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INFLUENCE OF BLADDER VOLUME AND CENTRAL TANDEM LENGTH ON OPTIMUM DOSE TO OAR IN INTRACAVITARY BRACHYTHERAPY OF CARCINOMA CERVIX

Oncology

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ABSTRACT

PURPOSE: The aim of this study is to find an optimum bladder volume and central tandem length to minimize the dose to pelvic OARs.

METHOD : This study was done between 2017-2018 among 40 histologically proven squamous cell cervical cancer patients who received concurrent chemoradiation of dose 50Gy in 25 fractions, 2Gy per fraction over 5 weeks along with weekly Inj.Cisplatin of dose 40mg/m2 followed by 3 sessions of HDR intracavitory brachytherapy with dose 7.5Gy per session once weekly from the Department of Radiation oncology, Father Muller Medical College. Patients were classified into four groups based on their bladder volumes measured – (i) Group A with less than 70 cc, (ii) Group B with 70 to 110 cc, (iii) Group C with 110 to 170 cc, and (iv) Group D with greater than 170 cc. The rational for this type of patient classification was to calculate the bladder, rectal and sigmiod doses based on different bladder volumes and to fix a routine filling protocol. Another classification was made based on the physical tandem length into two groups (a) the patients who were treated with tandem lengths equal to or less than 4 cm,and (b) those who were treated with tandem lengths longer than 4 cm. The bladder, rectum, and sigmoid DVH parameters such as D0.1cc , D2cc and D10, D30, D50 were recorded in terms of percentages of the planning aim dose after each treatment plan.

RESULTS - BLADDER: The results of this study indicate that the minimum dose to the most exposed small volumes of the bladder (i.e., D0.1cc and D2cc),increased as the bladder volume enlarges. On the other hand, large volume doses (i.e., D10, D30, and D50) decreased by increasing bladder volume. Tandems longer than 4 cm increase the dose to the bladder up to about 4% more (of the planning aim dose) compared to the shorter tandems.

RECTUM: Rectum dose reaches its minimum and maximum levels for <70cc and 110-170 cc bladders, respectively. Choosing a longer tandem leads to about 5% more dose to the rectum.

SIGMOID: When the bladder volume is 70-110 cc, the sigmoid dose will be minimum. Tandem lengths have a direct relationship with sigmoid dose.

CONCLUSION : In conclusion, choosing a bladder with a volume of about 70 cc or less and tandem length of <4cm is recommended when taking into account the high dose volume parameters for bladder, rectum, and sigmoid.

KEYWORDS

INTRODUCTION

Cervical cancer ranks as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women with an estimated 570,000 cases and 311,000 deaths in 2018 worldwide. Cervical cancer is the most commonly diagnosed cancer in 28 countries and the leading cause of cancer death in 42 countries, the vast majority of which are in the Sub-Saharan Africa and South- Eastern Asia[1]. In India, cervical cancer ranks the third most common cancer with 8.4% of new cases and 7.7% of deaths reported in 2018[2].

For patients suffering from locally advanced cervical cancer, external beam radiotherapy (EBRT) in combination with 3D image guided brachytherapy (IGBT) is the general modality of treatment. Intracavitary brachytherapy (ICBT) forms the foundation of treatment for cervical cancer. The International Commission on Radiation Units and Measurements (ICRU) Report 38 in 1985, have given ICRU definition to define and report reference bladder and rectal point doses during ICBT on conventional radiography. In recent past, use of newer imaging modalities like computed tomography (CT), magnetic resonance imaging (MRI), and image-based treatment planning has permitted for better evaluation in terms of dose-volume parameters rather than ICRU point doses[7]. This has allowed a better understanding of the dose volume histogram (DVH) effects on the organs at risk (OAR's), mainly rectum, bladder and sigmoid. Various studies have shown that the ICRU points do not represent the actual doses to these normal surrounding structures, especially bladder. The filling status of organs, like the bladder or rectum, has an effect on organ dosimetry[3]. In 2005 and 2006, GEC-ESTRO (Groupe Européen de Curiethérapie – European Society for Radiotherapy and Oncology) published recommendations on target definition and dose-volume histogram (DVH) parameters. In 2012, the American Brachytherapy Society (ABS) endorsed the GEC-ESTRO recommendations to have "a common language" between distinctive brachytherapy centers. The ICRU/GEC-ESTRO report 89 summarizes the state of the art recommendation for reporting and recording dose and volume parameters. Dose-volume histogram of OARs and clinical target volumes (CTVs), recommended by GEC-ESTRO, can be affected by bladder volume[7].

