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Dosimetric Correlation between Point Doses and Volumetric Doses in Gynecological Intracavitary HDR Brachytherapy: A statistical analysis

KEYWORDS: Volumetric dosimetry, Intracavitary Brachytherapy, Organ at risk, Regression Linear Curve.

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ABSTRACT *Objective: Recent studies have reported that ICRU-38 point doses did not provide accurate estimations and clinical correlations. In this study the significance of the correlation between 2cc volumetric doses and point doses have been statistically analyzed.*

Methods: Sixty intracavitary gynecological applications has been selected. Patients were treated with EBRT dose of 46Gy/23# followed by 9Gy/2session of brachytherapy. Each patient underwent for CT-simulation scan and 3D treatment planning for brachytherapy session. Bladder and rectum were contoured and doses to the bladder and rectum were reported according to ICRU-38 and GEC-ESTRO recommendations.

Result: The data was analyzed in SPSS 16.0 software. Q-Q plot test showed that data is normally distributed and unweighted for bladder and rectum. For bladder and rectum, the ratio test was found to be1.009 and 1.056 respectively for point dose to 2cc volume dose. The Pearson correlation coefficient is found to be 0.685, 0.639 and covariance is 67.51, 26.65 for bladder and rectum resp. Mean standardized residual came 0.000, 0.000 and standard deviation evaluated is 1.019 and 0.991 for bladder and rectum resp. The Kruskal Wallis test showed p value for bladder 2cc volumetric and point dosimetry is 0.018 and for rectum 0.004*. The regression analysis curve fit line equation has been modeled from intercept model. The regression equations shows that it is under estimating the dose to the bladder as well as it is over estimating the rectum doses.*

Conclusion: However, point dosimetry might not be the alternative for defining the doses to the OARs. Thus for precise and accurate dosimetry of OARs (bladder and rectum) three dimensional imaging and volumetric dosimetry is necessary.

Introduction:
Intracavitary Brachytherapy combined with external beam therapy is the mainstay for the management of carcinoma of cervix.[1] High Dose Rate brachytherapy has replaced Low Dose Rate brachytherapy due to its precision and sophisticated dose delivery mechanism through remote after-loading system, improved safety and patient comfort. [3,4] Various fractionation regimen are used to reduce the normal tissue complications.[1,5] The rapid dose fall-off in brachytherapy facilitates delivery of high dose to tumor while sparing the critical and normal organs such as bladder and rectum. [2]

Classically for dose prescription to the tumor volume and to analyze the doses received by bladder and rectum, the International Commission on Radiation Units and Measurements (ICRU) report-38 recommendations were followed. [6] Two Dimensional Radiograph-based treatment planning was used for dose reporting in Intracavitary Brachytherapy. Reference points for Bladder and rectum used to be marked on the orthogonal radiograph with the help of radio-opaque markers.[7-9]

The recent advances in imaging technique have helped in the three dimensional image acquisition and volumetric dosimetry for the tumor and normal organs. The gynaecological (GYN) brachytherapy group of European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) has published its guidelines for 3-dimensional brachytherapy treatment of cervix. It is recommend that normal organ volumetric doses of 0.1cc, 1cc, 2cc, 5cc and 10cc be reported and dose volume histogram (DVH) be analyzed.[10] for improved care and evaluations.

Several studies had found the correlation between ICRU point doses and 2cc volumetric doses.

Various Studies supported the equivalence of 2cc volume to the ICRU prescribed point and the doses were compared. The present study has been designed to analyze statistically the suitability and feasibility of correlation between point doses and 2cc volumetric doses and its significance.

Material and Methods:
Sixty intracavitary brachytherapy applications have been

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selected in this study which were performed between Jan-2014 to Dec-2014. Patients with radical hysterectomy were excluded. High-dose-rate (HDR) remote after-loading brachytherapy system (microSelectron HDR V3) with Ir-192 source used to deliver the prescribed dose. Prior to the procedure an informed consent had been taken for intracavitary application and CT scanning individually.

