative study by Mazeron R et al. [20], it was concluded that the Rectal ICRU Point dose significantly underestimates the D2cc. This difference probably results from the optimization process itself, which consists in

increasing dwell times above the ICRU point in the cervix. A study by Datta NR et al. [21], concluded that prescription based on Point A ICRT doses could lead to uncertainty and under dosage in tumor. ICRU 38 maximum bladder and rectal doses significantly underestimate the maximum doses to these organs and represent the 90th and 95th percentile of the maximum doses to these organs, respectively.

Based on the above studies, this study was carried out to comparatively assess point dose versus volumetric dosimetry and its correlation with clinical control & toxicity in patients of carcinoma uterine cervix undergoing HDR Intracavitary Brachytherapy. The secondary objective was to comparatively assess the clinical correlation with toxicities and local control in point dose versus volumetric planning in these patients. It was a single institution study at a multispecialty tertiary care centre of the Indian Armed Forces. The cases of advanced Carcinoma Cervix from the representative population which included serving defence persons & their families belonging to any race, ethnicity, or age throughout the country who are referred to or first diagnosed at this centre from both rural as well as urban background including both inpatient and outpatient cases who consented to be a part of the study with a signed informed consent. The study was conducted over a period of two years from Jul 2016 to Jun 2018. Consecutive patients as per the inclusion & exclusion criteriae were accrued into the study & the follow up was continued. The median follow up duration was 1.25 years. However, for standardization purpose, the follow up record was done at 6 weeks, 6 months & 1 year post ICRT. Every patient received fractionated HDR ICRT as per the accepted institutional protocol i.e. 3 fractions, 7 Gy each. We used "parametric test" for analysis. In this case sample size was calculated to be at least 30 to retain 80% power of the study and 95% confidence level keeping in view at the most 5% risk, with minimum 80% power and 5% significance level (significant at 95% confidence level). The Type I error probability associated with this test of this null hypothesis is 0.05, α = 5% (i.e. Confidence level = 95%). All patients were included in the study group only after an Informed consent. Histologically confirmed locally advanced Carcinoma of Cervix of any histopathology who were candidates for HDR Brachytherapy), FIGO Stage IB2-IIIB (FIGO Staging for Carcinoma Cervix 2009) with no history of previous radiation, recurrence or distant metastasis. Patient characteristics were females with age < 80 yrs, KPS >= 80%, non-pregnant, with normal Biochemical profile and without any significant medical comorbidities. Consecutive patients meeting the inclusion criteria were recruited into the study. The patients excluded were those with early stage operable disease (Stage I/IBI FIGO 2009) Cervix of any Histopathology, history of previous pelvic irradiation within past 5 years and recurrent or metastatic disease. Also those patients were excluded whose age >80 yrs, KPS <80%, were pregnant, had undergone hysterectomy for any reason, those with abnormal Serum Biochemical Profile, or significant medical co morbidities and prior radiotherapy for any pelvic malignancy. All patients were subjected to a thorough clinical evaluation as per standard guidelines. Performance Status were evaluated as per KPS Scale & documented. Symptoms & Clinical findings were recorded. All patients underwent the physical examination including the following baseline investigations as per NCCN Guidelines): CBC- Complete Blood Count, LFT- Liver Function Tests, RFT- Renal Function Tests, Blood Sugar levels, CXR PA View-Chest X-Ray PA view, Biopsy, Histopathology examination, ECG-Echocardiogram, 2 D Echocardiography, USG Abdomen-Ultrasonography Abdomen, CECT pelvis and abdomen-Contrast Enhanced Computed Tomography & Whole Body FDG PET/ CT scan 18-FluoroDeoxyGlucose Positron Emission Tomograpgy/ Computed Tomography. Patients were given conventional EBRT treatment with 5 (five) fractions a week, (dose 45-50.4Gy/25-28 fractions/5weeks) along with weekly Inj Cisplatin (40 mg/m^2) 5(five) cycles. One week after conclusion of EBRT, patients were assessed for HDR brachytherapy and were subjected to three (3) weekly fractions of 7Gy each as per our Institutional protocol. EBRT was given with a Linear accelerator (LINAC-Model Primus from Siemens,Germany) using 15 MV X-rays, with conventional 2D planning by AP-PA or four field technique to pelvis. HDR brachytherapy fractions started after completion of EBRT. Tandem and ovoid type applicators (Stainless Steel Fletcher-Williamson Asia Pacific applicator from Nucletron, Holland) based on Manchester geometry were used to deliver HDR ICRT. All applications were performed under spinal anaesthesia Vaginal packing with gauze was done to fix the applicator in position and to displace the bladder and rectum away from the vaginal applicators. As a departmental policy we used the same applicator for all three fractions. After the applicator insertion, 7 cc of radio-opaque dye (1: 6 dilutions) was instilled in the balloon of Foley's catheter and patient taken for CT simulation on a helical CT scanner-Philips Brilliance 16 Slice CT Scanner V-2.3.0 2012. Care was taken to ensure that there is minimal applicator position movement during transfer of the patient from the Operation Theatre to the CT scanner and then to the treatment suite. Contiguous slices of thickness 3.0 mm were taken from about 2.0 cm above the tip of the tandem to about 5.0 cm below the inferior surface of the ovoids on a helical CT scanner. No dummies /radio-opaque markers were placed for reconstruction of the applicator geometry or identification of dwell positions. The axial CT images were used for applicator reconstruction as well as for OAR contouring. Sagittal and coronal reconstruction images were used for supporting the contouring. Rectal marker was also inserted during the CT imaging. Rectum was contoured as a solid organ from tip of the coccyx till the sigmoid flexure. Oncentra TPS (Treatment Planning System) V 4.5.3 Year 2016 & control system used for the ICRT delivery was ONCENTRA (Nucletron) TCS Version 3.1.5.500 Year 2016. Bladder was also be contoured without separate bladder-wall contouring. Sigmoid was contoured from the recto-sigmoid till at least the tip of the tandem. The Remote afterloading Brachytheapy machine model utilized for treating the patients with ICRT was single source 444GBq maximum capacity Microselectron HDR V3 (18 channel) by Nucletron. Standard loading was used for creating the typical pear-shaped dose distribution. A dose of 7 Gy was prescribed to point A for each fraction. Dose volume histograms were used to analyse doses to the OARs. Manual dwell position, dwell time optimization was used occasionally to ensure safe OAR doses. The maximum point doses to these organs, along with the minimum dose in the most irradiated tissue adjacent to the applicator for 0.1, 1, and 2 cm^3 ($D_{0.1\ cc}$, $D_{1\ cc}$, and $D_{2\ cc}$) volumes, were noted for all fractions. Once the plan was approved the ICRT was delivered using Ir-192 based HDR brachytherapy machine.

