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"A Retrospective Study of Correlation Between Reported Dose Volume Parameters For Urinary Bladder, Rectum & Sigmoid Colon With Clinical Outcome In High Dose Rate Brachytherapy of Carcinoma Cervix"

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I. Introduction

Today point-based two-dimensional Brachytherapy (BT) is most often used for definitive radiotherapy in cervical cancer [1]. Results of Computer tomography (CT)/Magnetic Resonance Imaging (MRI) guided 3-Dimensional brachytherapy are very promising and paving the way to image based Brachytherapy. Feasibility to conform dose in image based BT allowed clinicians to adapt dose distribution in organs at risk and tumor in each fraction. Centers practicing image based BT showed improved dose distribution and outcome and decreased morbidity [1].

The GEC-ESTRO working group published recommendations for reporting target delineation and DVH parameters in MRI-based cervix cancer Brachytherapy [2, 3]. According to available literature [4, 5 and 6], reporting of small volume high dose regions for OAR is recommended. D_{2cc}, D_{1cc} and $D_{0.1cc}$ of any OAR are defined as the minimum doses to the most exposed 2, 1 and 0.1 cc of the respective OAR.

Late side effects in rectum and urinary bladder have always been a major concern in ICBT [7-16]. Till now there is limited data available to correlate clinical outcome with reported doses in image based ICBT and there is no consensus regarding which dose volumes are more important in predicting late toxicities [7-20].

Georg P *et al.* [17] did a study to correlate dosimetric parameters for MRI based 3D planning with rectoscopic findings and clinical rectal side effects. In this study the locations of mucosal changes detected by rectosigmoidoscopy correlates to the MRI defined high dose volumes. The authors established a clear dose-effect and volume- effect relationship in clinic-pathological changes in rectum.

Recently, EMBRACE (An International study on MRI guided brachytherapy in locally advanced cervical cancer) [1], a multi centric prospective study has been started from July 2008 to correlate MRI based DVH parameters for the clinical target volume and for organs at risk with outcome. Study has not completed yet.

Keeping these previous works in background this study aims to search for clinical correlations between reported dose volumes for High Dose Rate ICBT in carcinoma cervix and definite clinical toxicities.

II. Materials and methods

Study

At the study hospital during 2006-2010, 227 patients with cervix carcinomas FIGO Stages IB-IVA were treated with combined EBRT and CT based brachytherapy ± concomitant chemotherapy. All patients were followed up periodically for response and toxicity assessments. Data from this patient pool was gathered retrospectively for assessment in this study. During follow-up, patients were evaluated for bladder, rectal/sigmoid colon morbidity. Recto-sigmoidoscopy and cystoscopy was not done routinely. It was only done if there was any reported history of rectal bleeding or hematuria. Written consent was obtained before the examination. Patients having age 18-70 years without any history of total hysterectomy and/or radiation therapy for any other reason were included in the study.

Patients underwent EBRT with 50Gy in 25 fractions 5 days a week over 5 weeks in AP-PA technique with ^{60}Co machine (Theratron 780C, Best Theratronics Ltd, Ottawa, Ontario, Canada) with or without concurrent chemotherapy(with Cisplatin 40mg/m^2 weekly). During Brachytherapy patients underwent catheterization followed by insertion of the intrauterine tandem (by Manchester or Fletcher Suite type applicator).The empty bladder was instilled with diluted contrast material to define the bladder wall just before taking CT images and the whole organ was delineated and planning was done (Brachyvision TPS, Eclipse, Varian Medical Systems, Palo Alto CA) on the reconstructed CT images. Rectum was defined from ano-rectal junction (levator ani muscle was used as anatomical surrogate for ano-rectal junction a to recto-sigmoid flexure).For defining sigmoid colon we used the protocol used by Georg P *et al*. [17] i.e. from recto-sigmoid flexure to that part of sigmoid which was dislodged more than 2 cm from uterus or parametria. Point A left and right and ICRU bladder and rectal points were marked on the digitally reconstructed radiographs (DRR).