To achieve sufficiently high-dose levels to the tumor, the organs at risk (OARs) should be spared to reduce radiation related morbidity. Due to the dose-response effect, it is important to limit dose levels below the defined dose constraints. The dose to the target and OARs can be optimized by using brachytherapy applicator with appropriate geometries and dwell time optimization based on the anatomical situation at the time of brachytherapy. The filling status of the bladder, has an effect on organ dosimetry[3]. In the female pelvis, OARs are located in the close proximity to the intracavitary applicators, and there is a high-dose gradient from the dwell positions inside these applicators. Therefore, the influence of the bladder volume on the received dose by the OARs located in the pelvis can be evaluated to find the optimized bladder volume[3]. Intrauterine tandem length and tip angle are different depending on patients anatomy, especially the uterine cavity length and malignancy extension, which was also found to affect these parameters.

The purpose of this study is to find an optimum bladder volume and the central tandem length to minimize the dose to pelvic OARs, namely bladder, rectum and sigmoid.

MATERIALS & METHODS

CASE SELECTION

Forty patients with histologically proven squamous cell carcinoma of cervix with clinical FIGO (International Federation of Gynecology and Obstetrics) stage IIB-IVA treated at the Department of Radiation oncology, Father Muller Medical College between 2017 to 2018 were included in this study after obtaining an informed consent from the patient and ethical clearance from the institution. Patients included were (i) pathological diagnosis of cervical cancer with curative intent of radiotherapy, (ii) intact uterus without previous hysterectomy surgery (not for post-operative radiotherapy), (iii) Karnofsky Performance Score >70%, (iv) FIGO stage II to IVA cases, (v) a good candidate for ICBT after EBRT (those who had tumor regression and cervical os can be identified clearly). Metastatic cervical cancer and post operative patients were excluded. These patients received external beam radiotherapy (EBRT) with 6 MV linear accelerator to a dose of 50 Gy in 25 fractions, 2Gy per fraction, 5 fractions per week over 5 weeks duration along with weekly concurrent cisplatin (40 mg/m^2) chemotherapy. One week after completion of the external radiation, the patients were treated with 3 fractions (7.5 Gy each once weekly) of HDR-ICBT[4].

PATIENT PREPARATION, APPLICATOR INSERTION AND IMAGING

The procedure were performed under spinal anesthesia in the operation theater. All patients were examined in lithotomy position to document the extent of the disease. After sterile preparation and draping of the patient, a Foley's catheter was inserted into the patient's bladder before implantations and the catheter balloon was inflated with 4 cc contrast agent and 3 cc distilled water. The uterus was sounded (with ultrasound guidance as and when required) and the intrauterine tandem was inserted. Depending on the disease extent and the vaginal distensibility, ovoids were placed. All these patients underwent HDR-ICBT with CT compatible tandem-ovoid fletcher suite applicators with different tandem lengths, i.e., 4 cm, 5 cm, and 6 cm were used depending upon the length of the uterine cavity and ovoid caps of 2-3 cm diameter were used for different vaginal dimensions. The cases were chosen to be treated using a 30-degree tilted tandem applicator. These applicators were fixed in the vaginal fornix by using gauze packing that served also to lower the rectal dose by keeping an adequate distance from the applicators. In addition, we immobilized the apparatus by two gauze strings between the applicator and the patient. In our center, the Foley catheter was kept open during the whole procedure (i.e., imaging and treatment). All CT scans were performed with 5 mm slices from the lumbosacral junction of the whole pelvis in the supine position, as they were during the time of the treatment. All CT slices were imported to the treatment planning computer system, Oncentra Workstation.

