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Feasibility of vaginal dose points reporting in cancer cervix patients treated by external beam radiotherapy and brachytherapy

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ABSTRACT

Background: Cervical cancer is the second most common malignancy among women in India. The standard of treatment for locally advanced lesions is Concurrent Chemoradiation with External Beam Radiotherapy followed by Intracavitary Brachytherapy (GEC-ESTRO). The dose received by the entire vagina cannot be accurately measured by a vaginal dose point assessment at the level of the ovoids alone. **Aims and Objectives:** Our study aims to see the feasibility of measuring vaginal dose at various levels and define the dose points that can be practiced in 2D and 3D external radiation and brachytherapy (BT). **Materials and Methods:** Radiotherapy plans of 29 patients with stages IIA to IVA cancer cervix treated with concurrent chemoradiation from January 2020 to December 2020 were retrospectively reviewed for the feasibility of measuring the vaginal dose points throughout the vagina. Every patient underwent cisplatin-based weekly chemotherapy along with BT and external beam radiotherapy. We have assessed the vaginal dose locations 2 cm above and below the point of the posteroinferior border of the pubic symphysis (PIBS). The superior surface of the ovoid to the PIBS point constitutes the vaginal reference length (VRL). **Results:** The mean and median doses from external beam radiation therapy (EBRT) were 50Gy and 51 Gy at PIBS, 52 Gy and 53.5 Gy at +2 cm, and 18Gy and 28 Gy at -2 cm, respectively. The combined mean and median EQD2 doses from EBRT and BT at PIBS, PIBS+2, and at PIBS-2 were 56 and 57 Gy, 65 and 66 Gy, and 35 and 31 Gy, respectively. The mean VRL was 5.25 cm before EBRT and 4.75 cm before BT. **Conclusion:** Our study found that it is feasible to measure the dose received by the vagina using the PIBS system and large dose variations throughout the vagina were observed.

Key words: Cervical cancer; Radiation; Brachytherapy; Pubic symphysis

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INTRODUCTION

Cervical cancer is the second most common malignancy among women in India. The standard of treatment for locally advanced lesions is Concurrent Chemoradiation with External Beam Radiotherapy followed by Intracavitary Brachytherapy (GEC-ESTRO).[1,2] The organs at risk (OAR) during radiation of cervical cancers are rectum, bladder, small bowel, sigmoid colon, and head of the femur. Several studies validated that D2 cc is the predictor of bladder, rectal tolerance for Image based Intracavitary Brachytherapy (BT).[3] A study by Au and Grigsby[4] showed vaginal LDR tolerance dose was above 150 Gy. The vagina receives very high radiation dose due to its proximity to the tumor region. The site of the tumor does not correlate with the vaginal necrosis. The upper vaginal tolerance is more than that of the lower vagina and it was not recommended as an OAR in ICRU 38.[5] Vaginal necrosis and fistula occurs infrequently in the lower vagina. In comparison to the other walls, the posterior vaginal wall was more vulnerable to radiation damage when employing the Fletcher Suit Applicator.[6]

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Even though the incidence of severe vaginal morbidities occurring within 2 years of treatment is very less (3.6%); in image-guided external beam radiation therapy (EBRT) and BT techniques, the incidence of grades I and II vaginal morbidities is significant (grade I is >89% and gr II >29%).[7] So the assessment of dose received by the various portions of the vagina and its clinical correlation such as vaginal stenosis, fistula, mucositis, dryness, bleeding, and other symptoms are essential.

Several complications following irradiation to the pelvic region have been documented such as Sigmoiditis, Fistula, Rectal ulcers, Urethral strictures, and small bowel necrosis.[7] Complications and toxicity to the vagina even though commonly occurring is rarely documented except in a study by Hartman and Diddle.[8] The vaginal morbidity includes atrophy, and telangiectasia which may lead to shortening of vagina. The main reason for fibrosis and vaginal dryness is due to the structural alteration which leads to less elasticity and increased connective tissue that leads to the development of vaginal fibrosis.[9]

Even though GEC-ESTRO (II) and ABS guidelines were recommended to include the vagina as an OAR they did not define the vaginal dose points.[1,10] Westerveld et al.'s[11] study showed a simple and reliable method which can be used for both 2D/3D reporting in which that comprehensive reporting of vaginal dose points measurements from EBRT and BT were feasible and concluded that large dose variations were present in different regions of the vagina.