Procedure was abandoned in case any patient sustaining injury in the form of perforation, vaginal tear, excessive bleeding etc. Patients were followed as per the (NCCN Guidelines Version 1.2016) post treatment & data collection was carried till Jun 2018. Statistical tests expected to be used for nominal/ordinal data in the analysis are Pearson chi-square test or Fisher exact test as applicable. Paired t-test was used to compare the difference in means for these dose volume parameters between three fractions. All tests were two tailed and *P* values of <0.05 were taken as significant. Appropriate Statistical test were used where deemed necessary. Data was presented as the mean (S.D). Categorical data are described as number of patient (n) and compared using Pearson chi-square/Fisher exact test. Comparison of mean values between more than two groups, ANOVA test followed by Post-hoc test was used. Student t-test was used to see the mean difference between 2 groups. To analyse the data SPSS version 16.0 was used, alpha value (significance value) was 0.05. Written informed consent was taken all cases. Histological Confirmation was ensured in all cases. Major allergy to Contrast Media was taken as an absolute contraindication to carry the CECT scan. Pregnant ladies, patients of renal anomalies/ deranged RFTs, severe LV dysfunction were excluded from the study. Stratification of patients was done as per the criteria decided above. Clinical evaluation of patients was as taught by standard medical textbooks & guidelines.

Results:

A total of 31 consecutive patients were included in this study. The patients were in various stages of disease as per FIGO classification. The dose was prescribed to Point A. The total ICRT dose prescribed was 21Gy/3# @7Gy per fraction which was delivered over 3-4weeks as per the institutional policy. The overall treatment time including 50.4Gy EBRT over 28 fractions over 6 weeks and 2-4 weeks of ICRT was 8-11weeks.In two cases, patient received 2 fractions of ICRT whereas there were three cases, which were given 4 fractions of ICRT. α/β for tumor is taken as 10 & for normal tissues α/β=3. In those patients who received two fractions of ICRT, the mean treatment time was 9 weeks, Total tumor EQD_2 was 69.39Gy , mean Total Bladder EQD_2 ICRU & 2cc were 72.75Gy & 72.45Gy respectively. Similarly mean Total Rectum EQD_2 ICRU & 2cc were 79.74Gy & 68.155 respectively. In those patients who received 4 fractions due to the OARs doses exceeding the tolerance doses as per the 3 fraction protocol, is as

tabulated below:

Table 1-EQD$_2$ doses of patients who received 4 fractions of ICRT along with standard 50.4Gy/28# EBRT

S No.	Total Tumor EQD2 (Gy)	Total Bladder EQD2 ICRU point (Gy)	Total Bladder EQD2 2cc (Gy)	Total Rectum EQD2 ICRU Point (Gy)	Total Rectum EQD2 2cc (Gy)	Total Sigmoid EQD2 2cc (Gy)
Case 1	81.72	80.46	101.39	89.95	70.56	85.46
Case 2	81.56	88.11	100.36	88.18	72.99	74.09
Case 3	87.31	75.07	107.73	89.71	72.52	95.48

It was observed that the mean total Tumor EQD$_2$ in those cases treated with 4 fractions of ICRT was 83.53Gy. Similarly, mean total Bladder EQD$_2$ ICRU & 2cc were 81.21Gy & 103.16Gy respectively, and mean total Rectum EQD$_2$ ICRU & 2cc were 89.28 & 72.02 respectively. Comparison was done between the point based dosimetry & image (CT) based or volume based dosimetry using the mean of all the doses received by OARs viz. Bladder & Rectum by entire patient cohort using Paired t-test. Bladder conventional dose was measured at ICRU Bladder point & was compared with D0.1cc, D1cc, & D2cc Bladder respectively. Similarly, dose received by Rectum ICRU point was compared with D0.1cc, D1cc & D2cc respectively. Sigmoid volume based doses were documented for all the fractions & mean dose calculated, however no comparison performed. The comparison between conventional point based dosimetry & volume based dosimetry was also expressed as ratio of volume dose to point dose for corresponding OARs. The fraction wise data analysis using both methods is as follows:

First fraction

The mean bladder dose by conventional Point based dosimetry was 5.32Gy ±2.08, whereas that received by 0.1cc volume of Bladder was 8.30Gy±2.18. With a mean difference of -2.98, & p-value<0.01, this difference was found to be significant. When compared with dose received by 1cc volume of bladder that received mean dose of 6.65Gy±1.64, difference was found to be significant, with the mean difference of -1.34. Similarly, when compared with D2cc volume, mean dose received D2cc was 5.99Gy±1.46, mean difference was -0.68, & p-value of 0.018, the correlation was found between Bladder D ICRU & D2cc with the difference being insignificant.

