Original paper

Interstitial high-dose-rate brachytherapy using cobalt-60 source for cervical cancer: dosimetric and clinical outcomes from a single institute

Mohan Kumar, MD, Revathy Thangaraj, MSc, Ram Charith Alva, MD, Kirthi Koushik, MD, Arul Ponni, MD, Manur Gururajachar Janaki, MD

Ramaiah Medical College, Bengaluru, India

Abstract

Purpose: To record and report dosimetric and clinical outcomes of interstitial brachytherapy using cobalt-60 (^{60}Co) source in cervical cancer.

Material and methods: Seventy patients who underwent external beam radiotherapy with dose of 45 Gy in 25 fractions, followed by interstitial brachytherapy (ISBT) 6.5 Gy × 4 fractions were included into this study. The ISBT applicators were inserted under combined spinal and epidural anesthesia. Computed tomography (CT) simulation was performed and axial CT images were transferred to treatment planning system. High-risk clinical target volume (CTV_{HR}) and organs at risks (OARs) were contoured. Four fractions of 6.5 Gy were prescribed to CTV_{HR} using inverse planning technique. Patients were followed-up for 3 years. Dosimetric parameters and clinical outcomes were recorded and compared with available literature.

Results: Seventy patients with FIGO stage IIB-IVA were included in the study. The median EQD_2 of 2 cm^3 of bladder, rectum, sigmoid and D_{90} CTV_{HR} were 70 Gy (53-75 Gy), 64 Gy (51-71 Gy), 48 Gy (44-72 Gy), and 77 Gy (70-86 Gy), and dose homogeneity index (DHI), dose non-uniformity ratio (DNR), coverage index (CI), overdose volume index (OI), and conformal index (COIN) were 0.58 (0.39-0.78), 0.42 (0.22-0.61), 0.87 (0.59-0.97), 0.19 (0.09-0.30) and 0.74 (0.52-0.85), respectively. Local control rate at 2 years was 87.14%. Eight patients had local recurrence and one patient had lung metastasis. Also, two patients with local recurrence had recto-vaginal fistula. Two patients had grade 2 proctitis (2.8%) and one patient developed grade 3 proctitis (1.4%). There was no grade 2 or higher bladder toxicity.

Conclusions: The dosimetric parameters, local control and toxicities of high-dose-rate interstitial brachytherapy in cervical cancer patients treated by ^{60}Co radioactive source are similar, compared to available literature using iridium-192 (^{192}Ir) source.

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Key words: interstitial brachytherapy, cobalt-60, cervical cancer.

Purpose

Concurrent chemo-radiation is the standard of care for locally advanced cervical cancer patients [1]. Radiotherapy is delivered in the form of external beam radiotherapy (EBRT) and brachytherapy (BT). BT plays a major role in delivering higher conformal dose to the tumor and sparing normal tissues. Intracavitary brachytherapy (ICBT) may not deliver adequate dose to the lateral part of parametrium and the lower part of vagina in locally advanced cervical cancer. Interstitial brachytherapy (ISBT) is a benefit to deliver higher dose to the parametrium and vagina [2,3,4,5].

The radioactive sources used for brachytherapy evolved from the era of radium, cesium to iridium and cobalt. Table 1 presents the different brachytherapy sources used [6]. In earlier days, ISBT was delivered by low-dose-rate (LDR) manual loading technique. Currently, it is replaced by high-dose-rate (HDR) remote afterloading technique, because of shorter treatment time and better radiation safety [5,7,8,9]. Iridium-192 (^{192}Ir) is exclusively used in interstitial brachytherapy by most of the institutes because of high specific activity and availability in smaller size. Now, even cobalt-60 (^{60}Co) source is available in miniature form, with a logistical advantage of longer half-life and financially favorable for developing countries [10]. In the literature, there are many dosimetric studies available comparing ^{192}Ir and ^{60}Co brachytherapy sources [11,12]. The present study was performed to record and report the dosimetric and clinical outcomes of HDR interstitial