Treatment Protocol
All the patients were treated with a standard dose 46Gy in 23 fractions of external beam radiotherapy (EBRT) followed by two sessions of high dose rate brachytherapy of 9Gy per session one week apart. Standard Fletcher's suite applicator was used for intracavitary Brachytherapy (ICBT) application.

Intracavitary Brachytherapy Procedure
Applicator insertion procedure was performed under general anesthesia. Vaginal packing was done using dry gauze to fix the applicator in position and to displace the bladder and rectum away from the vaginal application and the system fixed with the help of one stitch on the vulva. To mark the bladder points according to ICRU-38, Foley's catheter balloon inserted in bladder was filled with 7cc of radio-opaque dye (2.5ml of 2% potassium iodide (KI) diluted in 4.5 ml normal saline (NSS)) and slightly pulled to the base of bladder.

Imaging technique and Contouring
Somatom Emotion (16 slice, Siemens Ltd.) was used for CT simulation. The scanned CT volume was carefully selected for the topogram and extended 3cm superior from the tip of the tandem and 5cm inferior from the ovoid surface. CT scan was taken in 10 mm slice thickness and the images were reconstructed in 3mm slice thickness.

Oncentra three dimensional treatment planning system (VERSION 3.3 SERVICE PACK 3, Nuecletron) was used for contouring, planning, dose calculation and dose analysis. Rectum and bladder were contoured according to Radiation Therapy Oncology Group (RTOG) guidelines of female pelvis, 1 cm above from the tip of the applicator.

Catheter reconstruction was performed using sagittal and transverse plane from the connector end of the catheter. The stopper point was considered as an OS point (0,0, 0). The axes are adjusted and defined with the help of sagittal and coronal image view in such a way that it should pass through the central tandem axis. An offset of 5 mm from the tip of central tandem and ovoids was given for the dwell position with step size of 2.5 mm. Dwell positions of source were arranged to get the pear shaped isodose geometry matching to the topology of target volume.

geometry.

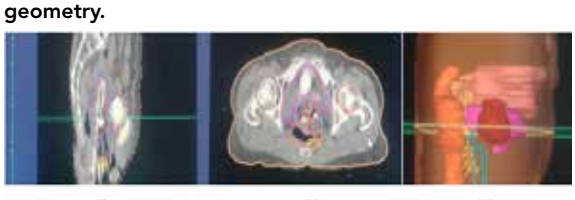

Fig (i): sagittal image of ICBT, axes should pass through the central tandem axis. Fig (ii) transverse image with contoured organs according to RTOG guidelines. Fig (iii) A three dimensional view of reconstructed catheter and organs.

Dose calculation and planning
Bladder and rectum points were marked as defined in ICRU-38 protocol in sagittal CT scan slice. The uterine tandem length for ICBT applications commonly used were 4 cm and ovoid's used were mostly of 2 cm diameter. The dwell positions were arranged in tandem and ovoid's to deliver desired dose matching with the target volume. Dose of 9Gy per session was prescribed and normalized at point A. No manual optimization was done and doses accrued at ICRU bladder and rectum point were noted. Dose volume histogram (DVH) was analyzed for 0.1cc, 1cc, 2cc, 5cc and 10cc (GEC_ESTRO reference) volumes doses of bladder and rectum. The equivalent doses (EQD_2 for 2Gy per fraction) were calculated for each ICBT session with the help of biologically equivalent dose by using the formula-

$$BED = D\,(1+D/(\alpha/\beta)) \quad \ldots. \quad (i)$$

$$EQD_2 = BED/(1+2/(\alpha/\beta)) \quad \ldots. \quad (ii)$$

Where D is the dose to a specific sub-volume of the organ for that specific session. The α/β ratio was taken 3 for rectum and 4.5 for bladder. [11]

Study design
Oncentra Master Plan version 3.3 SP3 has been used for brachytherapy planning and dose calculation. The dose calculation algorithm for brachytherapy application is recommended by American Association of Physicists in Medicine (AAPM), Task Group No.-43 (TG-43) which follows the inverse square law but doesn't consider the heterogeneity factor. [12, 13] Thus the point doses defined by the ICRU-38 can show correlation with any of the sub-volumes. 2cc volumetric dose data showed good correlation with point dosimetry data. Most of the studies have also found the correlation with 2cc and point doses. [14-17] Thus this study is designed to ascertain the correlation between point dose and 2cc volumetric doses and its significance.