Table 2- Comparison of Mean Bladder dose of first fraction between Volume based & ICRU based dosimetry

	N	Mean	Std. Deviation	Mean difference	t-value	p-value
Bladder Dose (Gy) ICRU pt. 1F	31	5.32	2.08	-2.98	-9.33	<0.001
Bladder Dose (Gy) 0.1 cc 1F	31	8.30	2.18			
Bladder Dose (Gy) ICRU pt. 1F	31	5.32	2.08	-1.34	-4.93	<0.001
Bladder Dose (Gy) 1 cc 1F	31	6.65	1.64			
Bladder Dose (Gy) ICRU pt. 1F	31	5.32	2.08	-0.68	-2.51	0.018
Bladder Dose (Gy) 2cc 1F	31	5.99	1.46			

As per this analysis, it is evident that during first fraction of ICRT, none of the Bladder volume doses correlated with the ICRU based point dose. However, Bladder V2cc correlated more with point based dose amongst the volume based doses. Hence, the Bladder V1cc did not correlate well with the ICRU Bladder point based dosimetry, with the maximum ratio going till the value of >2.5.Hence, there doesn't seem to be any correlation between ICRU Point & Bladder volume doses.However, amongst all the bladder volumetric doses, V2cc seems to be closer to the dose measured at ICRU Bladder point.

Mean dose received by Rectum ICRU point was 5.62Gy±1.85 for the first fraction. When compared with D0.1cc Rectum volume, mean dose received D 0.1cc was 6.15±1.64 with mean difference of -0.53, & p-value 0.088. Rectum mean D1cc was 5.02Gy±1.29, mean difference 0.6, p-value 0.051. Rectum D2cc mean value was 4.47±1.15, & p-value 0.001

Table 4- Comparison of Mean Rectum dose by volumetric & conventional method for first ICRT fraction

	N	Mean	Std. Deviation	Mean difference	t-value	p-value
	31	5.62	1.85	-0.53	-1.76	0.088
Rectum Dose (Gy) 0.1 cc 1F	31	6.15	1.64			
Rectum Dose (Gy) ICRU pt. 1F	31	5.62	1.85	0.60	2.03	0.051
Rectum Dose (Gy) 1 cc 1F	31	5.02	1.29			
Rectum Dose (Gy) ICRU pt. 1F	31	5.62	1.85	1.15	3.90	0.001
Rectum Dose (Gy) 2cc 1F	31	4.47	1.15			

As seen from the table the difference between ICRU point & volume doses is minimum with the 0.1cc but not statistically significant.

Hence from the above plots, it can be stated that none of the Rectum Volume dose correlated with the ICRU Point based doses. However, amongst all the volume based doses, it was found that V0.1cc & V1cc correlated well with ICRU based Rectum point dose for the first fraction of ICRT. Mean doses received by 0.1cc, 1cc & 2cc Sigmoid during first fraction were 5.78Gy±2.27, 4.5Gy±1.67, & 3.99Gy±1.51 respectively

SECOND FRACTION

During second ICRT fraction, the mean bladder dose by conventional Point based dosimetry was 5.22Gy ±2.41, whereas that received by 0.1cc volume of Bladder was 8.54Gy±2.83. With a mean difference of -3.32, t-value was 9.32& p-value<0.01. Mean dose received by 1cc volume of bladder was 6.78Gy±1.75, difference was found to be significant, with the mean difference of -1.56. Bladder D2cc, mean was 6.10Gy±1.45, mean difference was -0.8 & p-value of 0.007, the correlation was found between Bladder D ICRU & D2cc with the difference being insignificant.

Table 5- Comparison of Mean Bladder dose by Volume based & conventional Point based dosimetry for second fraction of ICRT

		Mean	Std. Deviation	Mean difference	t-value	p-value
Bladder Dose (Gy) ICRU pt. 2F	31	5.22	2.41	-3.32	9.32	<0.001
Bladder Dose (Gy) 0.1 cc 2F	31	8.54	2.83			
Bladder Dose (Gy) ICRU pt. 2F	31	5.22	2.41	-1.56	5.23	<0.001
Bladder Dose (Gy) 1 cc 2F	31	6.78	1.75			
Bladder Dose (Gy) ICRU pt. 2F	31	5.22	2.41	-0.88	2.90	0.007
Bladder Dose (Gy) 2cc 2F	31	6.10	1.45			

With the above table, it is evident that the Bladder ICRU point dose correlated well with the D2cc volume dose and that the V0.1cc Bladder doses do not correlate well with Bladder ICRU based point dose. The V1cc Bladder doses do not correlate with Bladder ICRU based point dose. Most of the values were between the ranges of 0.8-2 with an outlier at ~3.2.

