Abstract

Purpose: Dose received by organs at risk (OAR) in high-dose-rate (HDR) intracavitary brachytherapy (ICBT) for locally advanced cervical cancer impacts the late toxicity profile of the treatment. In the present study, we analyzed the inter-fraction variations of the minimum dose received by the most irradiated 2cc volumes (D$\text{$_{2cc}$}$) of the OARs in ICBT. Methods and Materials: This prospective study included 40 patients with cervical cancer stage FIGO IIB-IV A treated with HDR ICBT and concomitant chemoradiotherapy with Computerized tomography (CT)-based three-dimensional planning. In addition, for 20 (of the 40) patients, the first fraction plan was superimposed on the second fraction images for studying its dosimetric impact on the OAR. The D$\text{$_{2cc}$}$ data for the OAR was statistically analyzed for inter-fraction variations with Chi-square test or Fisher exact test as applicable. Paired t-test was used to compare the difference in means for the D$\text{$_{2cc}$}$ values between the three fractions. Results: The inter-fraction variations of the D$\text{$_{2cc}$}$ values of the OAR were statistically insignificant having P = 0.41, 0.8, and 0.20 for bladder, rectum, and sigmoid, respectively. Further, in 6 out of 20 cases, wherein first fraction plan was superimposed on second fraction images, the OAR doses exceeded the prescribed tolerance limits. Conclusion: We did not find variations in the OAR doses when each fraction was planned and treated individually. However, we found that if a single plan is used to treat subsequent fractions, OAR doses may exceed tolerance in about 30% of the cases. We believe that a larger sample size with improved compliance of bladder and bowel protocols would be needed to arrive at definitive conclusions.

Keywords: High-dose-rate brachytherapy, inoperable cervical cancer, inter-fraction variations

INTRODUCTION

Cervical cancer is the most common cancer cause of death among women in the developing countries.\textsuperscript{[1]} Mortality due to cervical cancer is also an indicator of the prevailing health inequities,\textsuperscript{[2]} as 86% of all deaths due to cervical cancer are in developing, low- and middle-income countries.\textsuperscript{[3]} According to a report by Indian Council of Medical Research, cancer of the cervix is the third most common cancer with an estimated 1 lakh new cases in 2016 and about 1.04 lakh during 2020.\textsuperscript{[4]} India also has the highest age-standardized incidence of cervical cancer in South Asia at 22, compared to 19.2 in Bangladesh, 13 in Sri Lanka, and 2.8 in Iran.\textsuperscript{[5]}

More than 80% patients of carcinoma cervix in India present in a fairly advanced stage.\textsuperscript{[6]} For women who develop locally advanced cervical cancer, the standard of care has evolved from external beam radiation therapy (EBRT) alone to EBRT plus brachytherapy, to combined EBRT plus brachytherapy with concurrent chemotherapy.\textsuperscript{[7,8]} The EBRT encompasses treatment to the pelvic lymph nodes, parametria, and primary tumor, to a dose adequate to control the microscopic disease. The addition of brachytherapy serves to boost the gross tumor and thus improves disease control and survival.\textsuperscript{[9,10]} The addition of chemotherapy serves predominantly as a radiosensitizer, resulting in improvement of about 5% in overall survival.\textsuperscript{[8]}

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Brachytherapy treatments are either interdigitated with EBRT (generally starting not earlier than 3rd week of EBRT) or are given after EBRT is completed. It is well established that the overall treatment time of EBRT and brachytherapy should be <8 weeks for patients treated with radiotherapy alone. Beyond this duration, the local control and survival have been shown to decrease by ~1%/day. “Historically, in the Paris System of intracavitary brachytherapy (ICBT), a single application was used to deliver 7200–8000 mg-h in 5 days while in the Manchester System 8000 R was delivered to point “A” in two sessions at an interval of 4–7 days, with duration of each session being 72 h with radium sources. Later, ICBT using cesium-137 was delivered over 1–2 fractions, with a typical treatment time of 1–3 days, and a point “A” dose rate of <0.4 Gy/h. Such treatment durations required prolonged patient immobilization as well. Since the early 2000s, there has been an increasing adoption and utilization of high-dose-rate (HDR) ICBT as opposed to low-dose-rate (LDR) one. Eighty-five percent of respondents in an American Brachytherapy Society survey (2010) reported having HDR at their institutions. While HDR ICBT has become popular due to its logistical advantages over LDR ICBT, it has necessitated dose fractionation to reduce normal tissue complications. This has resulted in potential inadvertent changes in the position/geometry of the applicators from one fraction to another. In addition, there are interfraction deformations in organs at risk (OAR) due to movement, shape changes, and variable filling of these hollow organs. This, in turn, may lead to OAR dose variations, which have important implications in dose reporting.

