Original Article

Interfraction Variations in Organ Filling and Their Impact on Dosimetry in CT Image Based HDR Intracavitary Brachytherapy

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Abstract

Aim: Since anatomical and geometric variations occur with every fraction, planning, and dose optimization is necessary for every fraction of high-dose rate intracavitary brachytherapy of carcinoma cervix. In this study, we have tried to quantify the differences in doses to organs at risk (OAR) for each fraction of brachytherapy. **Methods and Materials:** One hundred and seventy computed tomography datasets of cervical cancer patients receiving intracavitary brachytherapy at our institution between January and April 2015 were analyzed. The volumes of the high-risk clinical target volume and OAR contoured were recorded for every insertion. Dose-volume histograms were generated and D90 and D100CTV and D0.1, D1, and D2cc were recorded for bladder, rectum, and sigmoid for each insertion. **Results:** Sixty-one percent had a decrease in bladder volume in the second fraction, 35% had an increase in bladder volume and 4% had no change in bladder volume. There was a strong positive correlation between increase in volume and dose (D2cc), which was statistically significant, $r_s = 0.441$, $P = 0.013$. Nearly 49.4% of patients had an increase in rectal volume during the second fraction. 45.9% had decrease in rectal volume during the second fraction. There was a positive correlation between the increase in volume and dose (D2cc), which was statistically significant, $r_s = 0.393$, $P = 0.010$. About 63.5% of the patients had a decrease in sigmoid volume during the second fraction, whereas 30.6% had an increase in volume and 5.9% had no change in volume. **Conclusion:** First, this study emphasizes the importance of imaging and planning for every fraction of brachytherapy to quantify the exact doses to the target and OAR s. Second, it is important to follow a uniform bladder protocol for every fraction, and adequate bowel preparation is needed for every fraction to minimize the interfraction variations. Finally, it also opens the realm of an adaptive planning strategy in cervical cancers which are known for rapid tumor regression during radiotherapy.

Keywords: Brachytherapy, dosimetry, interfraction variations

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Introduction

Concurrent chemoradiation is the standard of care for locally advanced cervical cancers. External beam radiotherapy is combined with intracavitary brachytherapy to achieve optimal results. High-dose rate intracavitary brachytherapy is commonly practiced worldwide and is usually given in fractionations. The number of fractions varies between different institutions. An EQD2 of 85–90 Gy to D90 to high-risk clinical target volume is recommended for tumors larger than 4 cm at the time of brachytherapy.[1,2] The total dose limit including external beam radiotherapy and brachytherapy for the bladder is 90 Gy EQD2 and 70–75 Gy EQD2 for rectum and sigmoid.

Since anatomical and geometric variations occur with every fraction, planning, and dose optimization is necessary for every fraction.[3-5] Changes in anterior rectal wall dose between two applications were reported by Hoskin *et al*.[3] They found an anterior rectal wall movement between 0 and 22 mm in relation to the surface of the ovoid between the first and second fractions. Since the organ dose variations can have important clinical implications, it is imperative to determine the dose to the target and OAR with every insertion.

In this study, we have tried to quantify the differences in doses to organs at risk (OAR) for each fraction of high-dose rate

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intracavitary brachytherapy which arises due to anatomical variations.

Materials and Methods

Case selection

One hundred and seventy computed tomography (CT) datasets of 85 consecutive locally advanced cervical cancer patients receiving intracavitary brachytherapy at our institution between January and April 2015 were analyzed. All patients received external beam radiotherapy dose of 50 Gy to the whole pelvis in 25 fractions along with weekly doses of cisplatin.

Technique

The applicator insertion was performed under general anesthesia in the operating room. A CT-magnetic resonance imaging (CT-MRI) compatible tandem ovoid applicator or a metallic tandem ring applicator was used for the patients. The tandem angle was 30° for the tandem ovoid applicator and 45° for the tandem ring applicator. Different ovoid dimensions ranging from 1.5 to 3 cm were used.

The bladder was catheterized in all patients using a Foley's catheter. Three milliliter of contrast and 4 ml of normal saline was instilled into the Foley's bulb, and the bladder was left to drain. After inserting the applicator and securing its position, vaginal packing with gauze was done with a tandem ovoid applicator. A rectal retractor was used instead of posterior vaginal packing with tandem ring applicator.