Also the V2cc Bladder doses correlate with Bladder ICRU based point dose. Mean dose received by Rectum ICRU point was 5.94Gy±2.22 for the second fraction. When compared with D0.1cc Rectum volume, mean dose received D 0.1cc was 6.38±2.17 with mean difference of -0.43, & p-value 0.122. Rectum mean D1cc was 5.04Gy±1.58, mean difference 0.90, t-value 3.36, p-value 0.002. Rectum D2cc mean value was 4.44±1.34, with mean difference of 1.51, & p-value <0.001.

Table 6- Mean Rectum dose comparison between volume based & conventional ICRU point based dosimetry for second fraction of ICRT.

	N	Mean	Std. Deviation	Mean difference	t-value	p-value
Rectum Dose (Gy) ICRU pt. 2F	31	5.94	2.22	-0.43	1.59	0.122
Rectum Dose (Gy) 0.1 cc 2F	31	6.38	2.17			
Rectum Dose (Gy) ICRU pt. 2F	31	5.94	2.22	0.90	3.36	0.002
Rectum Dose (Gy) 1 cc 2F	31	5.04	1.58			
Rectum Dose (Gy) ICRU pt. 2F	31	5.94	2.22	1.51	5.31	<0.00 1
Rectum Dose (Gy) 2cc 2F	31	4.44	1.34			

It is observed that the V0.1cc Rectum doses correlate well with Rectum ICRU based point dose. Most of the values of the ratio were in the range of 0.6-1.2. It is observed that the V1cc Rectum doses correlate well with Rectum ICRU based point dose. Most of the observations were in the range of 0.5-1. Also, the V2cc Rectum doses correlate well with Rectum ICRU based point dose. Most of the values in the plot were between 0.5-1.0. Hence all the volume doses of Rectum V0.1cc, V1cc, & V2ccc for the second fraction correlated with the ICRU point based doses. Mean doses received by 0.1cc, 1cc & 2cc Sigmoid during first fraction were 6.88Gy±3.33, 5.05Gy±2.02, & 4.37Gy±1.67 respectively.

THIRD FRACTION

During third ICRT fraction, the dose received by the Bladder ICRU point was 5.69Gy ±2.27, whereas that received by 0.1cc volume of Bladder was 8.87Gy±2.67. The mean difference was -3.18, & p-value <0.001. Mean D1cc Bladder was 7.07Gy±1.65, difference was found to be significant, with the mean difference of -1.38, & p-value of 0.001. Bladder D2cc, mean was 6.41Gy±1.37, mean difference was -0.72, & p-value of 0.076, no correlation was found between Bladder D ICRU & D2cc.

Table 7- Comparison of Bladder dose by volumetric method & conventional point based dosimetry for third fraction of ICRT.

	N	Mean	Std. Deviation	Mean difference	t-value	p-value
Bladder Dose (Gy) ICRU pt. 3F	29	5.69	2.27	-3.18	8.22	<0.001
Bladder Dose (Gy) 0.1 cc 3F	29	8.87	2.67			
Bladder Dose (Gy) ICRU pt. 3F	29	5.69	2.27	-1.38	3.61	0.001
Bladder Dose (Gy) 1 cc 3F	29	7.07	1.65			
Bladder Dose (Gy) ICRU pt. 3F	29	5.69	2.27	-0.72	1.84	0.076
Bladder Dose (Gy) 2cc 3F	29	6.41	1.37			

It is clear from the above table that Bladder V2cc dose correlates better than V0.1cc; V1cc with the ICRU based Bladder point doses. Hence for the third fraction, the V0.1cc Bladder dose correlated well amongst the volume based doses with the ICRU based Bladder doses. Mean dose received by Rectum ICRU point was 5.55Gy±2.09 for the third fraction, by D 0.1cc was 6.28±1.83 with mean difference of -0.73, t-value of 3.44 & p-value 0.002. Rectum mean D1cc was 5.10Gy±1.42, mean difference 0.45, p-value 0.06. Rectum D2cc mean value was 4.58±1.23, with mean difference of 0.97, & p-value 0.001.

Table 8- Comparison of Rectum dose by volumetric method & conventional point based dosimetry for third fraction of ICRT.

	N	Mean	Std. Deviation	Mean difference	t-value	p-value
Rectum Dose (Gy) ICRU pt. 3F	29	5.55	2.09	-0.73	3.44	0.002
Rectum Dose (Gy) 0.1 cc 3F	29	6.28	1.83			
Rectum Dose (Gy) ICRU pt. 3F	29	5.55	2.09	0.45	1.96	0.06
Rectum Dose (Gy) 1 cc 3F	29	5.10	1.42			
Rectum Dose (Gy) ICRU pt. 3F	29	5.55	2.09	0.97	3.92	0.001
Rectum Dose (Gy) 2cc 3F	29	4.58	1.23			

This table implies that for the third fraction of ICRT in the study cohort, the Rectum V2cc dose correlates with the ICRU Rectum point based dosimetry. Mean doses received by 0.1cc, 1cc & 2cc Sigmoid during third fraction were 5.67Gy±2.17, 4.35Gy±1.54, & 3.87Gy±1.32 respectively.

