EPH - International Journal of Medical and Health Science
ISSN (Online): 2456-6063
Volume 03 Issue 01 March 2017

DOI: https://doi.org/10.53555/eijmhs.v4i2.25

IMPACT OF BLADDER DISTENSION ON ORGANS AT RISK IN 3D INTRACAVITARY BRACHYTHERAPY FOR CERVICAL CANCER

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Objectives:
To determine the effects of bladder distension on organs at risk (OAR) during ICBT for cervical cancer with 3D Imaging based Planning.

Materials and methods:
Twenty-eight patients with cervical cancer who received high-dose radiation (HDR) brachytherapy using 7Gy x 4 fractions, were included in the study. For three-dimensional (3D) analysis, pelvic CT scans were obtained with indwelling catheters in place (defined as empty bladder) and repeated scans with 200-cc of sterile water in their bladders (defined as full bladder). To compare the International Commission on Radiation Units and Measurements (ICRU) point doses with 3D-volume doses, the volume dose was defined by using two different criteria, D2cc (the minimum dose value in a 2.0-cm^3 volume receiving the highest dose) and D50% (the dose received by 50% of the volume of the OAR) for OARs.

Results:
For patients with a full bladder, the mean bladder D2cc increased from 395 to 558.4 cGy (41%, $p < 0.001$). However, the bowel D2cc and sigmoid colon D2cc decreased from 477.4 to 216.1 cGy (55.0%, $p < 0.001$) and 450.8 to 350.8 cGy (22%, $p= 0.001$), respectively. The mean D50% values of both the bladder and the bowel decreased from 301.6 to 227.3 cGy (25%, $p < 0.001$) and from 116.5 to 74.3 cGy (36%, $p < 0.001$) with a full bladder, respectively. The mean D50% for sigmoid colon also decreased from 148 cGy to 119.3 cGy (19%, $p< 0.001$) with bladder distension. However, there was no significant difference in rectal D2cc and D50% values.

Conclusion:
Full bladder technique reduces sigmoid colon and bowel wall radiation exposure. The bladder gets a higher point dose and rectum remains unaffected.

Key words; *organ at risk (OAR), HDR, D2CC, D50%*

INTRODUCTION:-

Cervical cancer is the fourth most common cancer among female population worldwide. 85% of all cervical cancers have been reported in developing countries where it is one of the leading causes of cancer death in women (1,2). Cervical cancer ranks third most common cancer amongst Pakistani females and contributes to approximately 3000 cancer related deaths each year (3). Concurrent chemoradiotherapy followed by intracavitary brachytherapy (ICBT) is considered the standard treatment for locally advanced cervical cancer (4,5). The recommended dose of radiotherapy for early and locally advanced diseases are 80-85Gy and 85-90Gy respectively. Improved survival outcomes at the expense of long term morbidity associated with this treatment remains a concern (6,7). Forrest JL et al. reported 14% incidence of grade 3 and 4 toxicity at 2 years for locally advanced cervical cancers treated with EBRT concomitant with chemotherapy followed by high dose rate (HDR) ICBT (7). Depending upon the patient-population, the reported rates of grade 3 and 4 toxicities vary between 6 to 23% for the mentioned treatment course (6). Several studies have shown that there is a linear correlation between radiation dose and late complications for the bladder, rectum and small bowl (8,9). It is, therefore, important to limit the dose to the organs at risk (OAR) as much as possible to reduce the incidence of treatment toxicities. Investigators have used bladder distension during ICBT as method to reduce radiation dose to OAR. Robert et al (10), for example, used 180cc of normal saline to fill the bladder and found that there was a significant reduction in the minimum dose to the highest irradiated volume of 2cc (D2cc) for small bowl and the dose received by 50% of the specified organ (D50%) for bladder and rectum. Similarly, Cengiz et al (11) found that bladder fullness changed the dose distribution to the D2cc and small bowl without affecting the target dose distribution during ICBT. However, despite encouraging results of the mentioned studies, performing ICBT with bladder distension is not the standard practice worldwide. Our institutional practice is to use indwelling catheter in bladder during Intracavitary treatment which usually follows concomitant chemoradiation for locally advanced cancers. The aim of this study is to evaluate the effects of bladder distension on the dose distribution to OARs including small bowl, sigmoid colon, urinary bladder and rectum during HDR ICBT, using 3-D CT based planning.

Materials and Methods

Study Setting

This study was carried out in the radiation department of Shaukat Khanum Memorial Cancer Hospital and Research Center (SKMCH & RC), Lahore, Pakistan. The tertiary care hospital has 195 beds and offers a complete range of health services including clinical, diagnostic and outpatient services.

