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COMPARISON OF DOSE VOLUME HISTOGRAMS AND INTERNATIONAL COMMISSION OF RADIATION UNITS AND MEASUREMENT POINT DOSES TO BLADDER AND RECTUM IN CARCINOMA CERVIX PATIENTS TREATED WITH INTRACAVITARY BRACHYTHERAPY IN DEPARTMENT OF RADIOTHERAPY

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Introduction: International commission of radiation units and measurement point doses to the bladder and rectum in carcinoma cervix patients treated with intracavitary brachytherapy in the department of radiotherapy.

The aim: to evaluate two-dimensional point-based dose planning and three-dimensional computed tomography-based dose-volume parameters for high-dose-rate intracavitary brachytherapy of cervical cancer.

Materials and methods: prospective study done between the years June 2018 to April 2020, a total of 50 prospectively registered women of non-metastatic carcinoma cervix treated with definitive concurrent chemo-radiotherapy followed by HDR intracavitary brachytherapy who met inclusion criteria were accrued in the study. All women in the study were treated with 50 Gy EBRT then assessment was done for response and adequacy for comfortable insertion of application. Brachytherapy procedure was performed under sedation in the lithotomy position.

Results: Median age of the entire group was 54.5 years, majority of them were in their 5th (34 %) or 4th (28 %) decade. Pathologically, all were squamous cell carcinoma. Most common subtype was large cell non keratinizing type (64 %). Major bulk of the study is contributed by stage IIA, IIB, IIIB. All patients were treated with external beam radiotherapy of 50Gy in 25 fractions with 2Gy per fraction followed by high dose rate brachytherapy of 7 Gy per fraction for 3 fractions, one week apart to a total intracavitary brachytherapy dose of 21Gy.

Conclusion: Results from the study suggests that rectum ICRU reference points can be surrogate markers for D2cc, but not for bladder and hence reporting should preferably be done in volumetric method rather than reference point doses

Keywords: international commission of radiation units and measurements, intracavitary brachytherapy, external beam radiotherapy

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1. Introduction

Carcinoma cervix is the 7th most frequent cancer with an incidence of 3.1 % among all ages across the world. In 2018, an estimated 570 000 women were diagnosed with cervical cancer worldwide and about 311 000 women died from the disease. In India, the Carcinoma cervix is the second most frequent cancer among females, with an incidence of 123907 in 2020, which is 9.7 % of all cancers of both sexes. Whereas among females it is 18.3 %. In FIGO STAGE IA, surgery has been the mainstay of treatment whereas, in stage IB or higher, definitive management is considered being concurrent chemo radiotherapy. Radiotherapy requires an integration of external beam radiotherapy and brachytherapy. Intracavitary brachytherapy has changed widely from the use of radium to the use of artificially produced radionuclides, after loading techniques, steeping source technology, computer imaging and technology. These led to the use of novel dose rate approaches (LDR, HDR) [1, 2].

Conventional brachytherapy is based on clinical examination and 2D point based planning using fixed bony landmarks and orthogonal x-ray images for dose calculations and prescriptions irrespective of size or

shape of tumour. This leads to inadequate target coverage and insufficient dose delivery and treatment failure for larger asymmetrical tumours. Prescription of dose is done to specific points. Like for tumor, dose is prescribed to point A and for bladder and rectum, dose is prescribed to reference points as defined by International Commission on radiation units and measurements (ICRU) in report No 38 are used. Radiograph based planning is simple and cost effective and thus it is still used for dose reporting [3].

Volume Based Planning dose prescription is based on the tumour volume rather than a specified common point. Thus, creating better conformal plans. Ideally, 3D imaging with MRI would be preferred for volume-based planning. MR based applications still being incorporated at different rates around various institutions. In cases, where MRI is not available, CT is an alternative. CT does not provide clear clinical target volume but can identify surrounding OARs and define dose distributions². Brachytherapy-related morbidity include ulceration, fistula, or circumscribed telangiectasia. these are usually related to small volumes receiving high absorbed doses. To assess such volumes and doses, authors suggested assessing small volumes of 0.1 cm³

and 2 cm³. Brachytherapy has a steep dose gradient. Dose measured at a single point does not indicate the dose received by the organ [4]. Depending on the application, D2cc may have different locations in OAR.