LOCAL CONTROL

Patients were kept under surveillance as per the latest NCCN guidelines at the time the treatment conclusion and frequency of review was 3 months. Local control and toxicity was assessed at 6weeks, 6months & 1 year. At 6 weeks, all the patients in the study cohort had good loco regional control but for one patient who had loco regional failure in the form of no response. At 6 months, 4 patients were found to have loco regional recurrence. Three of these patients developed distant metastases by this time for which they were started on palliative chemotherapy. At 1 year post treatment, the figure of patients who had loco regional recurrence risen to 5, whereas remaining 26 patients had no loco regional residue/recurrence & continue to be on surveillance as per the latest NCCN guidelines.

It was observed that total of 5 patients had poor loco regional control over a period of 1 year.

TOXICITY:

All toxicities were classified as per CTCAE version4.0. Irradiation to the pelvic region as part of treatment for cancer of the cervix can cause urinary problems due to injury to mucosa, vasculature, and smooth muscles. Acute reactions occur within 3 to 6 months of treatment. Chronic changes occur later. Acute reactions present as dysuria, frequency, and urgency as a result of radiation cystitis. Strictures or fistula can develop during the years following RT. After the entire course of treatment including EBRT followed by ICRT, the patient were followed up for toxicities in the entire study period. In this cohort, treatment related toxicities were recorded at 6 weeks, 6 months & 1 year duration. There were no toxicities at 6 weeks after treatment concluded. Few patients developed acute reactions in the form of vaginal stricture & proctitis, while some patients developed chronic toxicity like incontinence & severe anemia consequent to chronic radiation proctitis. However, late toxicities are contemplated it can be followed up in future.

Table 9-Toxicity at 06 weeks

TOXICITY AT 06 WEEKS	Frequency	Percent	Valid Percent	Cumulative Percent
None	31	100	100	100

At 6 months after the treatment concluded, 5 patients developed Grade 2 Vaginal stricture, 1 patient developed Grade 3 Radiation proctitis & Grade 2 fecal incontinence at this point of follow up.

Table 10- Toxicity at 06 months

TOXICITY AT 06 MONTHS	Frequency	Percent	Valid Percent	Cumulative Percent
None	25	80.6	80.6	80.6
GRADE 1 VAGINAL STRICTURE	2	6.5	6.5	87.1
GRADE 2 VAGINAL STRICTURE	2	6.5	6.5	93.5
GRADE 3 RADIATION PROCTITIS	1	3.2	3.2	96.8
GRADE 2 VAGINAL STRICTURE & GRADE 2 FECAL INCONTINENCE	1	3.2	3.2	100
Total	31	100	100	

At 1 year after the treatment concluded, 4 patients had Grade 2 Vaginal stricture, 3 patients developed Radiation proctitis, one Grade1, one Grade2 & one Grade3. One patient developed Grade3 anemia following bleeding per rectum as a treatment sequelae. Two patients developed Grade 2 fecal incontinence.

Table 11-Toxicity at 01 year

TOXICITY AT 01 YEAR	Frequency	Percent	Valid Percent	Cumulative Percent
None	24	77.4	77.4	77.4
GRADE 1 VAGINAL STRICTURE	1	3.2	3.2	80.6
GRADE 2 VAGINAL STRICTURE	4	12.9	12.9	93.5
GRADE2 FECAL INCONTINENCE	1	3.2	3.2	96.8
GRADE 3 RADIATION PROCTITIS; GRADE 2 VAGINAL STRICTURE; GRADE 3 ANEMIA	1	3.2	3.2	100
Total	31	100	100	

The rectum EQD_2 ICRU & rectum EQD2 2cc doses were compared with the toxicity observed in the study population. The area under the curve was 77.8% with standard error of 0.116 for Rectum ICRU EQD2 while that for Rectum 2cc EQD2 was 63.9% with standard error of 0.377.

The threshold EQD_2 dose for rectal toxicity was estimated with the help of curve coordinates & was found to be 89.15Gy for Rectum ICRU point with sensitivity of 75% and specificity of 77.8%. The rectal toxicity threshold dose V2cc EQD2 was found to be 72.18Gy with sensitivity of 75% & specificity of 59.3%. Thus, the correlation was established & it is depicted in the figure below.

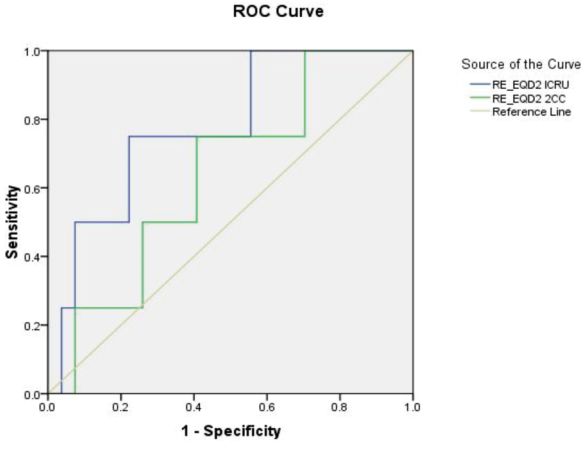

Figure 29-ROC curve for rectal toxicity

Discussion:

In this study, the conventional ICRT plan based on ICRU reference points and the CT-volume based ICRT plan in patients with cervical cancer was compared. Traditionally, dosimetry of ICRT of Ca Cervix was based on orthogonal radiographs recommended by ICRU 38 [4], which allow the evaluation of point doses such as Manchester points A, B, ICRU rectal and bladder reference points. Orthogonal radiographs provide spatial information of the applicator with respect to bony structures. However, this time-tested system has a limitation of computing the doses received by the volumes of the critical structures. Over the past two decades, there have been significant advances in imaging and volume- based brachytherapy planning, with an advantage to determine the dose volume parameters for the critical structures. We undertook this observational study to compare, validate and document the correlation between volume - based doses to rectum and bladder with the conventional standard ICRU 38 rectal and bladder points, and also find out the clinical correlation with local control and toxicity by doing post treatment surveillance of the patients observed.