Patient Selection *Between* February 2012 and May 2012, twenty-eight consecutive women were enrolled in a prospective registry after the approval of institutional Review Boards in SKMCH & RC. The inclusion criteria included histologically verified gynecologic non-metastatic squamous cell carcinoma of the cervix, ECOG performance status of ≤ 2, and age over 18 years. Informed consent was taken from each patient included in the study.

Radiation Treatment

All the patients received 45Gy in 25 fractions by EBRT using box field technique with 6/15 MV photon therapy followed by HDR ICBT with 700 cGy/fraction for 4 fractions. The patients received cisplatin 40 mg/m^2 weekly during the treatment. The overall treatment was completed within 56 days. Fletcher-type applicators were used to deliver ICBT. The applicators were placed in the uterine cavity and vagina. HDR brachytherapy was administered using Iridium-192 sources by the Gamma Medplus HDR afterloader unit (Varian Medical Systems, Palo Alto, CA, USA). The applicators were fixed in the vaginal fornix using cotton packing. The largest applicator that the patient could tolerate was used. A CT-compatible tandem and two ovoids were used for all patients.

CT Scanning

Two sets of pelvic CT scans were obtained for every fraction. The first CT scan was obtained with indwelling catheter in place, defined as empty bladder (figure 1) and for the second CT scan patients received 200cc injections of sterile water, defined as full bladder(figure 2). All CT scans were performed with 5 mm slices from the lumbosacral junction to upper one-third of thigh.

Organ Delineation

Following the CT scan, the images were transferred to Eclipse Brachyvision Treatment Planning System (Varian Medical System, Palo Alto, CA, USA) through the DICOMRT protocol. One experienced radiation oncologist delineated the external contours of the tumor volumes including the GTV, CTV and PTV as well as the organs at risk (OAR) in both sets of CT images for all patients. The marked OARs were: the small bowl, sigmoid colon, bladder and rectum. All tumor volumes and OAR were reviewed by an experienced radiologist. All the aforementioned volumes were delineated on each slice. The recommendations from (GYN) GEC-ESTRO were used as guidelines for organ delineation (12). The GTV was defined as the macroscopic tumor extension at the time of ICBT as detected by clinical examination and radiological findings. An additional 5 mm safety margin was given to the GTV to create the CTV. Based on institutional protocol, the PTV was created with no additional margins to the CTV. The dose was prescribed to the PTV. The outer wall of the rectum was defined from the anus to the recto-sigmoid flexure.The small bowel was defined as the bowel in the peritoneal cavity containing bowel excluding the sigmoid colon, rectum and bladder in the pelvis.The sigmoid colon was defined as the bowel segment above the rectum to the level of the lumbosacral interspace.

Treatment Planning Dwell positions were identified on the CT images of each patient and determined inside of the uterine tandem and ovoids. The treatment plan was optimized to dose coverage of the PTV by iterative manual trial, followed by

manual fine-tuning of the dwell points and its weights while monitoring the DVH data for both the PTV and OARs. Dose Volume Histograms (DVHs) were used to compare the maximum dose (D2cc) and the mean dose (D50%) of the OAR of an empty bladder to that of full bladder. D2cc was defined as the minimum dose in a volume of 2 cm3 which received the highest dose. The D50% was defined as the dose received by 50% of the volume of the specified organ.

Statistical analysis

The effect of bladder distension on treatment of OARs was evaluated by comparing two different dose volume parameters (D2cc and D50%). Based on bladder volume status, descriptive statistics were used to summarize the D2cc and D50% values. The percent change of dose between empty and full bladder was calculated for each patient. These differences were compared using a parametric, two sided pair t-test. The means and 95% confidence intervals (CI) of dose changes between full and empty bladders were calculated. Statistical analyses were performed using IBM SPSS software (version 23.0, Chicago, Illinois, USA). A p-value of less than 0.05 was considered statistically significant.

Results

OAR volumes

The mean empty bladder volume was 52.6 cc while the mean full bladder volume was 327.9 cc. The mean volume of the small bowl decreased by 20% with bladder distension from 362.7 cc to 291.1 cc. This change was statistically significant ($p = 0.007$ for paired t-test). The volumes of the rectum and sigmoid colon remained unaffected by bladder distension. (Table 1)

Effects on D2cc for OAR

The mean D2cc for small bowl decreased by 55 % (477.4 cGy to 216.1 cGy) with bladder distension and this change was statistically significant (paired t-test $p= 0.000$). Following the same pattern, the mean D2cc for sigmoid colon decreased by 22 % (450.8 cGy to 350.8 cGy) with bladder distension and this change was statistically significant (paired t-test $p= 0.001$).However, the D2cc for bladder increased by 41% (395.0 cGy to 558.4 cGy), and this was statistically significant (paired t-test $p = 0.000$. Bladder distension did not have any effect on the D2cc for rectum. (Table 2)