Contouring and planning

After the procedure, patients were shifted to CT simulator room (Somatom, Siemens, Erlangen, Germany) and computed tomography scans of the pelvis with 3 mm slices were taken. All CT images were exported to Oncentra planning system (Nucletron, an Elekta company, Stockholm, Sweden). GEC ESTRO GYN working group recommendations[6] were used to contour clinical target volume, bladder, rectum, and sigmoid for all patients. The volumes of the high-risk clinical target volume and OAR contoured were recorded for every insertion. High-dose rate brachytherapy was delivered with ^{192}Ir sources to a dose of 8 Gy to point A given 1 week apart for a total of two fractions. Dose-volume histograms (DVHs) were generated, volume of OARs, D0.1, D1, and D2cc (minimum doses to highest irradiated 0.1cc, 1cc, and 2cc area of OAR) were recorded for bladder, rectum, and sigmoid for each insertion.

Statistical analysis

The statistical analysis was performed using SPSS statistical package version 20 (IBM Corporation, New York, USA). Descriptive statistics such as median, interquartile range, minimum and maximum doses, and volumes were calculated. Spearman's correlation was used to find the correlation between changes in volume and dose. Patients were divided into two cohorts, namely those with an increase in volume in second fraction and those with a decrease in volume in the second fraction and significance of the changes in dosimetry were calculated using the Wilcoxon matched pair test.

Results

Variations in bladder volume and dose

Sixty-one percent had a decrease in bladder volume in second fraction, 35% had an increase in bladder volume, and 4% had no change in bladder volume. For patients with an increase in volume in the second fraction, the median increase in volume was 11 cc. The minimum increase in volume was 1cc and the maximum increase in volume was 127 cc (Range: 126). The median increase in D2cc bladder for the cohort of patients with an increase in volume in the second fraction was 0.90 Gy. For patients with decrease in bladder volume during the second fraction, the median decrease in volume was 9. The maximum decrease in volume during the second fraction was 15 cc (Range- 15). The median decrease in D2cc of the bladder for the cohort of patients with decrease in volume in the second fraction was 0.70 Gy [Table 1].

A Spearman's correlation was done to assess the relationship between increase in bladder volume and the increase in D2cc of the bladder in the second fraction. There was a strong positive correlation between increase in volume and dose (D2cc), which was statistically significant, $r_s = 0.441$, $P = 0.013$. There was a median increase in D2cc of 0.90 Gy in the cohort of patients with increase in bladder volume in the second fraction and this was found to be statistically significant by the Wilcoxon signed rank test ($Z = -4.801$, $P = 0.000$). There was a median decrease in D2cc of 0.70 Gy in the cohort of patients with a decrease in bladder volume in the second fraction and this was found to be statistically significant by the Wilcoxon signed rank test ($Z = -6.333$, $P = 0.000$).

Variations in rectal volume and dose

Nearly 49.4% of patients had an increase in rectal volume during the second fraction. 45.9% had decrease in rectal volume during the second fraction. The median increase in volume for patients with increase in volume in the second fraction was 8.5 cc. The minimum increase in volume was 1 cc and the maximum increase in volume was 54 cc (Range: 53). The median increase in D2cc rectum for the cohort of patients with increase in volume was 0.60 Gy. For patients with decrease in volume in the second fraction, the median decrease in volume was 7 cc. The maximum decrease in volume was 28 cc. The median decrease in dose for patients with decrease in volume during the second fraction was 0.70 Gy [Table 2].

A Spearman's correlation was performed to assess the relationship between increase in rectal volume and the increase in D2cc of the rectum in the second fraction. There was a positive correlation between increase in volume and dose (D2cc), which was statistically significant, $r_s = 0.393$, $P = 0.010$. There was a median increase in D2cc of 0.60 Gy in the cohort of patients with increase in rectal volume in the second fraction and this was found to be statistically significant

by the Wilcoxon signed rank test ($Z = -5.621$, $P = 0.000$) and there was a median decrease in D2cc of 0.70 Gy in the cohort of patients with decrease in rectal volume in the second fraction, which was found to be statistically significant by the Wilcoxon signed rank test ($Z = -5.621$, $P = 0.000$).

Variations in sigmoid dose and volume

Nearly 63.5% of patients had a decrease in sigmoid volume during second fraction, whereas 30.6% had an increase in volume and 5.9% had no change in volume. The median increase in volume for patients with increase in volume in second fraction was 4 cc. The minimum increase in volume was 2 cc and the maximum increase in volume was 13 cc (Range: 11). The median increase in D2cc sigmoid for the cohort of patients with increase in volume was 0.50 Gy. For patients with decrease in volume in second fraction, the median decrease in volume was 2 cc. The maximum decrease in volume was 21 cc. The median decrease in dose for patients with decrease in volume during second fraction was 0.30 Gy [Table 3].