ICRU 38 [4] recommends the reporting of reference volume which can be obtained from the product of height, width and the thickness of the pear-shaped isodose volume. Esche et al. [58] evaluated the reference volume from the milligram-hours radium. Other investigators [33, 59-60] calculated using the product of height, width and thickness of the pear-shaped volume. However, in the present study, reference volume was calculated from the CT based treatment plan after the implant placement followed by CT imaging at the Oncentra (Nucletron) Treatment Planning system at our centre. The conventional plan with the point-A dose calculation relies on reference points on orthogonal films, not tumor volumes defined on CT, which may cause underestimation of tumor doses. Likewise, the calculation of rectum and bladder doses made with ICRU reference points, not with rectum and bladder volumes, may not reflect the actual organ doses. Since the ICRU did not define standard points for the sigmoid colon and small bowel, it is not possible to compare doses to these organs with conventional point based dose. To overcome such problems, CT-guided 3D ICRT treatment planning has been used successfully for customizing the dose distribution according to tumor extent and providing detailed dose-volume information on the target volumes and surrounding tissues [6, 32]. The study by Onal C et al [14], demonstrated that CT-guided ICRT planning is superior to conventional point A planning in terms of both conformity of target coverage and evaluation of OARs, including the sigmoid colon, bowel, bladder, and rectum. Some investigators have reported that the point A-dose in the conventional plan overestimates the target volume dose coverage [19, 32]. In addition, more advanced tumor stages and larger target volumes receive less coverage with the prescribed dose, which may result in poor local control [9]. Datta et al. demonstrated that the percentage of tumor encompassed within the point-A dose envelope ranged from 60.8% to 100%, and this percentage depended on the tumor volume at the time of ICRT [21].

For evaluating the maximum doses to OARs, the dose to a clinically significant volume is used; that clinically significant volume can be defined as the volume exposed to a minimum dose in the part of the OAR that receives the highest dose. The size of this volume can be absolute (e.g., 1, 2, 5, or 10 cc) or relative (e.g., 1%, 2%, 5%, or 10% of the contoured OAR). Several investigators have compared the dose volume based on either the exterior organ contour or only the organ wall, for the bladder and rectum [25, 56-57]. To evaluate organ wall dose correctly, the volume of 2.0 cc is considered, because the V2cc computed for the external contour are almost the same as the V2cc to the organ wall. Also, this 2.0 cc volume of tissue in the highest dose region is probably more clinically relevant. In some past studies, the rectum and bladder doses were found to be greater than the corresponding ICRU reference doses [32, 42, 18, and 56]. In these studies, the true bladder and rectum doses were 1.5–2.5 times greater than the corresponding ICRU reference point doses. Pelloski et al.[15] compared the minimal doses delivered to 2 cc of the bladder and rectum (D_{BV2} and D_{RV2}) and found that ICRU bladder reference point dose was significantly lower than the D_{BV2}, but the ICRU rectum reference point dose was not significantly different from the D_{RV2} [56]. However, in this study, it was observed that the mean total Bladder dose ICRU point was 5.41Gy±2.25 as compared to mean total Bladder dose V0.1cc of 8.57Gy±2.56; mean total Bladder dose V1cc of 6.83Gy±1.68, V2cc mean total bladder dose of 6.16Gy±1.42; showing that ICRU point underestimated the Bladder dose significantly. Similarly, the mean total Rectum dose ICRU point in our study was 5.70Gy± 2.05 as compared to mean total Rectum dose V0.1cc of 6.27Gy±1.88, mean total Rectum dose V1cc of 5.05Gy±1.43, V2cc mean total rectum dose of 4.49Gy±1.24 ; showing that ICRU point overestimated the Rectum dose although V1cc is correlating better with ICRU based Rectal point dose. Studies [17, 33, 18, 61] had shown poor correlation of rectal doses from the CT plans with the ICRU rectal reference point dose. ICRU rectal reference point underestimated the maximum dose, and the ratio of the maximum dose and the ICRU rectal dose reported varies in the range of 1.4-2.8[17, 33, 18, and 61]. The large variations reported may be attributed to several factors such as different types of applicators used, inter-observer variability in contouring of critical structures, etc. van den Bergh et al. [23] suggested that a good correlation between ICRU rectal point from radiograph-based planning and the maximum dose from the CT planning could be obtained by calculating the maximal dose to the rectal wall as it could be better visualized on the axial section of the CT images. Pelloski et al. [15] reported almost similar results as that of Jamema et al. for rectum (Pelloski: 1.00; Jamema et al. [5], 1.11 ± 0.2). In this study, the ratio of volume dose and the ICRU dose was taken for various fractions. The mean value for the ratios for various fractions of ICRT was averaged & average value compared with unity. The mean