Effects on D50% for OAR

With bladder distension, the mean D50% for small bowl decreased by 36 % (116.5cGy to 74.3 cGy) and this was found to be statistically significant (paired t-test $p = 0.000$). Likewise, the mean D50% for bladder and sigmoid colon decreased by 25% (301.6 cGy to 227.3 cGy) and 19% (148 cGy to 119.3 cGy), respectively, and both these changes were statistically significant (paired t-test $p=0.000$). Contrary to the other OAR, the mean D50% for rectum increased by 49 % (201.1 cGy to 300.1 cGy), which was found to be statistically non-significant ($p = 0.292$). (Table 3).

Discussion

Our results show that bladder distension significantly reduces the D2cc and D50% for small bowl and sigmoid colon, and the D50% for bladder. However, as a result of bladder distension, the D2cc was found to be significantly higher in the case of bladder. This increase in D2cc for bladder can be compensated with reduced mean dose thus limiting the overall volume of bladder in the high dose range. Therefore it can be assumed that bladder distension can reduce treatment-related complications of the small bowl, sigmoid colon and bladder. There was no effect on D2cc and D50% for rectum with bladder distension. One to two days of inpatient course for LDR brachytherapy in the past not only rendered inability to inflate bladder for the desired outcomes, but also risked infections and related complications. HDR, with short treatment times and plausible protective techniques can minimize infection risks and spare nearby organs from radiation exposures. In the literature, different volumes ranging from 40 cc to 450 cc were used for bladder distension (10, 13, 14,15, 16, 17). The average volume of saline used in these studies was 200cc. We used 200 cc normal saline as a reference volume to assess the effects of bladder distension on the doses of OAR in our population. In this study, the D50% of the small bowl reduced by 36%, sigmoid colon 19% and the bladder 25%. The D2cc of the small bowl reduced by 55%, the sigmoid colon 22% while the bladder increased by 41%. These findings are consistent with the results reported by Kim et al. and Cengiz et al. (10,11). Nilandri et al. (13) found that bladder distension reduces the D50% for small bowl and bladder and D2cc for small bowl. Lack of bladder and sigmoid preservation in the study by Kim et al, can be explained by reduced distention volumes used in that study. Cengiz et al (14) found that bladder distension with saline (median volume 250cc, range 200 cc450 cc) also effected the rectal doses. The median maximal dose was found to be significantly lower in the distended bladder (481cGy vs. 628 cGy). However, the bladder distension had trivial effect on rectal doses in our patients which is consistent with the previous findings (10, 13,15,17). The difference can be explained either due to lack of distending volumes or difference in rectal contouring. The small bowl is more radiosensitive than the other OAR in the pelvis (18). Bladder distension is a useful technique to push the small bowl away from the radiation source during ICBT. In our study, we found that the mean decrease in small bowl volume was 71.6 cc (95% CI: 21.6 - 121.5) in the scanned images after filling the bladder. Sang Gyu et al. (19) also found that the upward displacement of the small bowel resulted in a significant reduction in the volume of the small bowl (median change 92.5 cc). In another study, Stewart et al (20) found that that the median distance to the nearest point of the bowl from the radiation sources increased by almost twice (from 5.75 mm to 11.6 mm) with bladder distention. This study, to the best of our knowledge, is the first one to describe effects of bladder distension to nearby organs using HDR brachytherapy in the region. There are some limitations also. Primarily, all the patients were treated with empty bladder it is difficult to comment on the comfort level of patients during ICBT had they been treated with full bladder. Niladri et al. (13) reported that all the patients tolerated the procedure of bladder distension well but the maximum volume used in that study was only 120cc. Secondly, we did not treat the

patients with full bladder in real time, the clinical significance of this approach will remain in question. Another limitation could be that we did not evaluate the effects of bladder distension on the ICBT implants and relevant isodose distributions. In conclusion, our findings suggest that bladder distention significantly reduces the doses received by the organs at risk during ICBT, namely the small bowl, bladder and sigmoid colon. We recommend further large scale randomized trials to assess the clinical implications of ICBT with bladder distension and its correlation to late toxicities.

Acknowledgment
We would like to say special thanks to Dr Mazhar Ali Shah (director of radiation oncology) and Abdul Rafay (chief medical physicist) for their continuous support throughout this project.