This study is done to evaluate two-dimensional point-based dose planning and three dimensional computed tomography based dose-volume parameters for high-dose-rate intracavitary brachytherapy of cervical cancer.

2. Materials and methods

Prospective study done between the years June 2018 to April 2020, a total of 50 prospectively registered women of non-metastatic carcinoma cervix treated with definitive concurrent chemo-radiotherapy followed by HDR intracavitary brachytherapy who met inclusion criteria were accrued in the study. Study was conducted in Osmania medical college with approval of ethics committee (ethical clearance number- ECR/300/ inst/AP/2013/RR-16) and informed consent was obtained from all participants.

Inclusion criteria: age 30–70 years. Positive biopsy for squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, stage IIA-IV carcinoma cervix patients according to FIGO staging system. Patients with an adequate vagina, adequate for comfortable insertion of applicators.

Exclusion criteria: immunocompromised patients and HIV positive patients, post hysterectomy status, patients with narrow vagina and poor symmetry.

All women in the study were treated with 50 Gy EBRT then assessment was done for response and adequacy for comfortable insertion of application. Brachytherapy procedure was performed under sedation in the lithotomy position. For brachytherapy we were giving fortwin and phenergan injection before procedure (short general anaesthesia). A Foley catheter was inserted into the bladder, and 7cc of radio-opaque contrast was injected into the balloon to aid in the identification of the ICRU bladder reference point. A thorough gynaecological examination was performed and tumour factors assessed. The length of the uterine cavity was determined using a uterine sound. The applicators used were CT/MR compatible tandem and ovoid. Betadine-soaked gauze is used to pack the vagina to fix the applicators in place and to push the bladder and rectum away. The patient was transferred to the CT simulator suite. CT scan of the pelvis was performed with the patient in a supine position using 3-mm slices and exported digitally to the brachytherapy planning system.

The outer wall of the rectum was contoured inferiorly 5 cm from anal verge and ends superiorly before it connects anteriorly with the sigmoid as per RTOG contouring guidelines v- The outer wall of the bladder was contoured from the base of the contrast-filled Foley catheter balloon to the superior most aspect of the bladder (dome of bladder). Radiopaque rectal probe is inserted per rectum for a length of 10cm. Manual optimization of the plan was done starting with standard loading pattern and dwell times; adjustments were made until an optimal plan result was reached. As much as possible, bladder dose was kept less than 80 % and the rectal dose kept less than 60 %.

The DVHs were calculated. The minimum dose to the highest irradiated 2 cc area of rectum and bladder were recorded (D2cc). Mean is calculated for ICRU D2cc and point based bladder & rectum doses comparison of mean is done by Student paired T Test. Correlation was done by Pearson's correlation coefficient.

Statistical analysis: difference between means is tested by paired t test and co relation is assessed by Pearson's correlation coefficient.

3. Results

Among the study population, majority belong to 51–60yrs of age (34 %) followed by 41–50 years (28 %), 61–70 years (20 %), 30 –40 years (20 %) and 71–80 years (2 %). Median age of the study population is 54.5, mean is 43.5 year (Table 1).

Table 1

Age group (years)	Frequency	Percent (%)
30–40	8	16.0
41–50	14	28.0
51–60	17	34.0
61–70	10	20.0
71–80	1	2.0
Total	50	100.0

Among the study population, majority belong to FIGO stage IIB (36 %) followed by IIIB (26 %), IIA2 (22 %), IIA1 (6 %), IIIA& IIIC1 (both 4 %) and IVA (2 %). Among the study population, all patients were diagnosed with squamous cell carcinoma. Majority of them are large cell non keratinizing (64 %) followed by moderately differentiated (16 %), large cell keratinizing (10 %), and poorly differentiated (4 %) (Table 2).

Table 2

Stage	Frequency	Percent (%)
IIA1	3	6
IIA2	11	22
IIB	18	36
IIIA	2	4
IIIB	13	26
IIIC1	2	4
IVA	1	2

Mean ICRU bladder point dose are 5.488±1.781, mean D2cc bladder dose are 7.05±1.72 r=0.38 (p= 0.01) (Table 3).