The prescription for HDR was found to be weekly: a) 7 Gy/# X 3 fractions, b) 9 Gy/# X 2, c) 8 Gy/# X 3 and d) 6 Gy/# X4 fractions to point A to get an EQD2 (EBRT + HDR ICBT) of 80 Gy (α/β= 10Gy). 3D manual optimization of the HDR plans was done to restrict the per-fraction D_{2cc} dose to the sigmoid, rectum and bladder, EQD2 (cumulative EBRT and all ICBT fraction doses) dose <75 Gy to the rectum and sigmoid colon and <85 Gy to the bladder(α/β= 3Gy) [1, 20].

Different volume doses to bladder, rectal and sigmoid colon (0.1cc and 2cc) were noted. All the patient were then treated by the GammaMed plus HDR after loader machine (*Varian Medical Systems, Palo Alto, CA*) using ^{192} Iridium.

Follow-up

Study subjects were followed up for late toxicities related to bladder, rectum and sigmoid colon if any every 3 monthly for first 2 years and 6 monthly thereafter.

Late toxicity assessment:

All patients were assessed upon taking history and clinical examinations. We assessed patients based on subjective complaints of the patient. Patients having late toxicities (any toxicity event occurring after 90 days from initial follow up) had undergone detailed clinical examinations and (after having consent) investigations (if needed).

Those patients having per rectal bleeding had undergone proctoscopy and or sigmoidoscopy. Patients having adverse events suggestive of cystitis or haematuria were undergone cystoscopy.

Following events were taken into consideration for toxicity analysis:

Rectal: Proctitis**,** Rectal pain**,** Rectal hemorrhage, Rectal ulceration, Rectal obstruction**,** Rectal perforation, Rectal fistula

Sigmoid colon: Colonic hemorrhage, Colonic ulceration**,** Colonic obstruction**,** Colonic fistula**,** Colonic perforation

Urinary tract: Hematuria**,** Cystitis

Common Terminology Criteria for Adverse Events version 4.02 (CTCAE v4) [21] was used for scoring the toxicity. Each type of toxicity was graded from 0-5. Maximum score in any symptom in any of the follow up visit was considered as score for statistical analysis. Mucosal changes extending both in rectum and sigmoid colon in endoscopic findings were reported in both groups separately for statistical purpose.

III. Statistical analysis

$D_{0.1cc}$ and D_{2cc} doses were calculated for the each of the organs (rectum, Sigmoid colon and Urinary bladder) adding EBRT and Brachytherapy doses (all fractions) considering α/β = 3Gy . The mean values and standard deviation were reported for each dose volume parameters. For statistical analysis, Independent t sample test (2-tailed) and Pearson correlation coefficient was calculated. $P < 0.05$ was considered as statistically significant value. Grade 1-2 were grouped as mild toxicity and grade 3 and above as severe toxicity. For dose–effect analyses, CTCAE grade ≥3 was used as quantal endpoints. All calculations were performed with the International Business Machine Statistical Package for the Social Sciences software version 20 (IBM SPSS, IBM Corporation, USA). Probit regression analysis was performed assuming and analyzing two binary variables toxicity or no toxicity to find out ED50 and ED5 values. Probit analysis was restricted only to those dose parameters which were significantly correlated in baseline analysis.

IV. Results

Descriptive statistics

Descriptive analysis of all 227 patients is detailed in Table 1.In our study most common age group was 45-60years (56.3%).Majority (71.35%) of the patients were post-menopausal. Majority (94.1%) were having squamous cell carcinoma. Majority patients presented with FIGO stage IIB (43.7%) and Stage IIIB (32%). Mean overall treatment time was 81± 19 days.7Gy/3# (50.3%) and 8Gy/3# (19.8%) were two most commonly used ICBT fractionations. In majority (67%) of cases Manchester Type applicator was used. Mean Point A dose was 80.2 ± 7.3 Gy.

Mean doses of EDQD2 $D_{0.1cc}$ and D_{2cc} of rectum, bladder and sigmoid colon were summarized in the **Table 2** below along with EQD2 Rectal Point and Bladder point dose ($D_{ICRU\ RECTAL}$ and $D_{ICRU\ BLADDER}$ respectively). Mean $D_{2cc\ \&}$ ICRU point doses of rectum and bladder were not comparable.

Follow up statistics

Patients were followed up till February 2015. Average follow up time was 40 month 20 days. Patients having minimum 3 months follow up (n = 206) were taken for analysis. The rest 21(9.4%) patients out of the 227 were excluded from the study.