In our retrospective study, we have analyzed the feasibility of those vaginal dose points in a set of patients.

Aims and objectives

Our study aims to evaluate the feasibility of measuring vaginal dose points at various levels based on the anatomical landmarks that can be practiced in 2D and 3D external radiation and BT. The dosemetric analysis of contribution of EBRT and BT to the various vaginal dose points is also assessed.

MATERIALS AND METHODS

After getting approval from the institutional review board, 29 radiotherapy plans of patients diagnosed with cervical carcinoma of FIGO stage IIA-IVA who received curative concurrent chemoradiation (Weekly Cisplatin dose of 40 mg/m^2) with EBRT dose of 50–50.4 Gy at 1.8–2 Gy/# to a total of 25–28#, delivered using True beam LINAC followed by intracavitary CT-based image-guided BT dose of 16–21 Gy of 7–8Gy/# with HDR intracavitary BT between January 2020 and December 2020 were analyzed retrospectively.

Our target volumes in conformal techniques were as follows: Clinical target volume (CTV)1 included gross tumor, cervix and uterus or vaginal cuff; CTV2 included parametrium and superior third to half of the vagina and CTV3 which included Common, external iliac, internal iliac, and presacral nodes.[12] For cases with involved Para Aortic nodes, a dose of 45Gy was prescribed to the para-aortic region with boost up to 60Gy to the involved node. For cases with lower vaginal involvement, the entire vagina was delineated and was prescribed a dose of 50 Gy. Using a radiopaque vaginal marker, the anatomical vaginal length and vaginal apex were identified on a CT scan. For BT, all patients had access to CT scan images with the applicator in place.

In patients who had residual illness at the time of BT, extensive stages IIA and IIIA got a larger dose to the entire vagina through external beam radiotherapy and additional treatment by BT. At point A, the planned goal was 82–90 Gy in EQD2. A tandem-ovoid applicator and the CT/SIM-guided technique were used to administer BT. A CT/SIM scan of the pelvis was performed, and the results were uploaded to the TPS.

The loading dosage was calculated using the BT Manchester system and the point a dose-evaluation method.[13]

The linear-quadratic model was used to calculate the sum of the BT and EBRT doses, using a 3:1 ratio.

The midline and bottom third of the vagina are measured from the posteroinferior border of the pubic symphysis (PIBS).[13] For EBRT and BT, the location at which this line crosses the applicator tandem and is 2 cm posterior to PIBS was designated as the PIBS vaginal dosage point. Doses were also measured at 2 cm above and below the PIBS both for EBRT and BT. The vaginal reference length (VRL) in BT images is calculated from the superior surface of the ovoid to the PIBS point (Figure 1). The VRL in EBRT is assessed using a CT simulation at mid sagittal views.

The EQD2 was obtained by adding the EBRT values and the values from all three BT fractions at each vaginal dose point. To determine the mean, median, standard deviation, and range, descriptive statistics was used.

RESULTS

Majority of the patients (n=20, 69%) were treated by 3D conformal radiation technique and few were treated by intensity-modulated radiation therapy (IMRT) and 2D. Out of 29 patients, 11 (38%) patients had stage II

disease and 15 (52%) patients had stage III disease. All patients had squamous cell carcinoma and majority were moderately differentiated type. 22 patients (79%) had vaginal involvement at presentation and only 5 patients (17%) had vaginal involvement after EBRT and at the time of first BT. Out of five patients only one showed upper 2/3rd involvement all others were residual growth only at the vaginal fornix. The median age of the study group was 57 years (Table 1).

The mean and median doses from EBRT at PIBS were 50Gy and 51 Gy, at +2 cm were 52 Gy and 53.5 Gy, and at-2 cm were 18Gy and 28 Gy, respectively. The results are shown in Table 2.

The mean VRL was 5.25 cm before EBRT and 4.75 cm before BT. The mean and median for combined EQD2 dose from EBRT and BT at PIBS, PIBS+2, and at PIBS-2 was found to be 65 and 66, 56 and 57, and 35 and 31, respectively (Table 3).

The patients were divided into two groups based on VRL into VRL <5 cm and VRL >5 cm. Independent sample t test was used to calculate the significance. A negative linear correlation was found between VRL and PIBS with correlation coefficient r=–0.322 with P=0.095 which is not statistically significant. Table 4 shows that the relationship between the doses at PIBS+2 and PIBS-2 with the VRL is inversely proportional and statistically significant (P=0.016 and 0.000, respectively) (Figure 2).