FIGURE 1 - Applicators fixed both anteriorly and posteriorly

CONTOURING, TREATMENT PLANNING, AND TREATMENT

The external contours of the bladder, rectum and sigmoid colon within the pelvis were delineated on each CT slice in the 3D treatment planning system (Oncentra Brachytherapy Mode) based on ICRU/GEC-ESTRO report 89 recommendation for reporting and recording dose and volume parameters. HDR intracavitary radiotherapy (ICRT) was performed using an 192Ir remote after loading system with the treatment device Nucleotron micro- Selectron (Nucleotron, The Netherlands)

Patients were classified into four groups based on their bladder volumes measured – (a) Group A with less than 70 cc, (b) Group B with 70 to 110 cc, (c) Group C with 110 to 170 cc, and (d) Group D with greater than 170 cc). The rational for this type of patient classification was to calculate the bladder, rectal and sigmiod doses based on different bladder volumes and to fix a routine filling protocol[5]. Another classification was made based on the physical tandem length into two groups (I) the patients who were treated with tandem lengths equal to or less than 4 cm, and (II) those who were treated with tandem lengths longer than 4 cm. The bladder, rectum, and sigmoid DVH parameters such as $D_{0.1cm3}$, D_{2cm3} and D_{10}, D_{30}, D_{50} were recorded in terms of percentages of the planning aim dose after each treatment plan[5].

STATISTICAL ANALYSIS

The DVHs of studied organs were compared descriptively among the cases in different classified groups to examine the effect of the bladder volume and tandem lengths on the OARs dose. Descriptive statistics was used for computing mean, median, range, and standard deviations. Numerical data analysis was performed through one-way ANOVA using SPSS (SPSS Statistics for Windows). Microsoft word and Excel have been used to generate graphs and tables.

RESULTS

The Patient and tumor characteristics included in this study are listed below

TABLE 1- Patient And Tumor Characteristics

CHARACTERISTICS	TYPE	NUMBER	PERCENTAGE
AGE (YEARS)	Median (Range)	55 (35-75)	
HISTOLOGY	Squamous cell ca Adenocarcinoma	40 0	100% 0
GRADE	Well differentiated Moderately differentiated Poorly differentiated	22 11 7	55% 27.5% 17.5%
FIGO STAGING	IIA IIB IIIA IIIB IVA	3 11 19 5 4	7% 47.5% 27.5% 12.5% 10%
RADIOTHERAPY SCHEDULE	Definitive RT – 50Gy/25 fractions	40	100%
CONCURRENT CHEMOTHERAPY	Cisplatin	40	100%
BRACHYTHERAPY SCHEDULE	7.5Gy per session	40	100%

EFFECT OF BLADDER VOLUME ON DOSE TO THE BLADDER

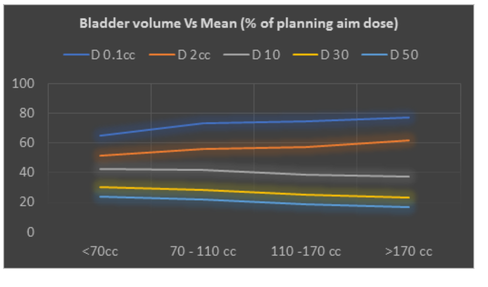
The detailed dose patterns of bladder doses of mean D_{2cc} and $D_{0.1cc}$ for bladder were noted and tabulated in the respective group according to different volume (Table 2). From the above table, it was calculated that when bladder volume increased from 70 cc to 110 cc (group A and B), the percentage increase in the mean D_{2cc} was 4.06%. Similarly, when the bladder volume increased > 170 cc (group A and D), the mean D_{2cc} increased by 9.71%.