Rectal toxicity

Proctitis, rectal ulcer and rectal hemorrhage were most common toxicities noted in our study. Analysing the follow up data we found 16.02% (n=33) patient had proctitis. CTCAE Grade 1, 2, 3 and 4 incidences were 2.04 %(n =5), 10.2% (n = 21), 2.9% (n = 6) and 0.05% (n = 1) respectively. 12.1% (n=25) patients had rectal pain, among them 2.9% (n = 6) had Grade 1, 5.8% (n= 12) had Grade 2 and 3.3% (n=7) were Grade 3. 18.45% (n = 37) patients suffered rectal hemorrhage. Incidences of Grade 1,2,3,4 rectal bleeding were 3.9% (n =8), 4.3% (n = 9) 6.8% (n =14) and 3.3% (n = 7) respectively. All the patients of rectal bleeding underwent proctoscopy and sigmoidoscopy. Patients having endoscopic evidence of rectal ulcer were classified in rectal ulcer group and analyzed separately.13.1% (n = 27) had rectal ulcer. 2.9% (n =6) had Grade 1, 5.8% (n = 12) had Grade 2 and 3.9% (n =8) had Grade 3 toxicity. There was no Grade 4 toxicity. One patient of rectal ulcer died in subsequent follow up. This event was scored as Grade 5 toxicity 0.05% (n = 1). No episode of rectal obstruction, fisuta and perforation noted.

Sigmoid colon toxicity

Sigmoid colon ulcer and hemorrhage were two morbidity patterns noted in the follow up. Events like Colonic perforation, obstruction and fistula was not seen in this study. Colonic hemorrhage and ulceration were classified on the basis of sigmoidoscopic apperences.9.7 %(n = 20) patients suffered from colonic hemorrhage. Among them incidences of Grade1, 2, 3 and 4 were 1.4% (n = 3), 2.4% (n =5), 3.9% (n = 8) and 1.9% (n = 4) respectively.6.7% (n = 14) patients were diagnosed to have sigmoid colon ulcer. 1.4% (n= 3) were Grade 1, 3.4% (n = 7) were Grade 2 and 1.4% (n = 4) had Grade 3 rectal ulcer. No patient had Grade 4 colonic ulcer.

Urinary tract toxicity:

Cystitis and hematuria were assessed for toxicity events if there was a positive history. Total 16.5% (n = 34) patients experienced cystitis during follow up period. 1.9% (n = 4) had Grade 1, 13.1% (n = 27) had Grade 2 and 1.4% (n=3) had Grade 3 cystitis. 6.7% (n = 14) patients experienced haematuria during follow up among which 2.9% (n =6) had Grade 2 and 3.4% (n =7) had Grade 3. No Grade 1 or Grade 4 haematuria was noted. One patient (0.05%) in hematuria group died later on due to intractable episodes. It was noted as Grade 5.

Dosimetry analysis:

Independent T sample test (2 tailed) was also done to establish difference between Groups with severe toxicities (CTCAE Grade≥ 3) with mild toxicities (CTCAE Grade 1-2).

Rectal toxicity

For proctitis significant differences were found in case of $D_{0.1cc}$ (110.3±16.9Gy & 89.9±17.5Gy,P = 0.003) and D_{2cc} doses (85.4±7.5 & 75.8±46.8 P = 0.037) of rectum. Dosimetric analysis also showed similar findings in case of Rectal haemorrhage ($D_{0.1cc}$ :: 106.1 ± 13Gy & 89.1 ± 17.6Gy ,P = **<0.001;** D_{2cc}: 84.4± 4.3Gy & 76 ± 5.2Gy,P= **0.041)** and Rectal ulcer ($D_{0.1cc}$: 104.5 ± 18.5Gy & 89.9 ± 17.6 Gy,P = **0.016;** D_{2cc} : 82 ± 7.7Gy & 75.9 ± 4.8Gy

No difference was found in colon and urinary bladder events. Details given in **Table 3**

Dose effect analysis:

Dose effect analysis was done using Probit regression model to find out ED5 and ED50 dose values. This analysis was restricted to only those dose volumes which showed statistical significant differences between Mild and Severe symptomatic groups. Results are summarized in Table 4. All dose–effect relationships were well defined, with p dose < 0.05. For proctitis with CTCAE Grade ≥3 ED5 increases from 68.75 Gy to 79.97 Gy for D_{2cc} to $D_{0.1cc}$ .The ED50 increases from 71.75Gy to 82.9Gy.For Rectal haemorrhage with CTCAE Grade ≥3 similarly ED 5 increases from 73.89Gy to 92.57Gy. The ED50 increases from 87.29 Gy to 122.47Gy. For rectal ulcer with CTCAE Grade ≥3 ED5 increases from 74.51Gy to 93.57Gy.Similarly ED50 increases from 99.38Gy to 150.63Gy.

