Original Research Paper

Volume - 11 | Issue - 09 | September - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Oncology

PROSPECTIVE TRIAL OF BLADDER FILLING AND ITS EFFECT ON THREE-DIMENSIONAL DOSIMETRY IN HIGH-DOSE-RATE VAGINAL CUFF BRACHYTHERAPY

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ABSTRACT

Purpose: To investigate non-invasively the effect of bladder filling on dose to OAR(bladder and rectum) and to determine the best bladder condition for vaginal cuff brachytherapy.

Methods and Materials: In this prospective clinical trial, a total of 30 women underwent vaginal cylinder high dose-rate brachytherapy. The bladder was full for Fraction 1 and empty for Fraction 2. Dose–volume histograms were generated for the bladder, rectum, and sigmoid. Paired t tests, Pearson correlations, and regression analyses were performed.

Results: The volume and surface area of the irradiated bladder were significantly smaller when the bladder was empty than when full. Of the several dose–volume histogram parameters evaluated, the bladder maximal dose received by 2 cm3 of tissue(D2cc), volume of bladder receiving >/=50% of the dose(V 50) and volume of bladder receiving >/=70% of the dose (V 70) significantly predicted for the difference between the empty vs. full filling state. Bladder filling did not alter the volume or surface area of the rectum irradiated.

Conclusions: Patients undergoing vaginal cuff brachytherapy treated with an empty bladder have a lower bladder dose than those treated with a full bladder.

KEYWORDS : Vaginal cuff brachytherapy, bladder dosimetry, bladder filling

INTRODUCTION

Vaginal cylinder brachytherapy, either alone or after external beam radiotherapy (EBRT), is a time tested treatment strategy in certain gynaecologic malignancies [1,2,3]. The most common use of vaginal cylinder brachytherapy is in the primary adjuvant treatment of endometrial cancer [4]. After total abdominal hysterectomy and bilateral salpingo-oophorectomy, RT might be indicated, depending on the surgical stage and histologic features,especially grade of the resected tumor [5,6,7]. The purpose of this treatment modality is to deliver the highest dose of radiation to the vaginal mucosa while limiting the dose to the surrounding normal structures such as the bladder, rectum, and small intestines,compared to pelvic EBRT.HDR brachytherapy using 192Ir sources is the preferred method of delivering intravaginal RT. The type of applicator used is generally a cylinder.The role of high dose-rate (HDR) vaginal cylinder brachytherapy has been proven in many previous publications [8,9,10].

The use of vaginal cuff brachytherapy reduces local recurrence rates but can increase the risk of normal tissue toxicity [11,12]. Therefore, it is important to measure the dose received by the normal tissues in the pelvis during vaginal cuff brachytherapy. The international standard of critical structure dose measurement in gynaecologic brachytherapy (International Commission on Radiation Units and Measurements [ICRU] report 38) has several limitations[13]. For example, the dose points are not representative of the volume and surface area of the normal tissue irradiated [14,15,16]Also,the dose measured at a particular point in a tissue may underestimate the dose received by the organa as a whole, because some other part of the tissue might be closer to the brachytherapy source. Another disadvantage is that calculation of the ICRU bladder dose point requires placement of a urinary catheter.Patient discomfort has decreased its routine use during outpatient HDR treatment. Most physicians prescribe the dose at a uniform distance from the cylinder, with no dose sculpting to avoid normal tissue. Therefore, the conformation of bladder filling for patients undergoing vaginal cuff brachytherapy has been examined by Hoskin and Vidler[17], who used urinary catheterization to ensure consistent states of bladder filling before vaginal cuff brachytherapy. However, alternative, less-invasive methods of bladder filling and bladder dose estimation are needed for routine daily practice. Three-dimensional image-based contouring of the organs at risk with computerized dosimetry is one non-invasive method of determining the doses received by the normal tissues during vaginal cylinder brachytherapy. This prospective trial assessed the normal tissue doses during vaginal cuff brachytherapy and examined the effect of non-invasive bladder filling on normal tissue dosimetry using computed tomography (CT).

METHODS AND MATERIALS

Patients

Between March 2019 and December 2019, 30 women were enrolled in a prospective clinical trial approved by the relevant institutional review boards. The inclusion criteria included previous hysterectomy, histologically verified gynaecologic carcinoma, Eastern Cooperative Oncology Group performance status of 2, and age >18 years. Patients with distant metastases or inoperable disease were excluded. Each patient provided written informed consent to participate in the study.Those patients who merited a EBRT+brachy combined treatment were taken up for brachytherapy 1 week after completion of EBRT(External Beam Radiotherapy).EBRT dose of 50Gy/25#, 200cGy/#,5 fractions per week,over 5 weeks,was delivered using 2D/3DCRT 4 field box technique with Co60/linear accelerator.