A Spearman's correlation was done to assess the relationship between increase in sigmoid volume and the increase in D2cc sigmoid in second fraction. There was a strong positive correlation between increase in volume and dose (D2cc), which was statistically significant, $r_s = 0.485$, $P = 0.000$. There was a median increase in D2cc of 0.50 Gy in the cohort of patients with increase in sigmoid volume in second fraction and this was found to be statistically significant by the Wilcoxon signed rank test ($Z = -6.318$, $P = 0.000$) and there was a median decrease in D2cc of 0.30 Gy in the cohort of patients with decrease in sigmoid volume in second fraction, which was found to be statistically significant by the Wilcoxon signed rank test ($Z = -4$, $P = 0.000$).

Influence of bladder volume on rectal and sigmoid dosimetry

For the cohort of patients with increase in bladder volume during second fraction, variations in rectal and sigmoid dosimetry were analyzed. For patients with increase in bladder volume in second fraction, there was an increase in mean D0.1cc, D1cc, and D2cc of rectum. The average increase in D0.1cc, D1cc, and D2cc was 0.43 Gy, 0.44 Gy, and 0.40 Gy, respectively. A Spearman's correlation was used to assess the relationship between increase in bladder volume and the increase in D2cc of rectum. There was a positive correlation between increase in bladder volume and increase in D2cc of rectum, which was statistically significant, $r_s = 0.407$, $P = 0.023$.

For the cohort of patients with decrease in bladder volume during second fraction, there was a decrease in mean D1cc and D2cc of rectum. There was an average increase of 0.035 Gy to D0.1cc of rectum. The average decrease in D1cc and D2cc of rectum was 0.002 and 0.11 Gy, respectively. A positive spearman's correlation was found between decrease in bladder volume and decrease in D2cc of rectum, which was statistically significant, $r_s = 0.351$, $P = 0.009$.

Table 1: The median and interquartile range values of volume and dose for the two cohorts of patients with increase in volume in second fraction and decrease in volume in second fraction

Increase in volume in 2nd fraction	Median	Interquartile range
Bladder volume	11 cc	17
D0.1 cc	0.80 Gy	1
D1 cc	0.70	1
D2 cc	0.90	1
Decrease in volume in 2nd fraction	**Median**	**Interquartile range**
Bladder volume	−9 cc	7
D0.1 cc	−1.1 Gy	4
D1 cc	−0.90 Gy	2
D2 cc	−0.70 Gy	3

−: Decrease in volume/dose in second fraction

Table 2: The median and interquartile range values of volume and dose for the two cohorts of patients with increase in volume in second fraction and decrease in volume in second fraction

Increase in volume in 2nd fraction	Median	Interquartile range
Rectal volume	8.5	12.3
D0.1 cc	0.45 Gy	1.7
D1 cc	0.40	1.6
D2 cc	0.60	1.4
Decrease in volume in 2nd fraction	**Median**	**Interquartile range**
Rectal volume	−7 cc	8.5
D0.1 cc	−0.5 Gy	0.9
D1 cc	−0.50 Gy	0.7
D2 cc	−0.70 Gy	0.8

−: Decrease in volume/dose in second fraction

Table 3: The median and interquartile range values of volume and dose for the two cohorts of patients with increase in volume in second fraction and decrease in volume in second fraction

Increase in volume in 2nd fraction	Median	Interquartile range
Sigmoid volume	4 cc	4
D0.1 cc	0.70 Gy	1
D1 cc	0.60 Gy	1
D2 cc	0.50 Gy	0.8
Decreasein volume in 2nd fraction	**Median**	**Interquartile range**
Sigmoid volume	−2 cc	2
D0.1 cc	−0.10 Gy	1.1
D1 cc	−0.30 Gy	1.2
D2 cc	−0.30 Gy	1

−: Decrease in volume/dose in second fraction

For the cohort of patients with increase in bladder volume during the second fraction, the average increase in D0.1cc, D1cc, and D2cc of sigmoid was 0.30 Gy, 0.21 Gy, and 0.09 Gy, respectively. For the cohort of patients with decrease in bladder volume during the second fraction, there was an average increase in D0.1cc, D1cc, and D2cc of sigmoid. The average increase was 0.41 Gy, 0.16 Gy and 0.18 Gy, respectively, to D0.1cc, D1cc, and D2cc of sigmoid. A positive spearman's correlation was found between increase in bladder volume and D2cc of sigmoid but was not statistically significant, $r_s = 0.048$, $P = 0.798$. A negative spearman's correlation was found between decrease in bladder volume and D2cc of sigmoid, which was not statistically significant, $r_s = -0.006$, $P = 0.965$.