Mean ICRU bladder point dose is 5.49±1.78. Mean D0.1cc volume dose are 10.59±3.54 R=0.18 (p=0.25) (Fig. 1).

Table 3

Histopathology	Frequency	Percent
K SCC	3	6.0
LCK SCC	5	10.0
LCNK SCC	32	64.0
MD SCC	8	16.0
PD SCC	2	4.0
Total	50	100.0

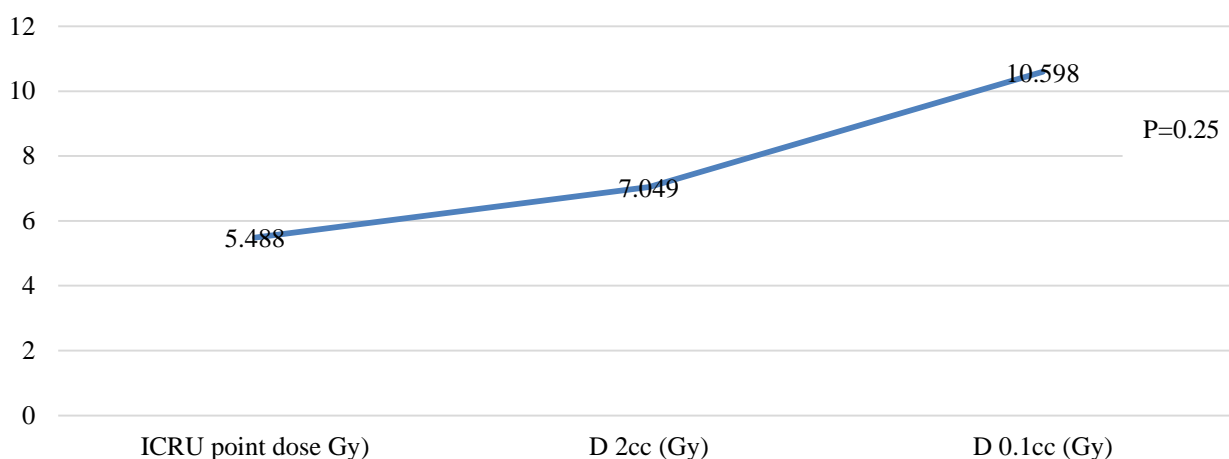


Fig. 1. Bladder doses and their means with p values and correlation coefficient

Mean ICRU point rectum dose is 6.175 ± 1.556 , mean D2cc volumetric dose is 5.775 ± 1.421 with Pearson's correlation coefficient of 0.53 ($p=0.001$). Mean

rectum point dose is 6.175 ± 1.556 and D0.1cc rectum volumetric dose is 9.118 ± 6.141 with Pearson's correlation coefficient of 0.31 ($P=0.04$) (Fig. 2).