Statistical Analysis
Statistical Analysis was performed using SPSS version 16.0 software (SPSS, Chicago II). ICRU defined point doses were compared with 2cc volumetric doses. Ratio test was performed between ICRU point dose and the volumetric doses. The Q-Q plot provides information about normal and unweighted distribution of the collected data. For validation of the study the Q-Q plot has been plotted. The Pearson correlation coefficient and covariance had been obtained for ICRU point doses and 2cc volumetric doses. The correlation is stated strong when the correlation coefficient is equal to or more than 0.6. Linear Regression test has been performed for the best curve fit and linear regression equation were generated for bladder and rectum. The non-parametric test, Kruskal-Wallis test is performed to ascertain the significance of the analyzed data.

Results
The statistical test conducted on the data obtained about the volumetric doses from TPS and its anatomical correlation with CT imaging have demonstrated significant outcomes. The ratio test compares the data of two groups and provides a comprehensive list of summary statistics for describing the ratio between two scale variables. For ICRU defined point doses and 2cc volumetric doses the ratio test is 1.009 and 1.056 for bladder and rectum respectively.

The Q-Q plot has been plotted for the validation of the

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study. It showed that the data is unweighted and normally distributed. The Q-Q plot has been plotted between point dose data of bladder and rectum and for 2cc volumetric data of bladder and rectum. The standardized observed values and expected normal values showed a good correlation. This validate that study is non-biased and observed data is valid.

Correlation test was performed and the Pearson correlation coefficient was found for bladder is 0.685 and for rectum is 0.693 and the covariance is found to be 67.51 for bladder and 26.65 for rectum respectively. Standard deviation is 1.019, 0.991 for bladder and rectum respectively. It demonstrates a strong correlation in ICRU point doses and Volumetric 2cc doses.

The linear regression equations was generated for the bladder and rectum using intercept model-

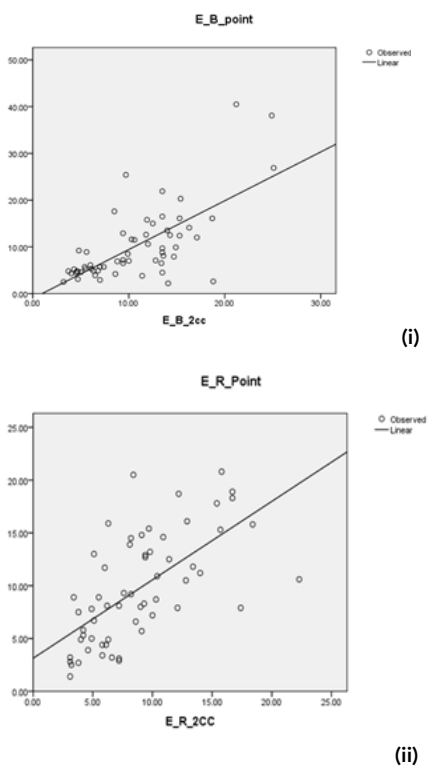
For Bladder-
E2cc= 0.9578 Epoint + 0.968 ..... (iii)

For Rectum-

E2cc= 1.346 Epoint – 4.21 ..... (iv)

All the doses in the equations are with doses normalized at point A.

The best curve fit for bladder and rectum shown here-



Graph 2: The Linear regression curve fit lines of (i) Bladder (ii) Rectum point doses vs. 2cc volumetric doses.