Discussion

In the recent years, three-dimensional image-guided brachytherapy[7-10] is slowly replacing the conventional X ray-based, point A-based dose reporting in gynecological brachytherapy. Groupe Européen de Curiethérapie– European Society for Radiotherapy and Oncology has published guidelines on target volume definitions and DVH parameters.[6,11] Organs at risk located in the pelvis are highly distensible organs. The changes in filling of these organs can have a significant impact on the dose delivered to these organs. There are some institutions which follow a fixed bladder protocol and several studies have reported the dosimetric changes arising out of differences in the organ volumes.[12,13]

Interfraction variations in dosimetry can arise as a result of organ deformation, tumor response during treatment and variations in applicator placement. Variations arising due to applicator placement can be minimized by using the same applicator for every insertion and by using rigid/fixed applicators like tandem ring. Imaging modalities with better soft tissue delineation like MRI can be used to assess tumor response during treatment. By following a uniform bladder filling or emptying routine, it is possible to minimize the variations arising due to organ deformation.[14] In the present study, the same type of applicators was used during subsequent fractions for each patient and a standard loading pattern was followed with each insertion.

In a study by Kirsitis *et al*., using TR applicators and MRI imaging, the mean variation in rectal 2cc dose was found to be 3.5 Gy and the mean variation in bladder 2cc dose was found to be 4.2 Gy.[15] They reported that 21% of their patients would have received more doses to the OAR in the second fraction if subsequent imaging was not done for the second fraction. A mean variation of 61% to D2cc bladder was reported by Davidson *et al*.[14] They found a mean variation of 1.7 Gy to D2cc of rectum. In the present series, 35% of the patients had an increase in dose to 2 cc of the bladder in second fraction. A median increase in dose of 0.60 Gy to D2cc rectum was found during the second fraction. Nearly 30.6% of the patients in the present series had an increase in volume of sigmoid during the second fraction and the median increase in dose to sigmoid was 0.50 Gy.

In the present study, more number of patients had decrease in bladder volume during the second fraction; although, all patients were catheterized during the procedure and the bladder was left to drain. Larger filling volumes of OARs expose more of the organs to a higher dose. Here, we found a significant correlation between the organ filling volumes and the corresponding D0.1cc, D1cc, and D2cc doses to OAR. Does that mean that organ volumes should be kept to a minimum to decrease the dose received by these organs?

The present study shows an impact on rectal dosimetry with changes in bladder filling, but there is no significant impact on sigmoid dosimetry. There are some studies which have shown decrease in the small intestine and sigmoid doses when the bladder is distended during brachytherapy.[16] Although a decrease in volumes of OARs led to a decrease in dose during the second fraction, when there is a major organ deformation in successive fractions, there is a high chance of different subvolumes of OAR receiving a high dose.

The limitations of the present study include the retrospective nature and the contouring uncertainties of the organs on CT images. Changes in clinical target volume with every fractionation and the consequent changes in dosimetry were not analyzed in the present study. Since bladder filling seems to have an impact on the OAR dosimetry, future studies should aim to determine the optimal bladder filling protocol to minimize dose to OARs.

Considering the interfraction variations which can occur during intracavitary brachytherapy, it is necessary to repeat imaging before each fraction to accurately quantify doses to the target and OAR. Individualized planning with each insertion helps in accurate estimation of doses to OAR, failing which detrimental effects will be seen in the clinical scenario.

Conclusion

The present study highlights the magnitude of variations in the volumes of organs and the target and the corresponding doses received by them in successive fractions of brachytherapy. First, this study emphasizes the importance of imaging and planning for every fraction of brachytherapy to quantify the exact doses to the target and OARs. Second, it is important to follow a uniform bladder protocol for every fraction, and adequate bowel preparation is needed for every fraction to minimize the interfraction variations. Finally, it also opens the realm of an adaptive planning strategy in cervical cancers which are known for rapid tumor regression during radiotherapy.

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Conflicts of interest

There are no conflicts of interest.

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