Technical Note

Interfraction Dose Variations in Organs at Risk during CT-Based High-Dose-Rate Brachytherapy in Locally Advanced Carcinoma Cervix: An Early Experience of a Tertiary Care Center

Neelam Sharma, Manoj K. Semwal[1], Abhishek Purkayastha

Department of Radiation Oncology and [1]Radiation Physics, Army Hospital Research and Referral, New Delhi, India

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_{2cc}) of the OARs in ICBT. **Methods and Materials:** This prospective study included 40 patients with cervical cancer stage FIGO IIB-IVA 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 dosimteric impact on the OAR. The D_{2cc} data for the OAR was statistically analyzed for interfraction 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_{2cc} values between the three fractions. **Results:** The interfraction variations of the D_{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

Received on: 04-11-2017 **Review completed on: 01-05-2018** **Accepted on: 01-05-2018**

Introduction

Cervical cancer is the most common cancer cause of death among women in the developing countries.[1] Mortality due to cervical cancer is also an indicator of the prevailing health inequities,[2] as 86% of all deaths due to cervical cancer are in developing, low- and middle-income countries.[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.[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.[5]

More than 80% patients of carcinoma cervix in India present in a fairly advanced stage.[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.[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.[9,10] The addition of chemotherapy serves predominantly as a radiosensitizer, resulting in improvement of about 5% in overall survival.[8]

Access this article online

Quick Response Code:

Website: www.jmp.org.in

DOI: 10.4103/jmp.JMP_136_17

Address for correspondence: Dr. Neelam Sharma, Department of Radiation Oncology, Army Hospital Research and Referral, Dhaula Kuan, Delhi Cantt, New Delhi - 110 010, India.
E-mail: nlmshrm76@rediffmail.com

How to cite this article: Sharma N, Semwal MK, Purkayastha A. Interfraction dose variations in organs at risk during CT-based high-dose-rate brachytherapy in locally advanced carcinoma cervix: An early experience of a tertiary care Center. J Med Phys 2018;43:136-40.

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.[11] "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.[12]

While HDR ICBT has become popular due to its logistical advantages over LDR ICBT, it has necessitated dose fractionation to reduce normal tissue complications.[13] 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%.[14] 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 VXR 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 cm^3 OAR volumes (D_{2cc}) 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 D_{2cc} (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 (EQD_2). 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/m^2) 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 D_{2cc} values for all the OARs along with interfraction comparison *P* values. The average value of D_{2cc} 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 $D_{2cc}$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 D_{2cc} 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 values of EQD_2 (EBRT plus ICBT) for bladder and rectum were 82.74 ± 10.05 Gy, 69.57 ± 6.4 Gy respectively.

As is evident from the *P* values shown in Table 2, the interfractions dose variations for all OARs were statistically insignificant. The minimum and maximum D_{2cc} 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 EQD_2 (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 D_{2cc} 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 D_{2cc} 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 weekly HDR ICBT, the efforts were made to keep the total EQD_2 to bladder and rectum (D_{2cc} value) below 90 Gy and 75 Gy, respectively.

The average interfraction variations of D_{2cc} 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/m^2.[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 D_{2cc} (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 D_{2cc} (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 EQD_2 (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 EQD_2 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 D_{2cc} 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 D_{2cc} 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

Table 1: Interfraction D_{2cc} comparison for bladder, rectum, and sigmoid

Organ at risk	Bladder		Rectum		Sigmoid	
	Average dose±SD (range) in Gy	*P*	Average dose±SD (range) in Gy	*P*	Average dose±SD (range) in Gy)	*P*
First fraction	5.65±1.76 (1.3-8.5)	0.410 (I vs. II)	4.16±1.26 (1.4-6.4)	0.894 (I vs. II)	3.89±1.30 (1.7-7.0)	0.205 (I vs. II)
Second fraction	5.89±1.48 (1.6-9.4)	0.537 (II vs. III)	4.19±1.28 (1.4-6.9)	0.362 (II vs. III)	4.19±1.48 (1.6-6.5)	0.928 (II vs. III)
Third fraction	6.06±1.45 (3.0-8.9)	0.118 (I vs. III)	4.42±1.21 (2.5-7.0)	0.301 (I vs. III)	4.21±1.35 (1.6-6.8)	0.163 (I vs. III)