Dose effect relationships are also illustrated graphically in **Figure 1 & 2.**

On analyzing influence of 'brachytherapy fractionation' schedule on toxicity outcome no statistical difference was found (**Table 5**). There were dosimetric differences while comparing brachytherapy fractionation schedule which did not convert to toxicity parameter differences.

V. Discussion

In the treatment planning for cervical cancer brachytherapy, MRI- or CT-based 3D treatment planning is being increasingly used these days. To assess the dose to the rectum, 3D dose-volume parameters, including $D_{0.1cc}$, D_{1cc}, and D_{2cc} of the rectum calculated with DVH, are recommended for recording and reporting [2,3]. Several investigators reported the relationship between these 3D dose-volume parameters and clinical outcomes. Georg P *et al.* calculated MRI-based dose-volume parameters and analyzed their correlation with clinical symptoms and recto-sigmoidoscopic findings. They reported that D_{2cc} dose was significantly higher in patients with clinical symptoms or moderate to severe mucosal changes than in those without clinico-pathological changes. They also found a significant dose effect correlation. They also calculated ED50 values for higher grade rectal morbidities [17]. Koom *et al.* compared CT-based dose-volume parameters with the findings of rectosigmoidoscopy, reporting that $D_{0.1cc}$,D_{1cc} and D_{2cc} were significantly greater in patients with moderate to severe mucosal changes [22] .These data suggested that 3D dose-volume parameters may predict late rectal morbidity. However, long-term follow-up data on dose-volume parameters are quite limited. In case of bladder toxicity dose volume parameters are even more unclear. Researchers showed that CT and MRI-based scans at brachytherapy seem to be equally adequate for OAR DVH analysis [23]. At present, a large number of centers are practicing the MRI and CT based image guided brachytherapy planning. Standardization of this practice needs standard dose volume constrains guidelines. As the OARS are contoured using identical anatomical landmark a similar way in CT or MRI based planning, the same dose–volume constrains may be used in either case.In this present study attempts were made to establish dose effect correlation. The study was done in retro-prospective format of 206 patients with a mean follow up of 40 months (6 month – 72month).All patients not underwent endoscopic (cystoscopy/sigmoidiscopy) evaluation in fixed interval so a simpler grading system like CTCAE was used to evaluate morbidity pattern. Investigations were done only in symptomatic patients. Majority of colo-rectal occurred within first two years of follow up. Reported incidences of rectal bleeding are variable in literatures. In a study by Chun *et al.* incidence was 12.7% (n= 213)[29].Other older studies reported an actuarial rate for rectal complications between 14% and 18% at 5 years[15,22,29].But these studies [14,22,28,29] were based on two dimensional point based planning. In our study over-all colo-rectal morbidity was seen in 21% patients which is little less than previous published report by Chen *et al.* (n= 128, 29% in 43 months median follow up)[24] but similar to other reports [14,22,28,29] . Georg P *et al.* found even higher incidence rate (37%), but their study sample was very less (n=35) [17]. In the present study only symptomatic patients underwent endoscopic evaluation which might lead underestimation of true incidence. Some newer studies with MRI based planning and reporting dose volume parameters are available now but also with variable results [30-33] .In a study by Potter R and colleagues with 145 patient incidence of recto-sigmoid and bladder late morbidities were 8.9% and 14.5% respectively [30].