Table 1: Patient characteristics

Characteristic	No. (%)
Stages	
II	11 (38)
III	15 (52)
IV	3 (10)
Bulky	
>4 cm	16 (55)
Non bulky	
<4 cm	13 (45)
Vaginal involvement	
Upper 1/3	14 (48)
Upper 2/3	5 (17)
Lower 1/3	3 (10)
No involvement	7 (25)
Chemo	
CCRT	26 (90)
Radical RT	3 (10)
Para aortic involvement	
Present	3 (10)
Absent	26 (90)
Histology-squamous cell carcinoma	
Poorly differentiated	8 (27)
Moderately differentiated	21 (73)
Well differentiated	0
EBRT dose	
50 Gy	18 (62)
50.4	11 (38)
Brachytherapy	
7Gy/3#	26 (90)
8Gy/2#	3 (10)
EBRT technique	
3DCRT	20 (69)
IMRT	5 (17)
2D	4 (14)

EBRT: External beam radiation therapy

DISCUSSION

Radiation-related toxicities to the rectum and bladder are determined by the dosage administered to the target volume and the volume of irradiation.[14,15] Vaginal mucosa usually has a high range of tolerance to radiation and is called as radioresistant.[4,16] There are currently no clear recommendations for approved dosimetry, vaginal radiation tolerance, and the limitations of the vagina as an OAR. Vaginal stenosis (VS) lowers the patients' quality of life, and ICRU-R point and D2 cc in the vagina are the predictors of VS in few studies.[17]

Table 2: Mean and median doses from EBRT at PIBS, PIBS+2, and at PIBS-2

PIBS points	Mean	Median (range)
EBRT PIBS+2	52	53.5 (46–57)
EBRT PIBS	50	51 (43–54)
EBRT PIBS-2	32.6	28 (6.5–53.5)
VRL (B/F EBRT)	5.25 cm	
BT–PIBS	6.325	6.45 (3–11.4)
BT–PIBS+2	13.939	13. 8 (7.5–19.8)
BT–PIBS-2	2.72	2.7 (1.8–3.6)
VRL (A/F EBRT)	4.75 cm	

EBRT: External beam radiation therapy, PIBS: Posteroinferior border of the pubic symphysis, VRL: Vaginal reference length

Table 3: Combined EQD2 dose from EBRT and Brachytherapy at PIBS, PIBS+2 and at PIBS-2

EBRT+BCT (EQD2 α/β=3)	Mean	Median (range)
PIBS+2	65	66 (59–80)
PIBS	56	57 (48–63)
PIBS-2	35	31 (9.5–56.5)
VRL	5 cm	

EBRT: External beam radiation therapy, PIBS: Posteroinferior border of the pubic symphysis, VRL: Vaginal reference length

Table 4: Mean and standard deviation values of the two groups based on VRL

Parameters	VRL<5 (mean±SD) n=13	VRL>5 (mean±SD) n=15	Significance
PIBS	51.00±2.44	49.13±3.15	P=0.096
PIBS+2	52.86±1.79	50.66±2.66	P=0.016 (P<0.05)
PIBS-2	44.78±8.16	22.00±6.85	P=0.000 (P<0.001)

PIBS: Posteroinferior border of the pubic symphysis, VRL: Vaginal reference length