Average D_{2cc}±SD (range) in Gy of bladder, rectum, and sigmoid for each HDR ICBT fraction. *P* values for comparison of 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

Table 2: Interfraction D_{2cc} for bladder and rectum with single plan for two fractions

Organ at risk	First fraction D_{2cc} value average±SD (range) in Gy	Second fraction D_{2cc} (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

Average bladder and rectum dose values for first fraction (D_{2cc}) and for second fraction when treated with first fraction plan D_{2cc} (hypothetical) in Gy. SD: Standard deviation

D_{2cc} of bladder and rectum below EQD2 90 Gy and 75 Gy, respectively.[22] The average dose of EQD_2 for bladder was 92 ± 8 Gy and for rectum was 64 ± 3 Gy. The EQD_2 values, though not closely matching, show trends similar to our study.

A retrospective study by Kirisits *et al*.[23] 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 D_{2cc} 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 fraction plan for treating subsequent fractions for each patient would have resulted in two, one, and five additional cases of exceeding the total D_{2cc} 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 D_{2cc} constraints of these organs.

Chakraborty *et al*.[24] 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 (VAR_{act}) as well as interfaction hypothetical variation (VAR_{hypo}) 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 VAR_{act} for D_{2cc} 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. VAR_{hypo} explained 19% and 47% of the VAR_{act} observed for the bladder and rectum, respectively. They concluded that significant interfraction variations in OAR doses can occur in HDR ICBT. Organ deformations were mostly responsible for this variation. In our study, 20% each of HDR applications would have resulted in exceeding the bladder and rectum dose constraints, respectively. Organ deformation regarding changed organ volumes was one of the factors that resulted in variations between D_{2cc} and D_{2cc} (hypothetical) for the bladder in our case. There was an increase in the bladder volumes by an average of 55% when bladder D_{2cc} (hypothetical) exceeded the constraint for the second fraction. However, in the case of the rectum, the average rectum volume decreased by 18.7% when D_{2cc} (hypothetical) exceeded the tolerance in the second fraction.

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 D_{2cc} 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.

Conclusion

We found no statistically significant interfraction variations in the D_{2cc} 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 D_{2cc} 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.