D_{2cc} dose difference of rectum (proctitis [82.6Gy/74.9Gy],rectal bleeding [80 Gy/76.2Gy] and ulcer [81.1Gy/75.4Gy]) is little higher than previous report by Georg P *et al.*[17], but supporting the result of Chen *et al.* [24].Mean values of DVH parameters except $D_{ICRU\ RECTAL}$ point doses are significantly higher in Rectal CTCAE Grade ≥3 versus CTCAE grade 1-2.**(Table 3)** with a mean of 81.5 Gy vs. 75.4 Gy. Due to the different dose definitions and different assessment scales used rectal morbidity and dose volume relationship showed a wide range of variability in the literatures. Chen *et al.* defined a cut off value of cumulative rectal BED 110Gy (i.e. EQD2=183.7 Gy) with highly variable dosing schedule [24] .Clark et al. defined BED above 125 Gy3 (i.e. EQD2 = 208.8Gy) as rectal reference dose, which is higher than reported doses in this study. But majority of the previous literature used point based dose reporting [14, 15, 17, 22, 24-27] . .**Table 6** showed comparative description of mean volume dose parameters reported in some recently published literatures. No consensus developed regarding reporting. Few recent studies with MRI based planning described dose-effect cut off values for optimization [30,37,38] .Georg P *et al* in their studies [17,37,38] with MRI based adaptive ICBT recommended EQD2

D_{2cc} cut off dose of rectum, sigmoid colon and bladder to be 70 Gy ,70Gy and 90Gy respectively. The ongoing EMBRACE study [1] also gave emphasis over reporting small fixed dose volume in back ground of MRI based Image guided Brachytherapy (IGBT). Georg P *et al.* used ED values in dose reporting using linear quadratic equation based EQD2 values. However, similar to ongoing EMBRACE study [1] and previous studies [17, 37 & 38] our DVH results also showed precise dose –effect relationships. For rectal events (CTCAE Grade ≥ 3) mean ED5 values and ED50 values were 72.4 Gy and 86.2Gy respectively. Our results corroborates with previous studies [17, 30, 34, 35].

In our dose/ volume analysis, we have attempted to document the dose to the rectum separating it from that of the recto sigmoid. Most previous studies summed the proctitis and enteritis symptoms together [7, 9, 10, and 14]. But the risk is higher to the recto sigmoid part of the colon, and this, not uncommonly, passes unnoticed. Al-Booz H *et al.* [39] reported the recto-sigmoid colon as an unexpected OAR in a majority of cervix brachytherapy plans. Previous dose reporting of sigmoid colon were based on Point A or rectal dose parameters. In this study volume based dose parameters were determined. For sigmoid colon no significant difference exists for $D_{0.1cc}$ and D_{2cc} dose in Grade ≥3 vs. Grade 1-2 analysis **(Table3).** This variation may be due to inter-fraction mobility of the upper part of the sigmoid colon. Dose values are little higher described by earlier experiments, most probably because of the same volumes not receiving the highest dose at each fraction [1, 17, 30, 37, and 38].

There may be a little underestimation of these real incidence parameters in bowel toxicities as asymptomatic patients were not evaluated endoscopically, due to retro-prospective nature of the study. There might be some cases of asymptomatic mucosal changes (i.e. telangiectasia) which were not included in the analysis.

Except for cystitis (16.5%) haematuria was <7% in incidence. In our study urinary tract morbidities especially cystitis and hematuria were not well correlated with dose volume parameters. Previous studies also failed to correlate bladder point dose with late bladder complications [10,40] except for the study by Georg P et.al.[38]. The International Commission on Radiation Units Report 38 system defined a bladder dose point; however, this point is not actual surrogate of the CT-based dose volume reporting [41]. In this study Viswanathan A. N. *et al.* reported mean bladder D2cc dose cutoff of 95 Gy [41]. Georg P *et.al.* in a cohort of 141 patients with MRI based ICBT showed a dose effect correlation of bladder morbidities with EQD2 D_{2cc} dose. ED10 values were ≥ 101Gy for late urinary morbidities grade ≥2 [38]. More over urinary morbidities are better evaluated by scales based on subjective objective, quantitative, scoring systems like LENT/SOMA [41] .Due to retro-prospective nature of the study we did not used LENT/SOMA scales which may be another reason of not getting significant relationship in urinary morbidity irrespective of having large sample size.

VI. Conclusion

This study was able to find out significant dose effect correlation between different volume doses and clinically evident (≥ Grade 3) late morbidities in rectum. In rectal hemorrhage cutoff ED5 and ED50 doses were 92.6 ± 5.8Gy/122.5 ± 13Gy (for $D_{0.1cc}$) , and 73.9 ± 2.6Gy/87.3 ±3Gy (for D_{2cc}) respectively. For rectal ulcer these doses were 93.6±10.6Gy/150.6±20.8Gy, and 74.5 ± 4.6Gy/99.4± 9.2Gy respectively. But for sigmoid colon and urinary bladder toxicities this correlation was not fully established.