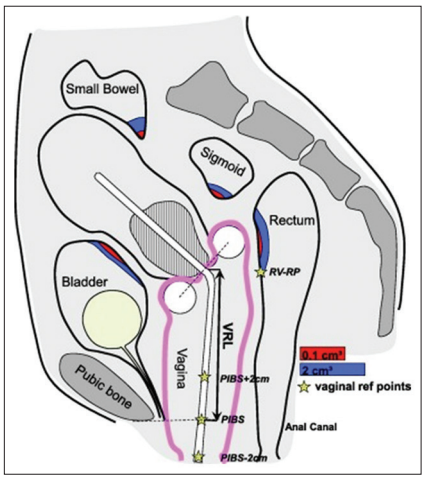

Figure 1: Vaginal dose points measurement

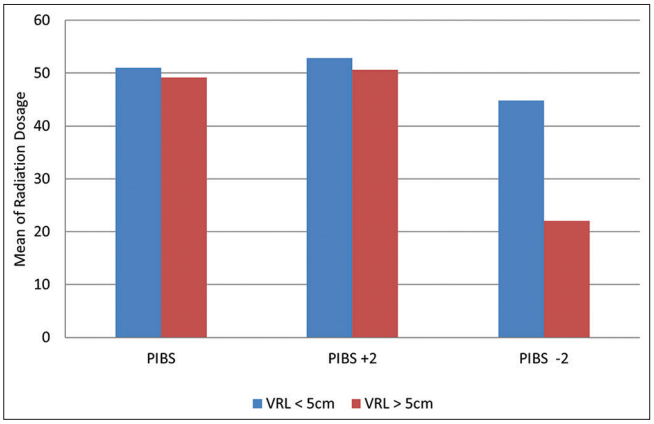

Figure 2: Mean radiation dosage of three sites posteroinferior border of the pubic symphysis (PIBS), PIBS+2, and PIBS-2 between two groups (Vaginal reference length [VRL] <5 cm and VRL <5 cm)

There were no predetermined restrictions for any of the OAR in the EMBRACE trial, including the vagina.[18] The recto-vaginal reference point is 5 mm behind the posterior vaginal wall on the axis which is perpendicular to the body, at the intersection between the tandem and the source positions in the ovoids or rings. However, the entire vaginal dose has to be considered for better evaluation.

The lack of vaginal dose assessment tools has led to the suggestion of a point dosimetric system as an alternative, which includes points in the mid and lower vagina as well as the high dose region of BT. This approach allows incorporation of EBRT and BT information along with cranio-caudal dose extension along the vagina.

The EBRT boundary, vaginal involvement during BT, and the VRL, which serves as the system's base for evaluating vaginal dose, determine the dose variations in the PIBS system. VRL is influenced by age, genetics, residual lesion post EBRT, and applicator type. VRL value in this study population is similar to that in a study by Westerveld et al.[11]

Significant impact of EBRT vaginal dose has been proven. Therefore, it is imperative to include the parameters that are relevant to both EBRT and BT dose contribution with its distribution along the vagina. In our study, the PIBS, +2 and −2 points received significant contribution from EBRT (50, 52, and 32.6 Gy, respectively) in contradiction to Westerveld et al.'s study.[11] This is due to fact that we had many cases with vaginal involvement (Upper 1/3–14 [48%], upper 2/3–5 [17%], lower 1/3–3 [10%]) and therefore the lower border of EBRT had to be lower.

Significantly large statistical differences were found between the two groups in the total EQD2 doses (EBRT and BT) at PIBS+2 and PIBS-2 and minimal variation was noted at PIBS. Thus, we can understand that VRL has a major impact on the dose variation at PIBS. Therefore, the PIBS point can be considered to be an excellent pointer of the vaginal dose and operate as a predictor of future morbidity, particularly in patients with a VRL shorter than 5 cm, where the PIBS+2 points alone got maximum radiation from EBRT. However, according to Westerveld et al.,[11] and our investigations, the maximal dose of BT was only administered to the PIBS+2 locations.

According to certain theories, vaginal tumor extension increases the probability of developing vaginal stenosis. According to the analysis of the EMBRACE trial, vaginal stenosis risk increased by 26%, 37%, and 61% over the course of 2 years in patients with tumor expansion at the time of diagnosis.[18] This result could be affected by the length of the vagina that was treated and the rate of tumor regression. Vaginal shortening can happen even when there is no vaginal involvement, according to data from elective vaginal BT for endometrial cancer, and the risk rises with the length of the vagina that has been exposed to radiation.

Limitations of the study

- Dose limiting
- Retrospective study
- Small sample size
- Clinical correlation not done.

CONCLUSION

Our study concludes that the measurement of vaginal dose using fixed anatomical points is an easy and simple clinical method. We noted that assessing the contribution of vaginal dose from EBRT and BT is feasible in our set up. The clinical correlation of these points with vaginal morbidity must be evaluated in prospective studies.

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Authors' Contributions:
GMPB - Original draft preparation, statistical analysis, and revision of final manuscript; **NPC -** Review of literature, acquisition of data, preparation of manuscript, review, and editing; **DPR -** Statistical analysis, interpretation of results; **JS -** Concept and design of the study, review of literature, original draft preparation, preparation of manuscript, interpretation of results, review and editing, and revision of final manuscript.

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