The study was designed to study the magnitude of interfraction dose variations in the OAR in our patient population.

Materials and Methods

This prospective study included patients with cervical cancer, Federation of International of Gynecologists’ and Obstetricians (FIGO) Stage IIB-IVA who were treated with concomitant chemoradiotherapy at our center. The study was conducted on a consecutive sample of 40 patients treated during the period August 2016–2017 when image-based ICBT was started at our center. Inclusion criteria were all females of inoperable cancer cervix of any histology, i.e., squamous or adenocarcinoma or adenosquamous with Karnofsky Performance Status >80%. All the patients in this study were taken up for brachytherapy after completion of EBRT. On post-EBRT, contrast enhanced computed tomography, a patient with any evidence of gross disease in the parametria was taken up for interstitial implant-based brachytherapy and not for ICBT.

The EBRT to pelvis was delivered on a linear accelerator model Primus (Siemens, Germany) using 15MV X-rays. A dose of 50–50.4 Gy in 25–28 fractions with a fraction size of 1.8–2.0 Gy was delivered using four fields. The EBRT was followed by HDR ICBT using Fletcher Williamson “Asia Pacific” applicators on the microSelectron HDR brachytherapy machine model V2 (Nucletron B. V., Veenendaal, The Netherlands). The brachytherapy dose protocol was 21 Gy in three fractions at weekly intervals. The rectum and bladder filling protocols required that a patient takes 20 mg bisacodyl laxative suppositories ( Dulcolax®) 12 h before every brachytherapy application. Before the scan, 7cc of iohexol an iodine-based nonionic contrast dye (1:6 dilution) was instilled in the balloon of Foley’s catheter. About 20 ml of the same contrast with a dilution of 1:20 was also instilled in the bladder at the time of imaging for better delineation of the bladder. All the ICBT implants were performed under spinal anesthesia. The vaginal packing with dry gauze soaked in betadine was done to fix the applicator in position and to displace the bladder and rectum away from the vaginal applicators. As a departmental policy, efforts were made to use the same applicator geometry in terms of tandem length and angle, and ovoid sizes for all the fractions as far as possible.

Computed tomography (CT) simulation was performed on a helical CT model Lightspeed VX R 16 (GE Medical Systems, Waukesha, USA) with 3 mm contiguous slice thickness protocol without any dummy markers inside the applicators. The bladder and rectum delineation were done on every CT slice. The rectum contouring started at 1 cm from anus to the recto-sigmoid transition. For all the OARs, the contouring followed the outer surface (wall) of the organs. The contouring, applicator reconstruction, and dose planning were carried out on Oncentra Brachy treatment planning system (TPS) version 4.5.1 (Nucletron, Veenendaal, The Netherlands). A dose of 7 Gy was prescribed to point A defined as per the International Commission of Radiological Units 38 definition. We used the standard loading pattern for all the three fractions unless OAR dose constraints were exceeded. In a latter situation, we either performed manual graphical optimization keeping in mind that the point A doses remain within acceptable values as far as possible or reduced the dose per fraction and accordingly increased the number of fractions to limit the OAR doses. The minimum dose in the most irradiated 2 cm³ OAR volumes (D2cm³) was estimated from the dose volume histograms.

For twenty cases, we superimposed first fraction dose plan on the second fraction CT images to observe its dosimetric impact on OARs. For this purpose, the second fraction image data set was first registered with the first fraction image data set and subsequently the D2cm³ (hypothetical) of bladder and rectum were estimated on the second fraction image set based on first fraction plan. This was aimed at mimicking a practice prevalent at some centers where the first fraction plan is delivered for the subsequent fractions as well. The two sets of CT images were registered using landmark-based method available in the TPS. The bones chosen were pubic symphysis and ischial tuberosity. The maximum error acceptable was ±1.5 mm. We believed that the accuracy of the OAR doses estimated from this registration process would be satisfactory enough for noticing the interfraction variations.
The total dose to a patient from EBRT and ICBT was summed up based on the biologically equivalent dose concept of linear quadratic (LQ) model. The total dose was estimated regarding 2 Gy/fraction equivalent dose schedule (EQD2). For the LQ model calculations, α/β values were taken as 10 Gy for tumor and 3 Gy for OAR.[8,15,16]

Chemotherapy
All patients were given concurrent chemotherapy weekly with injection Cisplatin (35 mg/m²) with prehydration and premedication as per protocol for five cycles.