Radiotherapy

All patients were treated with HDR brachytherapy cylinder insertions to the vaginal cuff. Each patient received a minimum of two HDR treatments. Generally, patients who underwent EBRT to the pelvis received two cylinder insertions and those who did not, received three cylinder insertions. The cylinder diameter was 2.0–3.5 cm. The widest cylinder that the patient could tolerate was inserted to ensure the optimal coverage of the vaginal surface. The standard doses were 12Gy in two fractions after pelvic EBRT or 21 Gy in three fractions for brachytherapy alone, all with the dose prescribed at the cylinder surface. Variations from the standard dose were permitted if the clinical circumstances indicated. If the patient did not have risk factors for lower vaginal involvement, the upper half of the vagina (as measured on CT) was treated. Treatment was administered using a 192Ir HDR after loader (Nucletron, Elekta India Ltd, Veenandel, Amsterdam, the Netherlands). Bladder filling was varied for each fraction. At 1 h before Fraction 1, the patient consumed 1 litre of water[18,33] and did not empty her bladder till after treatment completion (designated "full bladder"-Bladder volume measured in

CT image 200 ml or more). Immediately before Fraction 2, the patient emptied her bladder ("empty bladder"). The cylinder angle was kept as close to horizontal as was physiologically comfortable. CT simulation was carried out after cylinder insertion (Siemens,Somatom Definition AS 20 Open Edition).After the first CT scan, an individual treatment plan was calculated. Brachytherapy was administered once the treatment plan was completed. The same was followed for subsequent fractions as well. The bladder and rectum were contoured in three dimensions and the location of the cylinder was marked. The structure contours were drawn and used to generate dose–volume histograms (DVHs) for the bladder and rectum. Dose parameters were evaluated on whole organ.

The volume of the bladder receiving >/=100% of the dose (V100)were recorded. The volume of the bladder receiving at least >/=100%, >/=90%, >/=80%, and >/=50% of the dose (V100, V90, V80, V50) and the volume receiving >/=70% (V70) of the dose were measured. The volume of rectum receiving >/=100%,>/=90%, >/=80%,>/=75%, and >/=55% (V100, V90, V80, V75, and V55 respectively) were measured. The reason for choosing these dose-reporting parameters were that similar volumetric parameters have correlated with the occurrence of late side effects in **both the bladder and the rectum in prostate cancer patients [19,20,21]**, and assessment of an absolute dose received allows for an accurate comparison of the difference between a surface area of tissue irradiated and a volume of tissue irradiated. The maximal dose received by 2 cm3 of tissue (D2cc) was recorded for the bladder and rectum. The D2cc measurement has been determined by the Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) to be representative of a clinically significant determinant of critical organ dosimetry in gynaecologic cancer [22,23] and has been correlated with the occurrence of late rectal side effects in cervical cancer [24].

STATISTICALANALYSIS

The study sample size was determined as follows. A preliminary data sample of 14 repeated measurements from 4 individual patients was taken.It revealed an average change standard deviation in bladder size between the empty and full states of 2.5-times. Using a conservative assumption of an average fold change effect size standard deviation of 2, it was estimated that with atleast 20 study subjects, the power to detect at least a twofold within-subject mean change in bladder size between full and empty using a two-sided paired t test at a 5% significance level was 90%. All dosimetric parameters outlined were summed, and the mean was calculated. A two-tailed paired t test was used to compare the difference in bladder and rectal volumes by CT scan between the full and empty bladder, and a Bonferroni correction was performed to assess the statistical significance. Pearson correlation analysis within each bladder filling state was performed to examine whether linear associations were present between cylinder size, vaginal treatment length and the bladder DVH, and D2cc and between rectal DVH and D2cc. Multivariate regression modelling was applied to all parameters.

RESULTS

Of the 30 patients enrolled, none had previously undergone vaginal cuff brachytherapy. **The cylinder size was 3.0 cm in 6,3.5 cm in 22 patients and 4 cm in 2 patients.** The median treatment length was **4 cm (range, 3–6 cm)**. No patients described discomfort from bladder filling during the course of insertion and treatment.In all these patients, vaginal cuff received adequate brachytherapy doses in both full bladder and empty bladder situations,which was a mandatory pre requisite in our study.The bladder volume and surface area were both significantly smaller in the empty state than the full state (Table 1). We decided that irradiated volumes of <1.5 to 2.0 cc was clinically negligible; therefore the V 100 ,V 90 and V 80 were not useful parameters to measure, because only 2 patients had values >2 cc for V90 and V100 and 4 patients for V80,respectively. Therefore, the V70 for each fraction was taken as the most appropriate volumetric parameter to analyze the greatest dose received by the bladder. The bladder V70,V50 and D2cc were significantly lower for the empty bladder than for the full bladder, with the V70 and D2CC remaining significant after Bonferroni correction (Table 2). For the rectum, the V100, V90, V80, and V75 were not considered useful parameters to assess because of the low volumes irradiated. The V55 and D2cc measured a clinically significant volume of rectal tissue; however, no significant difference was found in these parameters between the full and empty bladder state.