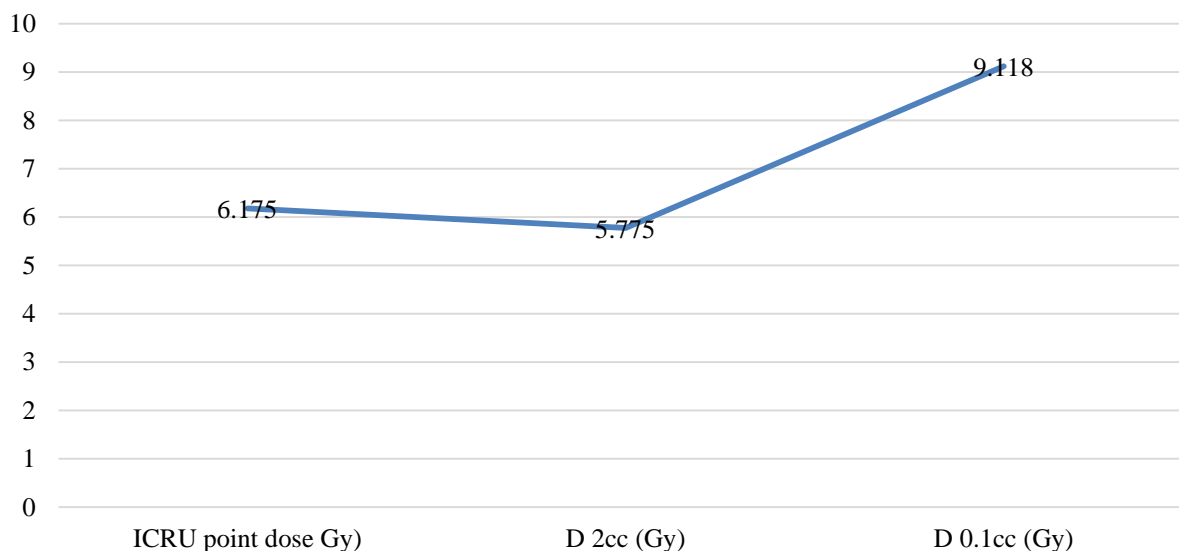


Fig. 2. Rectum doses and their means with correlation coefficient and p value

50 ICRT applications were studied; an FSD after loading tandem was used with ovoids. The mean doses to the ICRU reference points and the mean minimal doses delivered to various small volumes of the maximal organ dose are summarized in Table 3. For the rectum, the D2cc doses did not differ significantly from the doses calculated at the ICRU reference point ($p=0.001$); the mean difference was $40\text{cGy} (\pm 13\text{cGy})$. However, for the bladder, the doses calculated at the ICRU reference point were significantly higher than the D2cc doses ($p=0.01$). The mean difference was $2000\text{cGy} (\pm 7\text{cGy})$.

4. Discussion

This study included carcinoma cervix patients with median age of 54.5 years. Age-specific incidence of cervical cancer increases rapidly, usually reaching a peak at 40–50 years of age, followed by a plateau and a variable decline thereafter. Although a high prevalence of HPV exists worldwide, peaking at ages 25 to 35 years,

<15 % of exposed women develop persistent infection, results in dysplasia, whereas majority of women clear the infection within 2 years. Cervical cancer may develop 10 to 20 years after initial exposure to HPV. Thus, usual peak of incidence can be seen around 40-50 years of age. Wenkstetten-Holub et. al. [5], showed that Comorbid conditions in the elderly (>70 years) resulted in diminished ability to undergo intracavitary brachytherapy. Tumor recurrence and death from cervical cancer were more common in the elderly group. In this study, only 1 out of 50 patients in the study sample was more than 70 years.

In our study mean bladder D2cc dose differed significantly from the mean dose at the ICRU reference point ($p=0.01$) with a mean difference of 2.00Gy and ICRU bladder point has weak positive correlation with D2cc ($r=0.38$, $p=0.01$). Mean ICRU point dose differed from D0.1cc with a mere positive correlation or no correlation but this observation is not statistical-

ly significant. Mean rectum D 2cc dose does not largely differ numerically from the mean dose at the ICRU reference point, with mean difference of 0.40 Gy (statistically significant $p=0.001$). Thus, ICRU rectal point can be used as a surrogate to D2cc but with a positive correlation ($r=0.53$). Mean ICRU point dose differed largely from D0.1cc (mean difference is 3.34 Gy) with significant $p=0.04$ but with a weak positive correlation ($r=0.31$). The results of this study suggest during cervical cancer treatment the ICRU bladder reference point is acceptable surrogate for the maximal radiation dose delivered to the bladder. In this study, the D2cc was more than the ICRU reference dose always and was greater than the ICRU dose by 1.28-fold. Various studies have the same findings. Jamema, Swamidas & Saju, Sherly conducted studies concluded that there is correlation between D2cc and ICRU point doses for both the bladder and the rectum [6].

This study found no significant difference between dose to the 2cc volume of rectum and the ICRU point dose. The mean difference was 0.40Gy and the ratio of D (ICRU)/D2cc was 1.0. The DICRU also did correlate positively with D2cc ($r=0.53$). Similar results are seen in other studies (Vinod et. al. [7], Hashim N, et. al. [8], LalNyadav et. al. [9]). This study suggests that the rectal ICRU reference point dose can be used an acceptable surrogate to the dose received by 2cc volume of rectum.