- The results of this study indicate that the minimum dose to the most exposed small volumes of the bladder (i.e., $D_{0.1cm3}$ and D_{2cm3}), increased by the bladder volume enlargement.
- On the other hand, large volume doses (i.e., D_{10}, D_{30}, and D_{50}) decreased by increasing bladder volume.
- In all the classified groups, the differences in bladder DVH parameters were statistically significant (e.g. p value was obtained as 0.006 and 0.002 for D_{2cm3} and $D_{0.1cm3}$, respectively).

TABLE 2 – Bladder volume vs mean bladder doses

Bladder volume(cm3)	No.of patients	Mean$D_{0.1cc}$	Mean D_{2cc}	Mean D_{10}	Mean D_{30}	Mean D_{50}
<70	10	64.62%	51.67%	42.58%	30.39%	23.69%
70-110	14	73.07%	55.73%	41.89%	28.58%	21.81%
110-170	7	74.80%	57.03%	38.57%	25.18%	18.96%
>170	9	77.14%	61.38%	37.32%	23.17%	16.86%

GRAPH 1 – Bladder volume vs mean bladder dose



THE EFFECT OF BLADDER VOLUME ON RECTUM DOSE

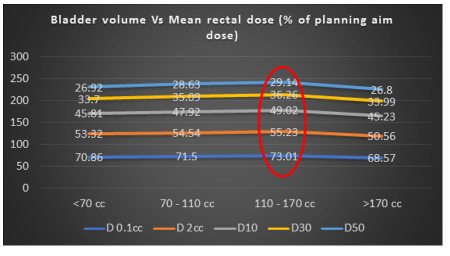
The dose patterns of mean rectal doses D_{2cc} and $D_{0.1cc}$ for rectum were noted and tabulated in the respective different bladder volume groups (Table 3). The rectum dose increased, as the bladder volume increased up to the volume of 140 cc. For higher bladder volumes, the rectum dose showed a decreasing trend, but were not significant.

From the table it is evident that the dose to the rectum was maximum, when the bladder volume was about 110- 170 cc. In this range, the D_{2cc} and $D_{0.1cc}$ of the rectum became about 55.23% and 73.01% of the planning aim dose, respectively. All the reported doses are a mean dose. However, these rectum DVH parameters (D_{2cc} and $D_{0.1cc}$) were 53.32% and 70.86% respectively, when the bladder volume was less than 70 cc and they were 50.56% and 68.57% when the bladder volume was more than 170 cc, respectively.

TABLE 3 – Bladder volume vs mean rectal doses

Bladder volume (cm3)	No.of patients	Rectal Mean$D_{0.1cc}$	MeanD_{2cc}	MeanD_{10}	MeanD_{30}	MeanD_{50}
<70	10	70.86%	53.32%	45.81%	33.70%	26.92%
70-110	14	71.50%	54.54%	47.92%	35.09%	28.63%
110-170	7	73.01%	55.23%	49.02%	36.26%	29.14%
>170	9	68.57%	50.56%	45.23%	33.99%	26.80%