No correlation was found between treatment length or cylinder diameter and the bladder V70, V50,D2cc for the full or empty bladder.

DISCUSSION

To our knowledge, this is the first prospective clinical trial in the Indian setup investigating normal tissue dose reporting and the effect of bladder volume using CT-based volumetric dosimetry in vaginal cuff HDR brachytherapy. Overall, the bladder and rectum received low radiation doses. The volume and surface area of the irradiated bladder were smaller when the bladder was empty than when it was full.This maybe because a full bladder generally drops around the posterior aspect of a vaginal cylinder in a post hysterectomy patient. Of the various dosimetric parameters assessed, the bladder V70,V50, and D2cc yielded the greatest difference between the empty and full filling states. Bladder filling did not alter the volume of the rectum irradiated. The use of vaginal cuff HDR brachytherapy is increasing in our country. Simulation, using two-dimensional fluoroscopic imaging, is performed at many centers to provide documentation of the cylinder size and bladder and rectal point dose estimates. For HDR administration, the standard recommendations include estimation of the bladder dose using a Foley catheter. The introduction of three-dimensional imaging for gynaecologic brachytherapy planning has obviated placement of a urinary catheter for bladder dose estimation. The use of CT scanning in vaginal brachytherapy has been reported [25,26,27], but the volumetric dosimetry to the organs at risk in HDR cylinder brachytherapy is unknown. Studies of tandem and ovoid brachytherapy for cervical cancer have assessed the conventional ICRU 38 reference points and compared them with CT-based volumetric dose estimations[28]. Schoeppel et al.[15] determined that the CT-determined maximal bladder and rectal doses might not be the best index doses to correlate with outcome, because the volumes irradiated are so small, and suggested that volumetric assessments would be preferable. Pelloski et al [22] reported that the ICRU 38 rectal point in low-dose rate tandem and ovoid brachytherapy was a reasonable surrogate for volumetric assessment of the rectal dose received (D2cc),but the ICRU 38 bladder point is not a reasonable surrogate for the bladder D2cc. Studies on the effect of bladder filling on normal tissue dosimetry in gynaecologic brachytherapy,have been reported earlier,but mostly focused on patients undergoing brachytherapy with a uterine tandem in an intact uterus [29,30]. These studies required placement of a urinary catheter to facilitate bladder filling and emptying and for ICRU 38 dose point estimation. Sun et al.[30] found a statistically significant decrease in the V50 as contoured on a planning CT scan when a median of 220 mL of water had been instilled into the bladder before intracavitary cervical implantation. The median bladder wall dose, analyzed as a volume rather than a surface area, was significantly decreased when the bladder was full. The bladder D2cc was not affected by bladder filling. When considering the variations between our results and those of Sun et al.[30], it is important to consider that patients undergoing intracavitary implantation have an intact uterus, which could displace the bladder away from the implant, and also that intracavitary implant patients undergo vaginal packing to further displace the posterior bladder wall, which is not possible in vaginal cylinder brachytherapy. Also, hysterectomy requires removal of the paravaginal and parametrial support.

Hoskin and Vidler [17,31] examined the effect of bladder filling in patients undergoing vaginal cylinder brachytherapy. Their initial pilot study of 5 patients showed that the instillation of 70 mL of water into the bladder decreased the amount of small bowel in the field but increased the posterior bladder wall dose (32). However, a subsequent 30-patient study showed that the instillation of 100 mL of water into the bladder decreased the amount of small bowel in the field without significantly increasing the mean maximal bladder dose (17). The study analyzed only the mean maximal bladder dose and did not assess the volumetric parameters. Therefore, the possible effect of a larger proportion of bladder surface area coming into contact with the cylinder in the larger bladder was not assessed. The greater mean bladder volume of 390 cm3 for the full bladder state in our study could also have accounted for the differences. **A similar study was conducted in the US setting[33], where results were comparable, but in the study, apart from volume, surface area of bladder was also analysed, but sample size was less, compared to ours.**