Results from the study suggests that ICRU rectal reference points can be surrogate markers for D2cc.but not for bladder. Hence reporting in volumetric method is better than point based. Brachytherapy for cervical cancer has impressively progressed in the last decade through the introduction of image-guided brachytherapy. Image-guided brachytherapy is the new gold standard for cervix cancer brachytherapy.

Traditionally, intracavitary brachytherapy treatment planning and technique is done using 2D orthogonal film-based approach. 2d based planning prescribed dose to point A, a position defined with respect to the applicators. A standardized system of dose reporting has been established by the ICRU report. Point based reporting is based on points representing parametria, pelvic side walls and rectum and bladder,, these point do not act as a best surrogate marker .

Between reference points and volumetric image-based 3D dose calculation, there are inconsistencies and they cannot best estimate late complication to organs at risk (Hashim N, et. al. [8], LalN yadav et. al. [9])

Conformal treatment is possible with 3D image-based brachytherapy, as it integrates the anatomy, tumor factors, and response of tumor to EBRT. 3D spatial reconstruction of tumor applicators and normal tissue is possible, enabling delineation of tumor and OAR accurately and thus conformal dose to tumor can be prescribed while respecting normal tissue tolerance. Takenaka T et al, [10] Point A prescription may over treat small tumors but may result in suboptimal dose distribution for larger tumors.

As the imaging modalities are improved, improvement in quality of dose prescription in brachytherapy could lead to a better clinical outcome and reduced late radiation toxicities. Tan LT et al [11], 96 % pelvic

control rate and 3- year cancer-specific survival of 81 % was reported in 3 yrs. experience with CT image guided brachytherapy using tandem and ring. Implementation of a CT-based tandem-ring HDR brachytherapy technique along with individual dose adaptation has resulted in a significant local control without increasing the risk of serious toxicity. These studies signify a real improvement in the therapeutic ratio by use of image guided brachytherapy

Nancy E et al [12] survivors are at risk for impaired QOL up to several years after diagnosis. Younger women, especially those at high risk for lower QOL, may need interventions that specifically target their needs related to menopausal symptoms and problems with relationships, sexual functioning, and body image. If the late complications are minimized, there will be a better quality of life for cancer cervix survivors.

There are variations in mean doses with the other studies, it could be due to many uncertainties as bladder and rectum are hollow organs and their filling status will alter their positions and thus could change the dose received by those organs [13]. Any variations in contouring could cause inter and intra observer variations. Contouring in CT films is quite difficult as the contrast and tandems cause lot of artefacts which interfere in our contouring and delineation of structures. Radiopaque markers are usually not recommended as they distort the rectal wall position. Rigid rectal probe is used in this study.

Based on clinical research and understanding of biological mechanisms, OAR dose volume constraints should evolve with time. This will help in development of treatment techniques. Further research is needed to assess clinical complications and volume attributing to the complication, to evaluate and minimize the complications.

Limitations of this study:

- Only one fraction of intracavitary brachytherapy was simulated, imported, and planned
- Doses were not equated to EQD2, hence total dose comparison was not done
- Clinical correlation was not considered
- Contouring on CT images

Prospects for further research. A larger study in like determine the clinical outcome, tumor control and toxicity to organs at risk will be worthwhile for resource-appropriate practice to further correlate the complications for better understanding of dose constraints.

5. Conclusions

Bladder D2cc was more than the ICRU reference dose and was greater than the ICRU dose by 1.28-fold. No significant difference between dose to the 2cc volume of rectum and the ICRU point dose and ratio of D (ICRU)/D2cc was 1.0. The DICRU also did correlate positively with D2cc ($r=0.53$). Results from the study suggests that rectum ICRU reference points could be surrogate markers for D2cc.but not for bladder and hence reporting should preferably be done in volumetric method rather than reference point doses. Contouring on Ct images pose a challenge as the applicator artifacts obscure the tissue delineation. MR compatible applicator with MR imaging will better help delineate tumor. As bladder and rectum are hollow organs, their filling status

varies thus simulation and planning should be done for every brachytherapy session

Conflicts of interest

The authors declare that they have no conflicts of interest.

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