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Table legends:

Table 1: Descriptive statistics

Baseline character	**N= 227 (%)**
Age distribution:	
Below 45 years	48(23.3)
45 – 60 years	116(56.3)
Above 60 years	33(16.01)
Median age of presentation	50 years
Menopausal status:	
Premenopausal	59 (28.6)
Postmenopausal	147 (71.35)
Commonest parity:	3
Pathological type:	
Squamous cell carcinoma	194 (94.1)
Adenocarcinoma	7(3.34)
Others	5(2.43)
FIGO stage distribution	
IB	9(4.3)
IIA	17(8.2)
IIB	90(43.7)
IIIA	16(7.8)
IIIB	66(32)
IVA	7(3.3)
IVB	1(0.5)
Treatment statistics:	
Mean overall treatment time	81± 19 days
EBRT BT gap	25 ± 19 days
Mean Follow up time	40month & 20days
ICBT statistics	
Fractionation schedule (1# / wk)	
7 Gy /3#	107 (52)
8Gy/3#	39 (18.93)
9Gy/2#	52(25.25)
6Gy/4#	7(3.4)
Applicator	
Manchester type	138(67)
Fletcher suit Delclos type	68(33)
Mean Point A Dose [EQD2 (α/β= 10Gy)]	80.2 ± 7.3 Gy

Table 2: Different fixed dose volumes of rectum, bladder and sigmoid colon calculated in EQD2.

Parameters		**Mean dose (Gy)**	**Standard deviation (Gy)**	**Comparison by Student t test (2-tailed p value)**	**Median dose (Gy)**
Rectum	$D_{0.1cc}$	90.6	17.8		90
	D_{2cc}	76.2	16		73.0
				0.0016	
	$D_{ICRU\ RECTAL}$	72.1	8.4		71.1
Bladder	$D_{0.1cc}$	105.8	24.5		103.9
	D_{2cc}	82.7	17.8		90
				< 0.0001	
	$D_{ICRU\ BLADDER}$	75.5	14.2		75.6
Sigmoid colon	$D_{0.1cc}$	96	26.5		92.6
	D_{2cc}	68.8	12.4		67

Table 3: Dose volume parameters in relation to clinical outcome in rectum, sigmoid colon & bladder according to CTCAE grading.

Event	Volume Dose	Grade 1-2 toxicity (Mean Dose in Gray)	Grade 3-5 toxicity (Mean Dose in Gray)	P value
Proctitis	$D_{0.1cc}$	89.9±17.5	110.3±16.9	**0.003**
	D_{2cc}	75.8±46.8	85.4±7.5	**0.037**
	$D_{ICRU\ RECTAL}$	71.9 ± 8.4	77.3 ± 8.5	0.148
Rectal haemorrhage	$D_{0.1cc}$	89.1 ± 17.6	106.1 ± 13	**<0.001**
	D_{2cc}	76 ± 5.2	84.4± 4.3	**0.041**
	$D_{ICRU\ RECTAL}$	71.9 ± 7.9	79 ± 7.5	**<0.001**
Rectal ulcer	$D_{0.1cc}$	89.9 ± 17.6	104.5 ± 18.5	**0.016**
	D_{2cc}	75.9 ± 4.8	82 ± 7.7	**0.015**
	$D_{ICRU\ RECTAL}$	72 ± 8.5	73.9 ± 6.9	0.148
Colon Hemorrhage	$D_{0.1cc}$	95.7 ± 21.5	128.8 ± 6.9	0.963
	D_{2cc}	64.2 ± 9.1	69.1 ± 12.5	0.101
Colon Ulcer	$D_{0.1cc}$	95.8 ± 26.4	126.6 ± 6.8	0.69
	D_{2cc}	65.5 ± 10	68.85 ± 12.4	0.552
Cystitis	$D_{0.1cc}$	96.8 ± 31.9	105.9 ± 24.4	0.670
	D_{2cc}	80.2 ± 15.8	83.2 ± 12.5	0.778
	$D_{ICRU\ BLADDER}$	66.6 ± 8.30	75.6 ± 14.2	0.187
Hematuria	$D_{0.1cc}$	102.4 ± 21.1	105.9 ± 24.6	0.656
	D_{2cc}	83 ± 12.4	84.8 ± 13.3	0.731
	$D_{ICRU\ BLADDER}$	72.3 ± 11	75.6 ± 14.3	0.438