GRAPH 2 – Bladder volume vs mean rectal dose



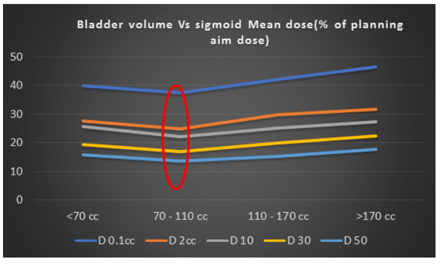
EFFECT OF BLADDER VOLUME ON DOSE OF SIGMOID

The dose pattern of sigmoid D_{2cc} and $D_{0.1cc}$ for sigmoid colon were noted and shown in Table 4. From the table, it is evident that the dose pattern obtained in sigmoid colon was more or less similar to that of the rectum, i.e., the sigmoid dose increased with the increase in bladder volume above 110 cc. The minimum dose to the sigmoid colon was obtained when the bladder volume was 70 - 110 cc. In this range, the D_{2cc} and $D_{0.1cc}$ were approximately 25% and 37.7% of the planning aim dose, respectively. The dose was maximum, when the bladder volume was above 170 cc. It was 31.9% and 46.5% for D_{2cc} and $D_{0.1cc}$ of the planning aim dose, respectively. The D_{2cc} dose was about 6% less, when the bladder volume was 70 - 110 cc, as compared to when it was above 170 cc. The *p* values were not found to be significant. The results obtained are shown graphically in Graph 3. According to GEC-ESTRO recommendations, D_{2cc} correlates with the late toxicity of the bladder, rectum, and sigmoid. $D_{0.1cc}$ was mentioned for recording and documentation of dose.

TABLE 4 – Bladder volume vs mean sigmoid dose

Bladder volume (cm3)	No.of patients	Sigmoid Mean $D_{0.1cc}$	Mean D_{2cc}	Mean D_{10}	Mean D_{30}	Mean D_{50}
<70	10	40.12%	27.64%	25.85%	19.57%	15.95%
70-110	14	**37.63%**	**24.99%**	**22.31%**	**16.86%**	**13.65%**
110-170	7	42.23%	29.86%	25.18%	19.86%	15.45%
>170	9	46.48%	31.85%	27.38%	22.34%	17.86%

GRAPH 3 – Bladder volume vs mean sigmoid dose



THE EFFECT OF TANDEM LENGTH ON BLADDER DOSE:

The results of the effect of tandem lengths on the bladder dose tests were not significant (*p* values were 0.06 and 0.08 for D_{2cm3} and D_{10}, respectively). The results show that the dose to bladder and the irradiated volume of bladder increased when longer tandems were used but not significant. Tandems longer than 4 cm increase the dose to the bladder up to about 4% (of the planning aim dose) more, compared to the shorter tandems. This increase in the dose was equal to 2.6% and 2.7% (% of the planning aim dose) for D_{2cm3} and D_{10} of this organ, respectively.

THE EFFECT OF BLADDER VOLUME AND TANDEM LENGTH ON RECTUM AND SIGMOID:

No statistically significant outcome on the bladder dose was obtained when considering applicator lengths and bladder volumes simultaneously. Choosing a longer tandem leads to about 5% more dose to the rectum. For the cases with tandems > 4 cm, D_{2cm3} of the rectum with bladder volumes more than 110 cm3 is about 10% (of the planning aim dose) higher compared to the cases with bladder volumes less than 70 cm3. Tandem lengths have a direct relationship with sigmoid dose but was not statistically significant.

DISCUSSION

The effects of bladder volume as well as the tandem length on DVH parameters of bladder, rectum and sigmoid in HDR intracavitary brachytherapy of cervical cancer patients were assessed. In our study, the optimum volume range of the bladder of 40 brachytherapy applications was analyzed.

In our study, it was observed that when the bladder volume increased from 70 cc to up to > 170 cc, the D_{2cc} of bladder increased by about 9.71% of the prescribed target dose. However, the dose to the bladder cannot be extrapolated for empty bladder. According to our findings, even in opened Foley conditions, there would still be about 60-70 cm3 urine. In principle, the dose to the bladder should decrease further in a completely empty bladder, but on the other hand, for a completely empty bladder, the anterior bladder wall would be in contact with the posterior bladder wall and, thus, the total volume of irradiated bladder wall is increased. Therefore, there is no evidence to treat patients with a completely empty bladder at this point[6].