Address for correspondence: Revathy Thangaraj, MSc, Department of Radiotherapy, Ramaiah Medical College, Bengaluru, India 560054, phone +91 803608888, ext. 2759, fax: +91 23601924, e-mail: revamscmedphy@gmail.com

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Table 1. Brachytherapy sources

No.	Radionuclides [6]	Atomic number (Z)	Mass number (A)	Half-life ($T_{1/2}$)	Mean energy (MeV)	Air kerma rate constant (μGy · m^2/ GBq · h)	Dose rate constant (cGy · h^{-1})/ (cGy · cm^2 · h^{-1})
1	Radium	82	226	1,600 years	0.83	195	–
2	Cesium	55	137	30.07 years	0.66	77.3	1.11
3	Iridium	77	192	73.81 days	0.37	108	1.12
4	Cobalt	27	60	5.26 years	1.25	309	1.11
5	**Gold**	**79**	**198**	**2.7 days**	**0.41**	**56.2**	**1.13**
6	**Iodine**	**53**	**125**	**60 days**	**0.028**	**–**	**–**
7	**Palladium**	**46**	**103**	**17 days**	**0.021**	**–**	**–**

brachytherapy using ^{60}Co source in patients with cervical cancer and compare with studies, in which ^{192}Ir was used.

Material and methods

Retrospectively, we analyzed seventy patients of locally advanced cervical cancer, treated from January 2015 to December 2016 with radical intent. Patients from stage IIB to IVA who underwent interstitial implants were included in the study after obtaining the approval of the internal ethical committee of the institution. EBRT was delivered by four field three-dimensional conformal radiotherapy (3D-CRT) technique on Elekta Synergy linac, with 6 MV photon beams, with a dose of 45 Gy in 25 fractions without midline shielding or parametrial boost. Additionally, concurrent weekly cisplatin chemotherapy (40 mg/m^2), followed by four fractions of ISBT of 6.5 Gy per fraction were applied.

ISBT procedure

Two weeks after the completion of the EBRT, patients received the insertion of ISBT applicator (Syed Neblett template with obturator ± uterine tandem, and 14 to 20 stainless steel hollow needles) under combined spinal and epidural anesthesia. Rectal enema was given two hours before the procedure to ensure rectal emptiness. Computed tomography (CT) simulation scan without intravenous contrast was performed, with 50 ml of diluted urograffine dye in the bladder and 20 ml in the rectum (Asteion VP; Toshiba). Axial CT slices of 3 mm thickness were taken from the upper border of third lumbar vertebra to the middle of shaft of the femur and the images were transferred to HDR Plus 3.0 treatment planning system (TPS). The organ at risks (OARs), including bladder, rectum, sigmoid, and high-risk clinical target volume (CTV_{HR}) were contoured. CTV_{HR} was defined based on the findings of examination under anesthesia during the insertion of applicator and CT scan images. Viswanathan *et al*. contouring guidelines were followed for CT-based contouring [13].

Planning and execution of the treatment

Applicators were digitized in the multi-planar reconstruction view. Surface control points were created on OARs and CTV_{HR}. Treatment plan was generated by inverse planning technique in HDR Plus 3.0 treatment planning system, using a task group (TG-43) algorithm. The dose constraints of 6.5 Gy to CTV_{HR}, 5 Gy to 2 cm^3 of bladder, 4 Gy to 2 cm^3 of rectum and sigmoid were given. The plan was optimized to achieve better D_{90} CTV_{HR} (dose received by 90% of CTV_{HR}) and minimize the dose to OARs by using isodose re-shaper tool. Four fractions of 6.5 Gy was delivered by Bebig Multisource HDR machine (Eckert & Ziegler), with ^{60}Co source. Bladder was filled with 50 ml of normal saline during all the fractions. Patient was hospitalized till the completion of all the four fractions of brachytherapy. Two fractions were delivered on the first day, with a gap of six hours and the remaining two fractions were delivered on the second day. All the four fractions were delivered by the same treatment plan. The tandem and needle positions were verified before every fraction.