References

1. Denny L. Cervical cancer: Prevention and treatment. Discov Med 2012;14:125-31.
2. Satija A. Cervical cancer in India. South Asia Centre for Chronic Disease. Available from: http://www.sancd.org/uploads/pdf/cervical_cancer.pdf. [Last accessed on 2014 Feb 16].
3. Yeole BB, Kumar AV, Kurkure A, Sunny L. Population-based survival from cancers of breast, cervix and ovary in women in Mumbai, India. Asian Pac J Cancer Prev 2004;5:308-15.
4. Indian Council of Medical Research on Incidence of Cancer in India by 2020; 2016. p. 1-2. Available from: http://www.mid-day.com/articles/over-17-lakh-new cancer-cases-in-India-by-2020-icmr/17248152. [Last accessed on 2018 Feb 05].
5. ICO Information Centre on HPV and Cancer (Summary Report 2014-08-22). Human Papillomavirus and Related Diseases in India; 2014.
6. Shrivastava S, Mahantshetty U, Engineer R, Tongaonkar H, Kulkarni J, Dinshaw K, *et al.* Treatment and outcome in cancer cervix patients treated between 1979 and 1994: A single institutional experience. J Cancer Res Ther 2013;9:672-9.
7. Green JA, Kirwan JM, Tierney JF, Symonds P, Fresco L, Collingwood M, *et al.* Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: A systematic review and meta-analysis. Lancet 2001;358:781-6.
8. NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer National Comprehensive Cancer Network; 2016. Available from: http://www.nccn.org. [Last accessed on 2016 Feb 27].
9. Lanciano RM, Won M, Coia LR, Hanks GE. Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: A final report of the 1973 and 1978 patterns of care studies. Int J Radiat Oncol Biol Phys 1991;20:667-76.
10. Logsdon MD, Eifel PJ. Figo IIIB squamous cell carcinoma of the cervix: An analysis of prognostic factors emphasizing the balance between external beam and intracavitary radiation therapy. Int J Radiat Oncol Biol Phys 1999;43:763-75.
11. Girinsky T, Rey A, Roche B, Haie C, Gerbaulet A, Randrianarivello H, *et al.* Overall treatment time in advanced cervical carcinomas: A critical parameter in treatment outcome. Int J Radiat Oncol Biol Phys 1993;27:1051-6.
12. Viswanathan AN, Erickson BA. Three-dimensional imaging in gynecologic brachytherapy: A survey of the American Brachytherapy Society. Int J Radiat Oncol Biol Phys 2010;76:104-9.
13. Nag S, Erickson B, Thomadsen B, Orton C, Demanes JD, Petereit D, *et al.* The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. Int J Radiat Oncol Biol Phys 2000;48:201-11.
14. Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: Reliability, validity, and guidelines. J Clin Oncol 1984;2:187-93.
15. Bahena JH, Martinez A, Yan D, Mele E, Edmunson G, Brown D, *et al.* Spatial reproducibility of the ring and tandem high-dose rate cervix applicator. Int J Radiat Oncol Biol Phys 1998;41:13-9.
16. Datta NR, Kumar S, Das KJ, Pandey CM, Halder S, Ayyagari S, *et al.* Variations of intracavitary applicator geometry during multiple HDR brachytherapy insertions in carcinoma cervix and its influence on reporting as per ICRU report 38. Radiother Oncol 2001;60:15-24.
17. Grigsby PW, Georgiou A, Williamson JF, Perez CA. Anatomic variation of gynecologic brachytherapy prescription points. Int J Radiat Oncol Biol Phys 1993;27:725-9.
18. Hoskin PJ, Cook M, Bouscale D, Cansdale J. Changes in applicator position with fractionated high dose rate gynaecological brachytherapy. Radiother Oncol 1996;40:59-62.
19. Kim RY, Meyer JT, Spencer SA, Meredith RF, Jennelle RL, Salter MM, *et al.* Major geometric variations between intracavitary applications in carcinoma of the cervix: High dose rate vs. low dose rate. Int J Radiat Oncol Biol Phys 1996;35:1035-8.
20. Datta NR, Basu R, Das KJ, Rajasekar D, Pandey CM, Ayyagari S, *et al.* Problems in reporting doses and volumes during multiple high-dose-rate intracavitary brachytherapy for carcinoma cervix as per ICRU report 38: A comparative study using flexible and rigid applicators. Gynecol Oncol 2003;91:285-92.
21. Marosevic G, Butler EB, Mileusnic D. Interfraction variations of D_{2cc} brachytherapy Dose received by bladder and rectum in patients with inoperable cervical cancer. Austin J Radiat Oncol Cancer 2016;2:1019.
22. Jürgenliemk-Schulz IM, Lang S, Tanderup K, de Leeuw A, Kirisits C, Lindegaard J, *et al.* Variation of treatment planning parameters (D90 HR-CTV, D_{2cc} for OAR) for cervical cancer tandem ring brachytherapy in a multicentre setting: Comparison of standard planning and 3D image guided optimisation based on a joint protocol for dose-volume constraints. Radiother Oncol 2010;94:339-45.
23. Kirisits C, Pötter R, Lang S, Dimopoulos J, Wachter-Gerstner N, Georg D, *et al.* Dose and volume parameters for MRI-based treatment planning in intracavitary brachytherapy for cervical cancer. Int J Radiat Oncol Biol Phys 2005;62:901-11.
24. Chakraborty S, Patel FD, Patil VM, Oinam AS, Sharma SC. Magnitude and implications of interfraction variations in organ doses during high dose rate brachytherapy of cervix cancer: A CT based planning study. ISRN Oncol 2014;2014:687365.