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Tables

Table 1: volume of OARs with empty and full bladder

OAR	Volume(cc) with Empty Bladder mean(SD)	Volume(cc) with Full Bladder mean(SD)	Mean change (95% CI)	P value
Small Bowl	362.7 (138.9)	291.1 (164.2)	-71.6 (-121.5, -21.6)	0.007
Bladder	52.6 (42.8)	327.9 (141.1)	275.3 (224.3, 328.2)	0.000
Sigmoid Colon	110.3 (35.8)	111.8 (44.4)	1.5 (-9.5,12.5)	0.780
Rectum	93.6 (23.5.)	95.3 (23.5)	1.7 (-4.3, 7.6)	0.576

Table 2. D2cc for OAR in full bladder compared to empty bladder

OAR	Empty Bladder	Full Bladder	P value
Small Bowl	477.4 CGy (mean ± 297.2)	216.1 CGy (mean ± 157.9)	0.000
Bladder	395.0 CGy (mean ± 115.1)	558.4 CGy (mean ± 115.8)	0.000
Sigmoid Colon	450.8 CGy (mean ± 237.0)	350.8 CGy (mean ± 208.7)	0.001
Rectum	533.9 CGy (mean ± 253.2)	529.7 CGy (mean ± 253.8)	0.850

OAR = Organs at Risk
D2cc = the minimum dose in a volume of 2 cm3 which received the highest dose
D50% for OARs in full bladder compared to empty bladder

Table 3

OAR	Empty Bladder	Full Bladder	P value
Small Bowl	116.5 CGy (mean ± 77.5)	74.3 CGy (mean ± 55.2)	0.000
Bladder	301.6 CGy (mean ± 46.5)	227.3 CGy (mean ± 121.0)	0.000
Sigmoid Colon	148 CGy (mean ± 93.6)	119.3 CGy (mean ± 75.9)	0.000
Rectum	201.1 CGy (mean ± 54.1)	300.1 CGy (mean ± 499.8)	0.292

D 50% = the dose received by 50% of the volume of the specified organ.

Figure 2. Transaxial CT slice with showing OAR in distended bladder

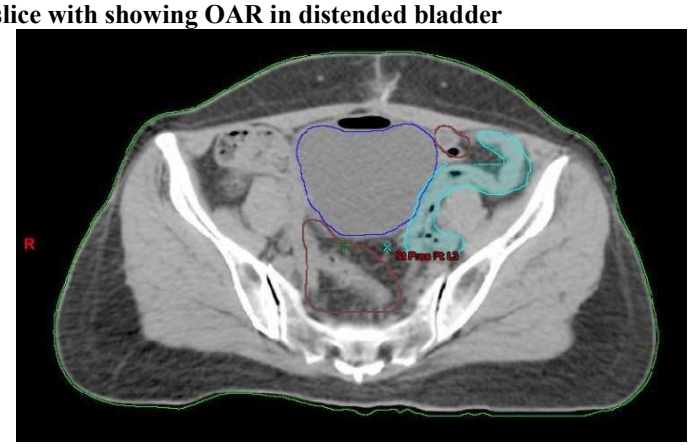
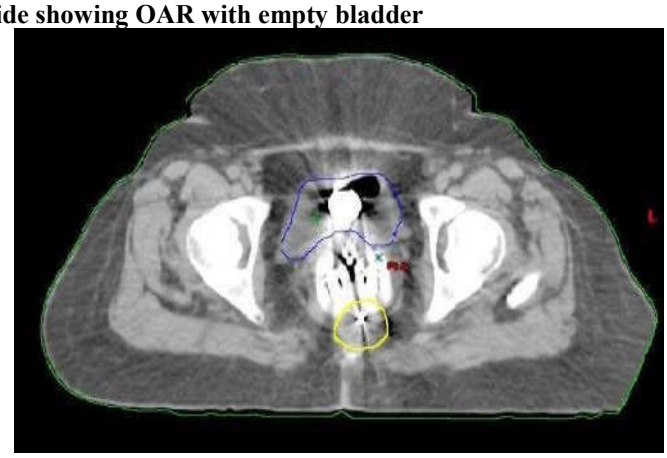


Figure 1. Transaxial CT slide showing OAR with empty bladder



List Of abbreviations

1: HDR	**High dose rate**
2: ICBT	**Intra-cavitary Brachytherapy**
3: D2cc	**dose to 2cc volume**
4: D50%	**dose to 50% volume**
5: OAR	**Organ at Risk**
6: EBRT	**External Beam Radiation Therapy**
7: MV	**Megavoltage**
8: 3-D CT	**Three dimentional computed tomography**
9: GTV	**Gross tumor volume**
10: CTV	**clinical target volume**
11: PYV	**planning target volume**
12: ECOG	**Eastern Cooperative Oncology Group**
13: LDR	**low dose rate**
14: Gy	**Gray**
15: CGy	**centi-gray**