Our results for the evaluation of bladder dose variations by increasing the bladder volumes are in close consistency with previous studies[6]. D_{2cm3} of this organ increased from about 51.6% to 61.4% (of the planning aim dose) by increasing the bladder volume from less than 70 to more than 170 cm3.

Kim *et al*. showed that an increase in bladder volume resulted in a significant reduction in D_{2cc} of the bowel, at the expense of a growth in D_{2cc} bladder volume doses. They concluded that treatment with full bladder (median value, 367 cc) is preferable to protect the bowel at the expense of the bladder[8]

According to our results attained from the rectum, it can be concluded that the rectum dose can be affected by the bladder volume. Increasing bladder volume to about 140 cm3 would cause pushing the applicator posterior towards the rectum and, thus, increasing the rectum dose. However, for patients whose bladder volumes were more than 140 cm3, this effect on rectal dose was negligible. This statement is in agreement with previous research results. By continuing the bladder distension (more than 140 cm3), most of its movement would be upwards (towards the head).

The dose to the sigmoid can be decreased by filling the bladder up to 70 - 110 cm3. For higher bladder volumes, the effect turns opposite again . This can be explained by taking into account the shifting of the bladder due to its various volumes. The discrepancy of the results in this study from those obtained by other authors [9] can be explained by the separate delineation of the rectum and sigmoid in the current study. For example, Yamashita *et al*. defined the rectum and sigmoid colon together as the recto-sigmoid in their study. They found significant reduction of hot spot dose to the small bowel, parallel to the growth of the bladder D_{2cc} dose, without any significant outcome in the rectum or sigmoid [9].

Our results showed that the dose to the OARs will be increased by increasing the tandem length. Knowing the relationship of this increase in the dose and the OARs volumes can help us with choosing the appropriate protocol for the patient preparation before the treatment. An increase in bladder volume has a direct impact on increasing their hot dose points and decreasing their D_{10}, D_{30}, and D_{50}. Increasing the D_{2cm3} and $D_{0.1cm3}$ of these organs like rectum and sigmoid will result in telangiectasia, bleeding, and fistula [10] . Therefore, controlling these parameters by finding the optimum combination of these organ volumes, bladder volumes, and also tandem lengths can prevent the occurrence of such complications [10].

Therefore, even though the tandem length is not a changeable factor in treatments, the patient's anatomical conditions conditions (filling status of OARs) can be adjusted to the appropriate length to expose the OARs by a lower dose. For example, the prescription of a two day bowel preparation before brachytherapy can have a significant impact on the patient's treatment quality

The limitations in the current research, the patients were not forced to obey any precautions before their therapy, and the effects of bladder volumes on their received dose were taken into account, in routine treatment conditions. For more accurate results, it is recommended that more research is conducted to consider these factors separately by applying specific protocols for patient preparation before the study. The other limitation of this study was that only the physical tandem length could be analyzed. It remains unclear if the main impact is due to the inserted length of the tandem or the length of source loading inside the intrauterine channel.

CONCLUSION

In conclusion, choosing a bladder with a volume of about 70 cc or less is recommended when taking into account the high dose volume parameters for bladder, rectum, and sigmoid. The most important findings of this study for different organs can be summarized as follows:

Bladder:
The results of this study indicate that the minimum dose to the most exposed small volumes of the bladder (i.e., $D_{0.1cm3}$ and D_{2cm3}) increased by the bladder volume enlargement. On the other hand, large volume doses (i.e., D_{10}, D_{30}, and D_{50}) decreased by increasing bladder volume. Tandems longer than 4 cm increase the dose to the bladder up to about 4% more (of the planning aim dose) compared to the shorter tandems.

Rectum:
Rectum dose reaches its minimum and maximum levels for <70cc and 110-170 cc bladders, respectively. Choosing a longer tandem leads to about 5% more dose to the rectum.

Sigmoid:
When the bladder volume is 70-110 cc, the sigmoid dose will be minimum. Tandem lengths have a direct relationship with sigmoid dose.

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