Table 4: Dose effect relationship in rectum for CTCAE Grade ≥3

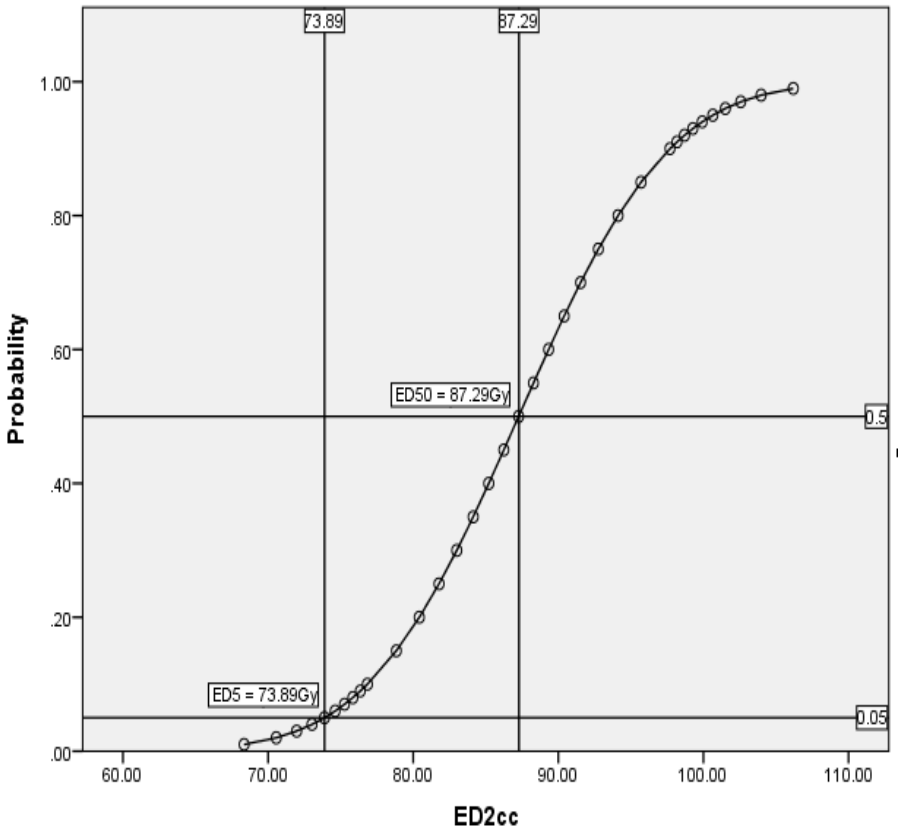
CTCAE Grade	Dose	ED5 (Gy)			ED50 (Gy)			
≥3	Vol	Mean	95% C.I.		Mean	95% C.I.		P value
Toxicity			Upper	Lower		Upper	Lower	
Proctitis	$D_{0.1cc}$	79.97	81.45	75.33	84.58	91.48	82.90	**0.002**
	D_{2cc}	68.75	69.84	64.84	71.75	78.92	70.64	**0.009**
Rectal	$D_{0.1cc}$	92.57	98.39	82.01	122.47	135.51	115.85	**<0.001**
Hemorrhage	D_{2cc}	73.89	76.44	69.13	87.29	93.22	84.29	**<0.001**
Rectal Ulcer	$D_{0.1cc}$	93.57	104.13	72.24	150.63	129.37	171.39	**0.003**
	D_{2cc}	74.51	79.12	65.03	99.38	114.53	90.15	**0.003**

Table 5: Analysis of correlation between fractionation schedule and toxicities

Serial	Toxicity	Significance (correlation by spearman's rho test)
1.	Proctitis	0.906
2.	Rectal hemorrhage	0592
3.	Rectal ulcer	0.865
4.	Colon hemorrhage	0.452
5.	Colon ulcer	0.389
6.	Cystitis	0.892
7.	Hematuria	0.752