Discussion
ICRU published its recommendations to standardize a protocol for uniformity of prescribing the dose and reporting the doses of OAR's. It also aimed to standardize the gynecological brachytherapy practices for better clinical correlations with the doses received by various organs and target volume[6]. Brachytherapy application has a sharp dose gradient so precise and reliable method of dose reporting is essential. Recent studied published had demonstrated that the doses to nearest point of rectum from applicator showed better correlation with the rectal toxicity data compared to ICRU point dose. [12-14]The radiograph based planning and ICRU defined point dose reporting is still followed in many centers even in the developed countries. [18, 7] The volumetric imaging facilitates the three dimensional view of the volume covered by prescribed dose and dose volume histogram can be analyzed for quantifying the doses even in a small volumes. ICRU-38 has specified point doses for bladder and rectum only. Three dimension imaging and doses display could provide doses data to sigmoid colon and bowel loops. The does received can be evaluated to these organs by delineating the organs using three dimensional volumetric imaging. [19, 10] and clinical toxicity could be explained based on doses to these organs. The two Dimensional ICRU-38 was totally silent about the doses to sigmoid colon and bowl loops. The advent of 3D multi-slice CT scanner in data acquisitions and isodose displays in 3D enabled planning systems have significantly altered the practices in gynecological practices . These new imaging and planning tools have enabled correlation between doses to local anatomy /critical organs and target volume. The correlation between the point and volumetric doses for bladder and rectum has been reported in several studies [22-27] and majority of them agree for good correlation between ICRU defined point doses and 2cc volumetric dose. [14-17]

However, Cheng et al [20] and Ferrigno et al [28] have shown that ICRU rectal point doses fail to correlate with the clinical toxicity observed. Cheng et al[20] also showed that the doses to nearest point to rectum correlated better with the rectal toxicity, as compared with the ICRU point dose. This also significantly elaborates that rectum is not a straight forward organ and point dose may not explain the doses and its consequences on the total lumen of rectum. Umesh et al[29] also suggested for additional points for rectal and sigmoid mucosal point rather than believing ICRU point doses relating late toxicity data. Since rectum and sigmoid colon are curved structure , hence point dose may not be sufficient to explain the effect of irradiation of the lumen.

These studies suggested even there is strong co-relation between ICRU point doses and 2cc volumetric doses but for toxicity estimation it does not corroborates. This study has also been done to establish the degree of correlation between ICRU point dose and 2cc volumetric doses and to estimate the dependency between them.

Specifically, covariance measures the degree to which two variables are linearly associated and it also measures how potentially the two variables are correlated. However, it is also often used informally as a general measure how monotonically related two variables are related. If two variables are independent, their covariance is 0. But, having a covariance of 0 does not imply that the variables are independent. The covariance is sometimes called a measure of "linear dependence" between the two random variables. In this study the covariance is found 67.51 and 26.65 for bladder and rectum respectively. The Pearson correlation coefficient which gives the goodness of the fit for the best possible linear function describing the relation between the variables, is found to be 0.685 and 0.639 for bladder and rectum respectively. This shows a good correlation be-

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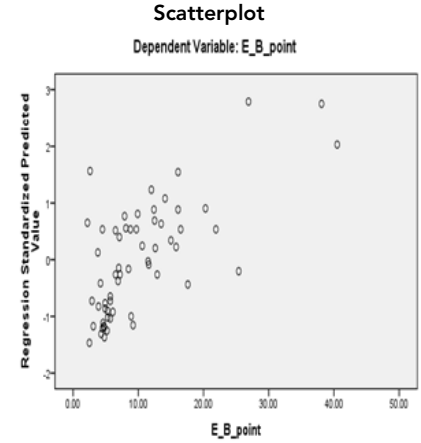
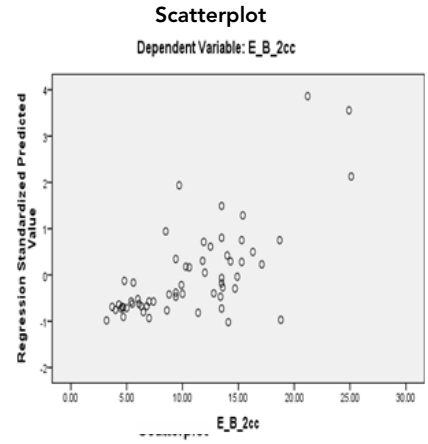
tween ICRU defined point doses and 2cc volumetric doses.