Follow-up

All patients were followed-up 15 days after the completion of brachytherapy, then once in 3 months for 2 years and once in 6 months after 2 years. Clinical examination was performed for all the patients during the follow-up. Patients with suspected recurrence underwent intravenous contrast CT scan and biopsy. Sigmoidoscopy was performed for patients who suffered a bleeding per rectum.

Dosimetric parameters

The equieffective dose in 2 Gy (EQD_2) of 2 cm^3 of bladder, rectum, sigmoid, D_{90} CTV_{HR}, and dose homogeneity index (DHI), dose non-uniformity ratio (DNR), coverage index (CI), conformal index (COIN), and overdose volume index (OI) were calculated by using following formulas [14,15,16]:

1. Equivalent dose in 2 Gy (EQD_2) = [nd (1 + d/α/β)]/ [1 + (2/α/β)], where n is the number of fractions, d is the dose per fraction, α/β ratio with 3 for normal tissue and 10 for tumor.
2. Dose homogeneity index: DHI = (V_{100} – V_{150})/V_{100}, where V_{100} and V_{150} are the volume of the CTV_{HR} re-

ceiving 100% and 150% of the prescribed dose, respectively.
3. Dose non-uniformity ratio: DNR = V_{150}/V_{100}.
4. Conformal index: COIN = $C_1 \times C_2$, where $C_1 = V_{100}$ and C_2 is the volume receiving 100% of the prescribed dose, which is outside the CTV_{HR}.
5. Coverage index: CI = V_{100}/CTV_{HR}, where CI is the ratio of the volume of CTV_{HR} receiving 100% of the prescribed dose to the total volume of CTV_{HR}.
6. Overdose volume index: OI = V_{200}/V_{100}, where OI is the ratio of volume of CTV_{HR} receiving 200% of the prescribed dose to the volume of CTV_{HR} receiving 100% of the prescribed dose.

Descriptive statistics for dosimetric parameters were expressed as mean ± standard deviation and median with range for continuous characteristics using Microsoft Excel.

The disease-free survival was calculated in months from the day of completion of brachytherapy till the day of diagnosis of the recurrence in patients who had a recurrence or the last follow-up for patients who did not had a recurrence. The local control rate at 2 years was reported in percentage as follows:

Local control rate = $(N_1/N_2) \times 100$, where N_1 is the number of patients who did not had any local disease at 2 years, N_2 is the total number of patients included in the study.

Table 2. Patients' characteristics

Parameter	
Total no. of patients	70
Age (years)	
Median	50
Range	35-70
Histopathology	
Squamous cell carcinoma	64 (91.43%)
Adeno cell carcinoma	6 (8.57%)
FIGO stage	
IIB	9 (12.86%)
IIIA	8 (11.42%)
IIIB	48 (68.57%)
IVA	5 (7.14%)
Follow-up (months)	
Median	19
Range	10-38
Clinical outcome at 2 year	
No evidence disease	61 (87.14%)
Local recurrence	8 (11.43%)
Distant recurrence	1 (1.43%)

Results

Seventy patients who underwent interstitial implants were included in the study. Patient characteristics and dosimetric parameters are presented in Tables 2 and 3. The median age was 50 years (35-70 years). Squamous cell carcinoma was the most common cancer (91.43%). About 90% of patients presented stage III disease. The median volume of bladder, rectum, sigmoid, and CTV_{HR} were 107 cm^3 (48-526 cm^3), 38 cm^3 (10-112 cm^3), 21 cm^3 (4-80 cm^3), and 63 cm^3 (26-95.6 cm^3), respectively. The median EQD_2 of 2 cm^3 of bladder, rectum, sigmoid, and D_{90} CTV_{HR} were 70 Gy (53-75 Gy), 64 Gy (51-71 Gy), 48 Gy (44-72 Gy), and 77 Gy (70-86 Gy), respectively. The median DHI, DNR, CI, OI, and COIN were 0.58 (0.39-0.78), 0.42 (0.22-0.61), 0.87 (0.59-0.97), 0.19 (0.09-0.30), and 0.74 (0.52-0.85), respectively. The median V_{150} and V_{200} of CTV_{HR} were 21 cm^3 (6-44 cm^3) and 9.5 cm^3 (2-23 cm^3), respectively. The median overall treatment time was 56 days (46-75 days). The median follow-up was 19 months (10-38 months). Sixty-one patients had no evidence of the disease at the end of two years. Eight patients had a local recurrence and one patient had a lung metastasis. All these nine patients were stage III disease at diagnosis and underwent palliative chemotherapy. The median disease-free survival was 18.5 months. The local control rate