Bladder V0.1cc to ICRU bladder point ratio was 1.7429, V1cc: ICRU point was 1.4006 & for V2cc bladder : ICRU was 1.2658, thus pointing towards the fact that ICRU Bladder point correlated best with V2cc Bladder dose amongst the volume doses. When comparing the ratio values for the Rectum dose, they were 1.168, 0.9489, & 0.838 for V0.1cc, V1cc, & V2cc respectively. This analysis showed that the value of ICRU Rectal point correlated well with V1cc Rectum dose amongst all the volume doses of rectum. In our study, the mean EQD2 V2cc of bladder was found to be 1.13 times the mean EQD_2 ICRU bladder reference point. These results differ from other studies published in the literature, where the ICRU bladder reference point underestimated the maximum dose by two to three times [17, 18, 60, 24]. Barillot et al. [60] found that the maximum dose in the bladder calculated from the trans-abdominal ultrasonography was an average 2.7 times higher than the ICRU bladder reference point. Good correlation was found between ICRU bladder reference doses calculated by ultrasonography and orthogonal radiographs. However, no correlation was found between the ICRU reference dose and the maximal bladder dose. Out of 69 cases evaluated, in 75% of patients the maximum dose exceeded the ICRU reference dose by 2-8 times [60]. The following authors also evaluated the ratio of maximum dose to the ICRU bladder reference point dose: Kapp et al., [22] 1.44 (range 1.0-1.7); Tan et al., [25] 1.32 (range 0.62-2.43); Fellner et al., [10]1.4 ± 0.5; Jamema et al., [5] 1.56 ± 0.3 and the present study 1.13 (range-0.54s-2.65). ICRU 38 [4] bladder point underestimates the bladder doses, and this finding has been consistent with those of many series mentioned above. However, the wide range of the ratio could be attributed to the various methods used, such as ultrasonography, radiographs and CT, to evaluate the maximum dose. However, the ratios found using the CT images [20, 30, 42, 61, and 64] were found to be in good agreement with each other and that found in the present study. In image-based dosimetry, reconstruction of applicators was done using the CT images. Ling et al., [3] minimized the metal artefacts by manipulating the CT window and level settings for standard Fletcher Suit applicators during the CT scan. Fellner et al [30] had followed the method of overlaying the isodose distribution calculated on the basis of radiographs on the CT images with the help of corresponding points (coordinate transformation method). Pelloski ,[15] reconstructed the metal Fletcher Suit applicators on the CT images, and the accuracy of reconstruction and source localization was evaluated by comparing the distances of certain points with the expected values (from the orthogonal radiographs). In study by Jamema et al., [5] reconstruction of the applicators using the CT images was difficult due to the artefacts produced by the metal applicators. Hence to evaluate the accuracy of reconstruction for quality assurance reasons, the CT reconstruction was compared with the orthogonal radiograph-based reconstruction of the applicator. The visualization of applicators in the orthogonal radiographs was of excellent quality, and it formed the baseline for comparison. The external reproducibility of the applicator with respect to the patient's leg position was maintained so that the movement of the applicator could be minimized. Sauer et al. [26] concluded that geometrical uncertainties such as mobility of the rectum, was estimated to be less than 3 mm before and after treatment. The uncertainty increases with increasing time between the application and the treatment. Thomadsen et al [27] concluded that no movement of the patient should be allowed because even small changes in the position of the legs can produce large change in the dose to the bladder and rectum. Grigsby et al [28] reported movement of ICRU bladder and rectal reference points and Manchester points A and B relative to bony structures during a time interval of two intracavitary implants. It was concluded that the mean shift of about 10-15 mm was observed with dose deviation as large as 35%. The successful implementation of image-based dosimetry for intracavitary brachytherapy for carcinoma of cervix depends on the accurate delineation of the critical structures and the target volume. The use of metal applicators in the present study produced artefacts that made delineation of the critical structures difficult to some extent. However, similar problem was faced by Jamema et al. [5], where the use of radiopaque gauze pack in the vagina helped to delineate rectum, and contrast medium in the bladder enabled to differentiate the bladder from the cervix and the vagina. Other imaging modalities such as Magnetic Resonance imaging/Positron Emission Tomography (MRI/PET)-based volume delineation would improve the accuracy of delineation of critical structures and the target volume, as reported [29-30]. Significant advances in imaging and planning systems have resulted in better evaluation and understanding of brachytherapy in carcinoma cervix. However, image-based brachytherapy is still not widely used in routine clinical practice due to various limitations. Metal applicators produce streak artefacts in the CT images - which makes reconstruction of the applicator difficult, which may lead to inaccurate applicator reconstruction. MRI/CT-compatible applicators are expensive and not as strong as metal applicators, which prohibits the use of these expensive applicators in routine clinical practice, especially in developing countries. Hence refinement of the existing applicators and development of new cost-effective applicators and fast reconstruction methods with delineation of targets and critical structures are required for the implementation of image-based brachytherapy in routine clinical practice. The rectum is the terminal portion of the large intestines that functions as a temporary storage for faeces, as well as providing the urge to defecate. A portion of the rectum is irradiated in patients undergoing radiation for gynaecologic cancer. Acute rectal toxicity includes diarrhoea or loose stools, tenesmus, proctitis, and rectal urgency and/or frequency. The most common late radiation-related rectal complication is bleeding. Rectal ulceration and fistula are much less common. Other late injuries include stricture and decreased rectal compliance, which can result in frequent small stool and/or tenesmus. The anus is also at risk of late complications including stricture and laxity, leading to faecal incontinence. The rectum extends from the rectosigmoid junction to the anus; with the inferior extent variably defined as the level of the anal verge the ischial tuberosities or 2 cm below the ischial tuberosities, or above the anus (the most inferior 3 cm of the intestines). The rectum should be segmented from above the anal verge to the turn into the sigmoid colon, though the superior and inferior borders of the rectum are not always easy to define on CT imaging, and definition of the cranial and caudal extents is variable [1]. The rectum is mobile and distensible, and therefore its position and volume can vary between and during radiation fractions. From historical data, the incidence of severe proctitis in patients with cancer of the cervix is dependent on the prescribed point A dose, with a <4% incidence with doses of <80 Gy, a 7% to 8% incidence after 80 to 95 Gy, and a 13% incidence for doses of ≥95 Gy. In a University of Chicago series of 183 patients treated with conventional radiation and brachytherapy, 9% developed grade 1 to 2 rectal toxicity and 7% developed grade 3 toxicity; a history of diabetes, point A dose, and the pelvic external-beam radiotherapy dose were most significantly correlated with rectal toxicity. Among patients experiencing diarrhoea or loose stools after pelvic radiotherapy, rectal toxicity becomes difficult to differentiate from small bowel toxicity. Rectal toxicity has been modelled using the Lyman-Kutcher-Burman NTCP model, mostly from patients treated with 3D conformal radiation. Most data are suggestive of a small volume effect, meaning that small volumes receiving high dose are most predictive for late effects [1]. In our study, we also tried to correlate the rectal toxicity (no bladder toxicities observed) with the dosimetry. This was done calculating the total EQD_2 dose to rectum at ICRU point and the largest volume based total V2cc EQD_2 dose. This was analysed using the Area under the ROC curve, & it was found that the rectal toxicities correlated well with V2cc EQD_2 dose. The threshold EQD_2 dose for rectal toxicity was estimated with the help of curve coordinates & was found to be 89.15Gy for Rectum ICRU point with sensitivity of 75% and specificity of 77.8%. The rectal toxicity threshold dose V2cc EQD_2 was found to be 72.18Gy with sensitivity of 75% & specificity of 59.3%.The Urinary bladder is a highly distensible organ that collects urine. Symptoms from late radiation-related toxicities include increased urinary frequency, haematuria, and dysuria. Necrosis, contracted bladder, and haemorrhage are less common, severe effects. Perhaps late bladder toxicity is underreported due to its long latency as well as toxicity being attributed to more common causes. Bladder injury can be broadly classified as focal damage (e.g., bleeding) or more global injury (e.g., reduced bladder capacity with secondary urinary frequency). Acute side effects from incidental bladder irradiation are common and include urinary frequency, urgency, and dysuria (symptoms that may also reflect acute urethral toxicity). Late effects attributable to global injury include dysuria, frequency, urgency, contracture, spasm, reduced flow, and incontinence. In contrast, late effects arising from focal injury include haematuria, fistula, obstruction, ulceration, and necrosis. The urinary bladder is a mobile and distensible structure, depending upon the volume of urine within the bladder. Post void residuals may vary due to variable emptying and constant filling. In contouring the bladder, either the volume of the bladder and contents or the bladder wall alone can be segmented (with the latter more representative of a surface) because the bladder is mobile and distensible, determining accurate dose–volume (or dose–surface) constraints is challenging. Detailed dose–volume (or dose–surface) constraints have not been published, in part due to the complexities of assigning dose–volume or dose–surface