Statistical analysis
In statistical processing of the results, standard methods of descriptive statistics were used (arithmetic mean with the standard deviation and the numerical range from minimum to maximum value). Paired t-test was used to compare the difference in means for these dose-volume parameters between three fractions. All tests were two-tailed and P < 0.05 were taken as significant. SPSS 17.0 (SPSS Inc., Chicago, IL, USA) statistics software was used for the data analysis.

RESULTS
A total of 120 brachytherapy applications were performed on the 40 patients included in the study. The average age of patients at the time of the treatment was 58.2 ± 10.7 years. Fifty-five percent of the patients were of FIGO IIb stage cervical cancer. Table 1 shows the average D2cc values for all the OARs along with interfraction comparison P values. The average value of D2cc of the bladder was the lowest for the first application (5.65 ± 1.7 Gy) and the highest for the third application (6.06 ± 1.4 Gy). The average value of D2cc for rectum was the lowest for the first application (4.16 ± 1.2 Gy) and the highest for the third application (4.42 ± 1.2 Gy). The average value of D2cc for sigmoid was lowest for the first application (3.89 ± 1.3 Gy) and the highest for the third fraction (4.21 ± 1.3 Gy). The average value of EQD2 (EBRT plus ICBT) for bladder and rectum was 82.74 ± 10.05 Gy, 69.57 ± 6.4 Gy respectively.

As is evident from the P values shown in Table 2, the interfraction dose variations for all OARs were statistically insignificant. The minimum and maximum D2cc for bladder, rectum and sigmoid ranged from 1.3–9.4 Gy, 1.4–7.0 Gy, to 1.6–6.8 Gy respectively across all fractions. The total EQD2 (EBRT plus ICBT) for bladder and rectum ranged from 58.7 Gy to 103.5 Gy and from 57.4 Gy to 88.3 Gy respectively.

The dose variations between first and second fractions for the 20 (of the 40) patients where the first fraction plan was imposed on the second fraction images have been shown in Table 2. The average D2cc values for bladder and rectum for the second fraction were higher by 1.10 and 0.03 Gy, respectively. The differences were statistically not significant with P = 0.238 and 0.788 for the bladder and rectum, respectively. In three cases for bladder and rectum each, the D2cc values exceeded the tolerance dose for the second fraction. In the three cases showing higher bladder dose, bladder volume was higher in the second fraction whereas in the case of rectum, the volume was lower in the second fraction.

DISCUSSION
Depending on the institutional protocols, HDR ICBT requires multiple applications. This could lead to interfraction variations in the applicator geometry and its spatial position in relation to the pelvic organs, pelvic bony anatomy, and the OARs.[17-19] These variations have been reported regarding changes in the uterine axis, uterine length, slippage of tandem, and colpostat separation resulting in fluctuations in spatial location of the applicator in craniocaudal axis, lateral, and anteroposterior rotation as well as variation in coronal, transverse, and sagittal planes.[20] This has been attributed to mainly patient movement, vaginal packings, and tumor regression during the interval between multiple fractions of HDR ICBT. In our protocol of 50 GY EBRT in 25 fractions followed by three fractions of BD ICBT, the efforts were made to keep the total EQD2 to bladder and rectum (D2cc value) below 90 Gy and 75 Gy respectively.

The average interfraction variations of D2cc for all the three OARs were statistically insignificant in our study. This could be due to the relatively small sample size as well as due to the fact that since each fraction was individually planned all attempts were made to keep the OAR doses below prescribed limits. Similar results have been reported by many previous studies. Marosevic et al. treated the patients with an EBRT dose of 45 Gy/25# along with concurrent chemotherapy with Cisplatin 40 mg/m².[21] They interdigitated HDR brachytherapy applications from the second week of EBRT for a total five fractions of 7 Gy each. They found the average value of D2cc (Gy) of the bladder the lowest for the second application (4.3 ± 1.4) and the highest for the fifth application (4.6 ± 1.3). In their study, the lowest average value of D2cc (Gy) of the rectum was for the fifth application (4.21 ± 1.3) while the highest value was for the second and fourth applications (5.0 ± 1.0). The average EQD2 (EBRT + ICBT) for bladder and rectum was 76.7 ± 5.6 Gy and 81.9 Gy ± 3.4 Gy, respectively. It is evident that the average EQD2 value is high for bladder and low for rectum in our case as compared to the quoted study. Like our results, Marosevic et al. also did not find statistically significant interfraction variations in the D2cc of bladder and rectum. However, they recommended CT-based planning for each fraction given a large range of minimum and maximum changes of the dose at D2cc of bladder and rectum. They recorded a minimum variation of ~2.2 Gy and maximum +2.7 Gy for bladder and a minimum ~2.2 Gy and a maximum +2.2 Gy for rectum for a 7.0 Gy dose prescription per fraction of ICBT.