Table 3. Dosimetric parameters

Parameter	Median (range)	Mean ± SD
Volume (cm^3)		
Bladder	107 (48-526)	126 ±80
Rectum	38 (10-112)	43 ±19
Sigmoid	21 (4-80)	25 ±14
CTV_{HR}	63 (26-95.6)	62 ±17
EQD_2		
Bladder (D_{2cm^3})	70 (53-75)	69 ±5.46
Rectum (D_{2cm^3})	64 (51-71)	63 ±4
Sigmoid (D_{2cm^3})	48 (44-72)	51 ±6
CTV_{HR} (D_{90})	77 (70-86)	77 ±4
DHI	0.58 (0.39-0.78)	0.58 (0.08)
COIN	0.74 (0.52-0.85)	0.72 (0.07)
CI	0.87 (0.59-0.97)	0.85 (0.08)
DNR	0.42 (0.22-0.61)	0.42 (0.08)
OI	0.19 (0.09-0.30)	0.19 (0.05)
V_{150} CTV_{HR} (cm^3)	21 (6-44)	22.43 (8.48)
V_{200} CTV_{HR} (cm^3)	9.5 (2-23)	10 (4.4)

EBRT – external beam radiotherapy, BT – brachytherapy, EQD_2 – equivalent dose in 2 Gy, D_{2cm3} – dose received by 2 cm^3 volume, D_{90} – dose received by 90% of the volume, CTV_{HR} – high-risk clinical target volume, DHI – dose homogeneity index, COIN – conformity index, CI – coverage index, DNR – dose non-uniformity ratio, OI – overdose volume index, V_{150} – volume received by 150% prescribed dose, V_{200} – volume received by 200% of prescribed dose

at 2 years was 87.14%. Two patients had grade 2 proctitis (2.8%) and one patient developed grade 3 proctitis (1.4%). The patient with grade 3 proctitis underwent argon photocoagulation. Recto-vaginal fistula was noticed in two patients with a local recurrence. One patient had vaginal stenosis. There was no grade 2 or higher bladder toxicities seen in the study.

Discussion

Interstitial brachytherapy is used in locally advanced cervical cancer to deliver higher dose to the target volume without increasing the dose to bladder and rectum. In earlier days, Paris technique was used in interstitial brachytherapy, which was based on point dosimetry [17]. In the year 1997, the International Commission on Radiation Units and Measurements published the dose and volume specification for reporting interstitial brachytherapy (ICRU-58) [18]. The change from two-dimensional X-ray-based planning to three-dimensional CT/magnetic resonance imaging (MRI) image-based planning along with computerized dosimetry has improved the accuracy of treatment planning in brachytherapy [9,19]. According to the American Brachytherapy Society (ABS) recommendation, the EQD_2 of 2 cm^3 of bladder, rectum and sigmoid are < 90 Gy and < 75 Gy, respectively, for HDR interstitial brachytherapy, following 45 Gy of EBRT [7]. In the present study, the median EQD_2 of 2 cm^3 of bladder, rectum, and sigmoid was 70 Gy (53-75 Gy), 64 Gy (51-71 Gy), and 48 Gy (44-72 Gy), respectively. The EQD_2 reported in different literatures using ^{192}Ir source for interstitial brachytherapy are presented in Table 4. Kannan *et al*. in their study reported the median EQD_2 to 2 cm^3 of bladder, rectum, and sigmoid for acceptable late complications as 70.8, 65.8, and 57.3 Gy, respectively [5]. In a study by Lee *et al*., the recommended dose to 2 cm^3 of rectum should be less than 62 Gy to avoid the late rectal complication [20]. In the present study, we have observed that the dose to 2 cm^3 of bladder, rectum, and sigmoid were within the recommended limits, as reported in the studies where ^{192}Ir source was used for interstitial brachytherapy. A five years follow-up study by Tantivatana *et al*. in patients undergoing ICBT using ^{192}Ir or ^{60}Co sources did not find any significant difference in overall survival (77% vs. 81.9%), disease-free survival (73.1% vs. 74.7%), and grade 3 and grade 4 complications (4.7% vs. 3.4%) [21]. The available literature using ^{192}Ir for ISBT have reported local control in the range of 61-88% at 2 to 3 years. In the present study, we have observed the local control of 87.14% at 2 years.