The limitations of this study included that the delineation of normal tissue may not be as accurate in CT,as in MRI. The reference standard for normal tissue contouring in gynaecologic brachytherapy is magnetic resonance imaging[16], which is limited by cost and availability. **However, contouring the organs at risk using CT has**

been shown to not be significantly different than magnetic resonance imaging[28]. CT-based contouring can be subject to inter observer variability of 11%[34]; however, the variation was minimized in our study by ensuring that one physician contoured all organs at risk. We did not ask patients to agree to oral contrast; therefore, we were not able to differentiate small bowel from large bowel for the bowel point dose estimation. After EBRT and intracavitary brachytherapy implantation for cervical cancer, a relationship is seen between the total dose to the bladder and rectum and the incidence of late toxicity [35,36]. The same relationship would be expected after EBRT and vaginal cylinder brachytherapy. However, it is important to remember that these studies used the ICRU 38 reference points for these associations. Koomet al.[24] demonstrated a positive correlation between the rectal D2cc dose and the risk of rectal damage seen on sigmoidoscopy in the treatment of cervical cancer.Additional work is needed with CT-based volumetric dosimetry and vaginal cylinder brachytherapy to determine the clinical outcomes related to D2cc measurements. In our study, toxicity was not assessed; prospective follow-up will determine whether the state of bladder filling at cylinder brachytherapy is associated with the risk of late complications. Bowel toxicity would be an important area to assess because of the decrease in the shortest distance to the bowel in the empty bladder state.

TABLE LEGENDS

TABLES

Table 1. Bladder volume and surface area in full and empty bladder filling

Bladder filling	Mean volume (cm3)	Range (cm3)
Full*	390	(200-664)
Empty	88.2	(35.82-108.33)
P value	0.003	

*Patients consumed 1 litre of water 1 hour before cylinder insertion

Table 2. Significant dosimetric parameters identified on comparison of bladder volume with full versus empty bladder

Mean bladder dosimetric value	Full bladder* (range)	Empty bladder (range)	P value
V70 (cm3)	2.4(0.02-13.34)	1.2(0.01-4.17)	0.001
V50 (cm3)	12.72(0.15-35.5)	5.8(0.13-12.5)	0.02
D2cc (Gy)	4.4(3.29-6.24)	3.8(2.38-5.1)	0.0056

Abbreviations: V70 = volume of bladder receiving >/=70% of dose; V50 = volume of bladder receiving >/=50% of dose; D2cc = maximal dose received by 2 cm3 of tissue;

* Patients consumed 1 litre of water 1 h before cylinder insertion. y Statistically significant p value. z Statistically significant after Bonferroni correction.

Table 3. Table showing Pearson correlation coefficient 'r' values obtained when dosimetric parameters in both bladder states were correlated with cylinder diameter and cylinder length

	Bladder D2CC Full bladder	Bladder V70 Full bladder	Bladder 2cc Empty Bladder	Bladder V70 Empty Bladder
CYLINDER DIAMETER	r=0.009156307 (No relation)	r=-0.073385805 (No relation)	r=0.061458157 (No relation)	r=0.153479093 (very weak relation)
CYLINDER LENGTH	r=-0.07691105 (No relation)	r=-0.191053821 (very weak relation)	r=0.136158322 (very weak relation)	r=0.045267492 (No relation)

CONCLUSION

The results of our study indicate that the HDR brachytherapy dose to the bladder is lower when the bladder is empty than when it is full. Future prospective studies of vaginal cuff brachytherapy might consider requiring treatment with an empty bladder to minimize the dose to the bladder. However, additional data on early and late bladder and bowel toxicity for this approach are necessary.

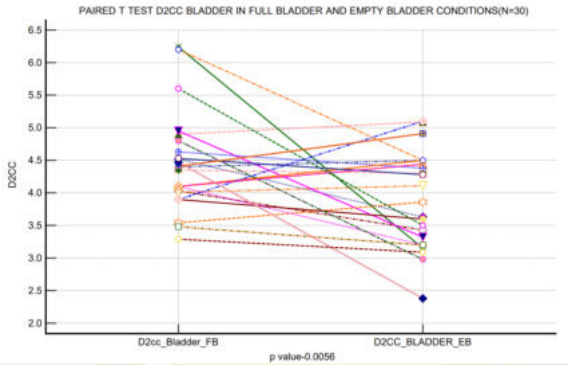

Figure 1.Dot and line diagram representing paired t test comparing D2CC values in full bladder and empty bladder states

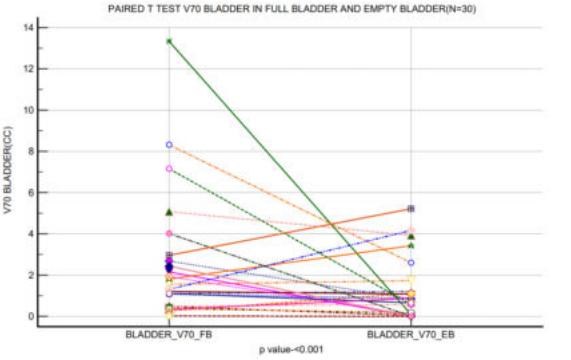

Figure 2. Dot and line diagram representing paired t test comparing V70 values in full bladder and empty bladder states

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