In a multicentric study by Jürgenliemk-Schulz et al., MRI-guided ICBT was carried out without planning optimization. One of the goals of the study was to keep
D₁₀₀ of bladder and rectum below EQD2 90 Gy and 75 Gy, respectively. The average dose of EQD₂ for bladder was 92 ± 8 Gy and for rectum was 64 ± 3 Gy. The EQD₂ values, though not closely matching, show trends similar to our study. A retrospective study by Kirisits et al. compared individual MRI-based three-dimensional treatment planning for each intracavitary application in 14 patients. Data using the individual approach were taken from the actual irradiated plans. The “single plan procedure” was simulated by matching the dose distribution of the first plan to the MRI datasets of each subsequent implantation. They found that the average D₁₀₀ increased by 3.5 Gy for the bladder, 4.2 Gy for the rectum and 5.8 Gy for the sigmoid. In their simulated study, they found that using first plan for treating subsequent fractions for each patient would have resulted in two, one, and five additional cases of exceeding the total D₁₀₀ constraints for bladder (90 Gy), rectum (75 Gy), and sigmoid (75 Gy), respectively. In our similar study of 20 cases, four and three cases for bladder and rectum, respectively, would have exceeded the D₁₀₀ constraints of these organs.

Chakraborty et al. carried out a study on CT-based two fraction HDR ICBT (each fraction of 9 Gy) on 44 patients. They estimated the interfraction dose variations (VAR₁₀₀) as well as interfraction hypothetical variation (VAR₁₀₀hyp) following rigid image registration of the two fraction images that allowed the quantification of the dose variations arising exclusively due to changes in applicator placement and geometry. They found that VAR₁₀₀ for D₁₀₀ of bladder and rectum were 1.46 and 1.16 Gy, respectively. Increased dose was seen in 16 and 23 patients in the subsequent fraction for bladder and rectum, respectively. Doses to OAR would have exceeded constraints in 16% patients if the second fraction was not imaged. The average bladder and rectum dose values for first fraction (D₁₀₀) and for second fraction when treated with first fraction plan D₁₀₀ (hypothetical) in Gy. The average dose of EQD₂ (range) compares the first fraction versus second fraction (I vs. II); second versus third (II vs. III); and first versus third (I vs. III) are also shown in the table. SD: Standard deviation, HDR: High-dose-rate, ICBT: Intracavitary brachytherapy.

Study limitation
With the amount of data and subsequent analyses presented in this work, we are not in a position to attribute any specific parameter(s) for observed interfraction variations in D₁₀₀ values of the OARs. We believe that a larger data set involving a more detailed study of all the parameters contributing to dose variations such as applicator geometry and organ deformation are needed for the purpose.

Table 2: Interfraction D₁₀₀ for bladder and rectum with single plan for two fractions

| Organ at risk | First fraction D₁₀₀ value average±SD (range) in Gy | Second fraction D₁₀₀ (hypothetical) value average±SD (range) in Gy | P |
|--------------|--------------------------------------------------|---------------------------------------------------------------|---|
| Bladder      | 6.05±1.24 (4.1-8.5)                              | 7.15±3.91 (3.7-20.6)                                          | 0.238 |
| Rectum       | 4.4±1.10 (2.8-6.4)                               | 4.51±1.45 (2.8-7.2)                                          | 0.788 |

Table 1: Interfraction D₁₀₀ comparison for bladder, rectum, and sigmoid

| Organ at risk | Average dose±SD (range) in Gy | P |
|--------------|-------------------------------|---|
| Bladder      |                               |    |
| Rectum       |                               |    |
| Sigmoid      |                               |    |

**Conclusions**
We found no statistically significant interfraction variations in the D₁₀₀ values for bladder, rectum, and sigmoid during the fractionated HDR brachytherapy of inoperable cervical cancer. However, the high range of dose variations was an indication of excess D₁₀₀ values in some cases. Moreover, it was observed that using a single plan (of the first fraction) to treat the subsequent fractions resulted in exceeding the dose constraints of the OARs in a considerable proportion of cases. It is, therefore, important to individually plan each HDR ICBT fraction to avoid higher doses to the OARs. As there are many confounding factors such as applicator geometry, organ deformation and target response which affect the dose.
distributions, more studies would be required to analyze the impact of each of these influence factors that lead to interfraction dose variations.

**Acknowledgments**
We would like to thank all the patients for allowing us to publish the study and use their inputs.

**Financial support and sponsorship**
Nil.

**Conflicts of interest**
There are no conflicts of interest.

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