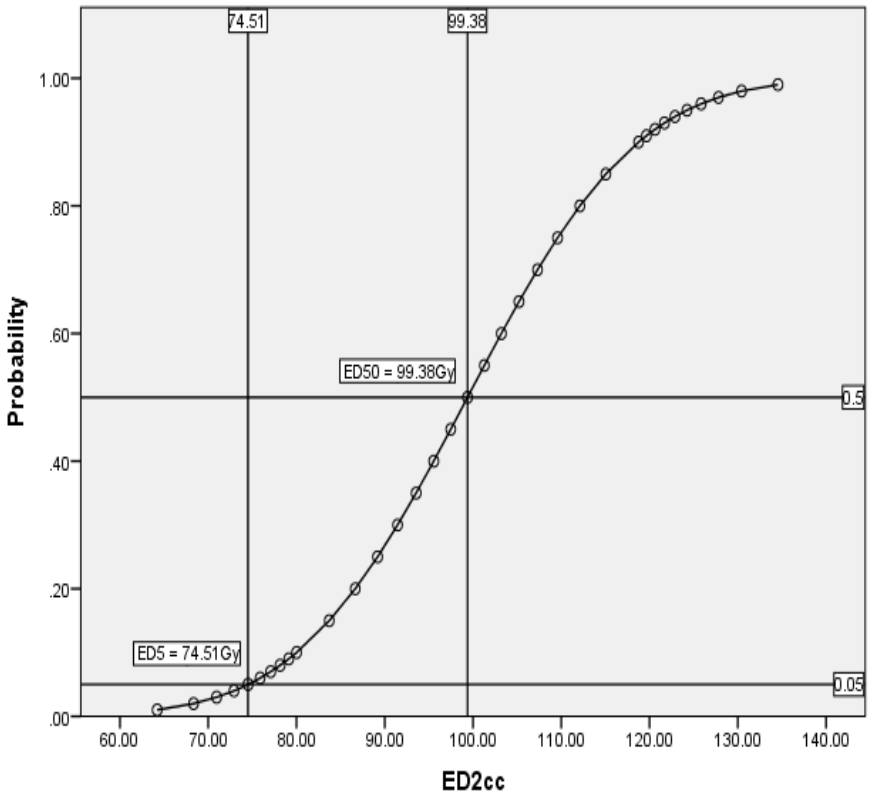
Table 6: Comparative description of dose volume parameters with some recently published studies

Variables EQD2 Dose in Gy (□/□ =3Gy)	U Mahantshetty et. al. [35]	Lindegaard et. al.[33]	Georg P et. al. [17]	Chargari C et. al. [32]	De Brabandere et. al. [34]	Current study
Rectal $D_{0.1cc}$	66.0 ±9.9	74± 9	86 ±27	70.6 ±11	68± 7	90.4 ±18
Rectal D_{2cc}	57.8 ±7.7	67± 6	65 ±12	60.5	62± 4	73.2± 8
$D_{ICRU\ RECTAL}$	63.5± 8.1	71± 7	67± 13	67.3± 8	66 ±9	72 ±8
Sigmoid colon $D_{0.1cc}$	109.4 ±45.2	79± 10	84 ±32	72.7± 18	82 ±13	96.4 ±25.6
Sigmoid colon D_{2cc}	74.6 ±19.6	69 ±6	62± 12	60.6± 6	68 ±7	68.7 ±12.4
Urinary Bladder $D_{0.1cc}$	139.1± 54.7	87.6± 12	162± 75	86 ±12	100± 12	106 ±23.4
Urinary Bladder D_{2cc}	93.4±24.6	73± 6	95± 2	71.7 ±6	82 ±6	82.6± 14
Urinary Bladder $D_{ICRU\ BLADDER}$	80.4 ±4.4	67 ±8	74 ±15	63.7 ±9	72 ±15	75.8 ±13.1



Correlation of ED2cc of rectum with probability of Rectal hemorrhage (CTCAE Grade ≥ 3, in dose intervals of 10 Gy. Plotted on the basis of Probit Regression analysis

Figure.1



Correlation of ED2cc of rectum with probability of Rectal Ulcer (CTCAE Grade ≥ 3) in dose intervals of 10 Gy. Plotted on the basis of Probit Regression analysis

Figure.2