DHI, DNR, CI, OI, and COIN are the objective parameters used to evaluate the conformity of a brachytherapy plan. Ideally, the value of DHI, CI, and COIN should be one, and the value of DNR and OI should be zero. Sharma *et al*. used Paris technique for dose prescription and found that DHI, DNR, and COIN were 0.61, 0.31, and 0.79, respectively [22]. Swetha *et al*. reported DHI, DNR, and COIN as 0.57, 0.43, and 0.73, respectively, in their study using inverse planning technique [23]. In the present study, the DHI, DNR, and COIN values were 0.57, 0.43, and 0.72, respectively, similar to Swetha *et al*.

The ICRU-89 recommends D_{90} CTV_{HR} to be > 85 Gy EQD_2. The EQD_2 of D_{90} CTV_{HR} in studies where CT-based planning was used were 70 to 82.9 Gy [3,5,20,24]. Lee *et al*. and Villalba *et al*. observed in their study that the CT images overestimated the CTV_{HR} and OARs volumes, compared to MRI images [20,25]. Few authors have reported EQD_2 of D_{90} CTV_{HR} in the range of 78.6 to 84.8 Gy, using MRI-based planning [25,26,27]. In the present study, we observed 77 Gy of median EQD_2 of D_{90} CTV_{HR}, with the range of 73 to 81 Gy by CT-based planning. Ret-

Table 4. Comparison of EQD_2 and local control

Study (no. of patients)	Total dose EBRT + BT	D_{90} CTV_{HR} [Gy]	Bladder D_{2cm^3} [Gy]	Rectum D_{2cm^3} [Gy]	Local control
Murakami *et al*. [3] (209)	50 Gy + 6 Gy × 4 fractions	74.2	71.0	67.5	87.8% at 3 years
Kannan *et al*. [5] (47)	45 Gy + 3.75-5 Gy × 5 fractions	70-79	70.83	65.79	61% at 2 years
Lee *et al*. [20] (68)	45 Gy + 3.9 Gy × 7 fractions	73.6	67.1	64.6	86% at 2 years
Souza *et al*. [24] (47)	45 Gy + 4.6 × 4 fractions or 9.2 Gy × 2	70.2	61.6	63.2	68% at 3 years
Villalba *et al*. [25]	50 Gy + 4 Gy × 6 fractions				88% at 3 years
CT (34)		75.8	79.8	75.3	
MRI (25)		78.6	77.1	69.90	
Bailleux *et al*. [27]	46 Gy + 7 Gy × 3 fractions				86.8% at 2 years
CT (16)		82.9	76.8	66.4	
MRI (17)		84.8	74.5	64.3	
Present study (70)	45 Gy + 6.5 Gy × 4 fractions	77	70	64	87.14% at 2 years

EQD_2 – equivalent dose in 2 Gy, CT – computed tomography, MRI – magnetic resonance imaging, CTV_{HR} – high-risk clinical target volume, D_{2cm^3} – dose received by 2 cm^3 volume, D_{90} – dose received by 90% of the volume

rospective analysis was the main limitation of our study. Other limitations included CT-based treatment planning because of limited resources and short-term follow-ups of the patients. However, all these patients will be followed-up further, and clinical outcomes will be recorded.

Conclusions

The dosimetric parameters, local control, and toxicities of high-dose-rate interstitial brachytherapy in cervical cancer patients treated by ^{60}Co radioactive source are similar compared to the available literatures using ^{192}Ir source.

Disclosure

The authors report no conflict of interest.

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