metrics to a mobile, distensible structure. Whole-bladder tolerances have been mostly studied in patients with urinary bladder cancer, while partial bladder tolerances have been mostly studied in patients with genitourinary (mostly prostate) and gynaecologic cancers [2]. For whole-bladder irradiation, doses in excess of 60 Gy, particularly with fraction sizes >2 Gy and/or accelerated radiation regimens, result in a significant risk of grade 3 or higher late toxicity. Risks are lower when the whole bladder receives 45 to 55 Gy followed by a boost to >60 Gy to a portion of the Bladder, though toxicity risk has not been correlated to dose– volume metrics. Prior pelvic surgery can result in increased risk of bladder toxicity as a direct result of bladder or urethral trauma and/or denervation of the bladder, which can cause urinary hesitancy or retention, resulting in overflow incontinence [2]. Patients receiving anticoagulants may be at greater risk of haematuria. Cytoxan, independently or with radiation, can cause chronic haemorrhagic cystitis, incontinence, contractions, and vesicoureteral reflux. Radiation-sensitizing chemotherapy may increase risk of acute and late bladder toxicity, though data supporting this are lacking. The bladder toxicities were not observed, probably because the bladder doses were overestimated & rectum toxicities were common, probably because the rectal doses were underestimated. With vaginal stricture (13%) common in the study population the need to evaluate the dose to vagina as a separate OAR has arisen & it has now been recommended to be evaluated by the ICRU 89 recommendations. With the 3% incidence of faecal incontinence in the study population, the rectal sphincter needs to be dosimetrically evaluated for prevention of this complication. Jamema et al. [5] observed that more precise analysis of the dose received by certain volume of OARs can be accomplished by utilizing the DVHs on CT-plans, which may be of critical importance in regard to normal tissue tolerance limits. To ascertain the potential benefit of treatment outcomes, such as tumor control probability and morbidity, ICRT with image-guided 3D planning will be pursued and correlated with the dose-volume parameters.

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