The standardized residual is the residual divided by its standard error. Standardizing is a method for transforming data so that its mean is zero and standard deviation is one. If the distribution of the residuals is approximately normal, then 95% of the standardized residuals should fall between -2 and +2. If many of the residuals fall outside of -2 or +2, they could be considered unusual. However, about 5% of the residuals could fall outside of this region due to chance. The standardized residual mean is 0.000 and standard deviation is 0.991 in this study. Residual mean is 0.004 and standard deviation is 1.019 for bladder. For rectum the standard residual mean is 0.000 and standard deviation is 0.991. The standardized residual is not defined for rectum.



(i)



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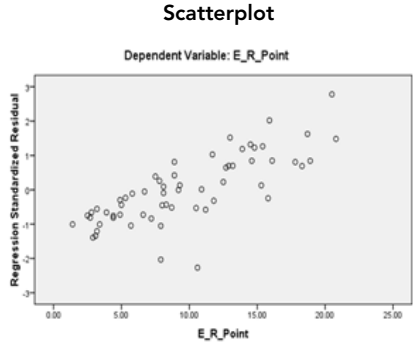
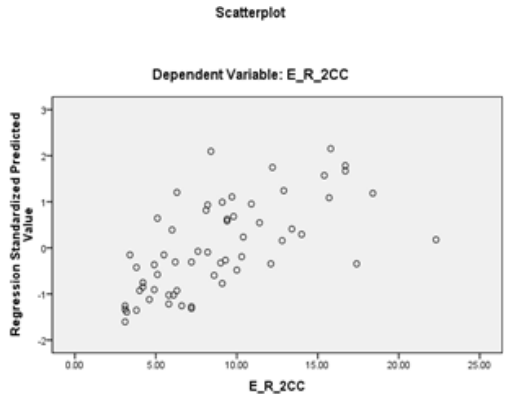


(iii)



(iv)

Graph 3: Residual statistics-Plots of standardized residuals for (i) Bladder point doses (ii) Bladder 2cc doses (iii) Rectum point doses (iv) Rectum 2cc doses.

The Kruskal-Wallis test suggests whether there is a statistically significant difference between the groups. Basically the Kruskal-Wallis is a rank-based nonparametric test that can be used to determine if there are statistically significant differences between two or more groups of an independent variable on a continuous or ordinal dependent variable. The Kruskal Wallis test showed p value for 2cc volumetric and point dosimetry is 0.018* for bladder and for rectum 0.004*.

Regression is about fitting a low order parametric model or curve to data. This is an approach for modelling the relationship between two variable in which one variable is correlated to other. The point doses are considered as dependent variables while the volumetric doses are independent variable. The regression equation would change with the sample size, thus to minimize the error an ample number of study had included.

Conclusion

This statistical study illustrates the strong correlation between the ICRU defined point doses and 2cc volumetric doses for bladder and rectum. The analytical test shows a linear relationship between point doses and 2cc volumetric doses. For bladder the ICRU point underestimating the doses although the volumetric doses are not showing much deviation from point doses. But for rectum the point doses overestimating the doses compared to Dose to 2cc so can't be used for toxicity estimation. Thus, ICRU point doses cannot be used to predict accurate doses of organs despite they show a good correlation through the regression equations. Thus, the volumetric imaging is necessary for analyzing and reporting OARs doses and for better visualization of isodoses covered the target volume.

*significant

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