High-Dose-Rate Brachytherapy in the Treatment of Uterine Cervical Cancer Using Cobalt-60 Radionuclide Source: Three Years Treatment Outcome

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ABSTRACT

Background: The Iridium-192 radionuclide source is commonly used for high-dose-rate brachytherapy of uterine cervical cancer. The cobalt-60 radionuclide source, which is more economical, is now available with dosimetric properties similar to iridium-192. **Objective:** To evaluate late gastrointestinal and genitourinary complications, and also the survival pattern in cervical cancer patients treated with cobalt-60 high-dose-rate brachytherapy, three years after treatment. **Materials and Methods:** Seventy patients, who were treated with high-dose-rate brachytherapy using the cobalt-60 radionuclide source were followed up for three years. All the patients received 45 Gy of external beam radiotherapy in 22 daily fractions, with 19.5 Gy from high-dose-rate brachytherapy, in three fractions, over three weeks, using the cobalt-60 radio nuclide source. The patients also received concurrent cisplatin-based chemotherapy. Late complications were assessed every three months, using Radiation Therapy Oncology Group (RTOG) late toxicity criteria. The pattern of disease control was also assessed. **Results:** Late complications in the bowel were, six (9%) grade 1, four (6%) grade 2, one (1%) grade 3, and one (1%) grade 4. The late complications affecting the bladder were 5 (7%) grade 1 and 1 (1%) grade 4. Twenty-eight patients (40%) were alive without disease, seven (10%) were alive with disease, seven (10%) died of persistent disease, four (6%) died of metastatic disease, while 24 (34%) were lost to follow-up. **Conclusion:** The late complications were similar to those reported for Iridium-192 as a source of high-dose brachytherapy. Cobalt-60 high-dose-rate brachytherapy is tolerable, effective, and economical for low resource settings.

Key words: Cervical cancer; Cobalt -60; high-dose-rate brachytherapy

Introduction

High-dose-rate (HDR) brachytherapy is a standard treatment method to boost the radiation dose for the management of cervical cancer. The Iridium-192 radionuclide source is widely used for HDR brachytherapy presently. Cobalt-60 (Co-60) as an HDR source was used in the early seventies, with good results.[1] It later became less popular, probably because the achievable sizes then, implied the use of larger diameter applicators compared to Iridium-I92 (Ir-192). At present, smaller sizes of Co-60 are available, with physical dimensions and dosimetric properties identical to Ir-192.[2]

The higher energy of Co-60 may portray possible adverse effects on patients, but it has been reported that clinical examples from intracavitary and interstitial applications using Co-60 brachytherapy sources, show dose distributions in the treatment volume practically identical to the Ir-192 sources.[3] Acute reactions have been reported earlier[4] and their evaluation three years after treatment is hereby presented.

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Objectives

To evaluate the late gastrointestinal and genitourinary complications and survival pattern in cervical cancer patients treated with Cobalt-60 HDR brachytherapy three years after treatment.

Materials and Methods

The initial 70 cervical cancer patients, who had treatment with

radiotherapy using HDR brachytherapy and chemotherapy at our center, between July 2008 and March 2009, are evaluated. HDR brachytherapy uses the Co-60 radionuclide source.The patients have also had concurrent cisplatin and 5 fluorouracil combination chemotherapy during the treatment.

All the patients had confirmed histology with International Federation of Gynecology and Obstetrics (FIGO) stages ranging from I to III. Their Eastern Cooperative Oncology Group (ECOG) performance status was at least 2 and they were all human immunodeficiency virus (HIV) seronegative. All the patients gave informed consent to be included in this assessment.

All the patients evaluated had chemotherapy, external beam therapy, and brachytherapy using a ring and intrauterine applicators.

Radiation therapy

The teletherapy dose was 45 Gy in 22 fractions, over 4-5 weeks, using the Cobalt 60 machine. Two treatment fields AP/PA (anteroposterior and posteroanterior) were used. Eleven patients with AP diameter more than 18 cm were treated with the four-field box technique. The treatment field borders were as follows.

Upper border — L4/5 border, inferior border — the lower margin of the obturator foramen or 2 cm below the lower extent of the tumor, lateral border — 2 cm lateral to the true pelvic diameter. The anterior border of the lateral field was anterior to the symphysis pubis, while the posterior border was at the posterior surfaceof the sacral promontory.

The HDR brachytherapy dose was 19.5 Gy in three weekly fractions, given from the second week of the external beam treatment. Treatment was done twice a week for some patients who completed the external beam treatment before brachytherapy, but the treatments were given after at least a 72-hour interval.[5] The brachytherapy treatments were done under conscious sedation. The ICRU 38 bladder point was identified using the Foleys catheter in the bladder with radiopaque material, while the rectal point was identified using gauze soaked in radiopaque material inserted on the posterior vaginal wall, and the rectal point was calculated at 0.5 cm from the posterior vaginal wall, using lateral X-ray images of the treatment applicators, obtained using the C-arm imaging device, after the insertion. The BEBIG HDR basic 2.2.treatment planning system was used and dose prescription was to point "A". External beam treatment and HDR brachytherapy were completed within eight weeks and a packed cell volume (PCV) of at least 30 was maintained during the treatment.

Concurrent chemotherapy

The patients also received three weekly chemotherapy courses using cisplatin 50 mg/m^2 and 5-fluorouracil 1000 mg/m^2. These were usually started after the initial clinical evaluation, while patients were waiting to commence radiation treatment, and six courses were given. Most patients commenced radiotherapy after at least one course of chemotherapy.

Follow up

Patients were reviewed once weekly during the treatment to access acute toxicities. The initial post-therapy follow-up was six weeks after radiation treatment, and thereafter, every three months. Toxicities and disease control were evaluated during these follow-up visits.

Survival was assessed every three to six months after the first 90 days post treatment and late toxicity was evaluated using the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) scoring scale as shown in Table 1.

Results

Seventy patients were evaluated and all patients were seen at least every three months post treatment. The characteristics of the patients are presented in Table 2.The treatment parameters of the evaluated patients are shown in Table 3. The linear quadratic formula was used to calculate the Biological Effective Dose (BED), using α/β ratio of 3 for late responding tissues and 10 for tumors. The average total BED for tumor was 86.2 (84.4-88.8) Gy, while that for the rectum was 124.4 (120–133) Gy.

The late complications recorded among the patients included rectal bleeding in 11 (15.7%) patients. One patient had grade III rectal bleeding necessitating a colostomy. Bladder complications (dysuria) occurred in five (7%) patients. One patient had vesicovaginal fistula (VVF). The late complications are shown in Table 4.

Table 1: RTOG/EORTC LATE Radiation Morbidity Grading scale[6]

Tissue	Grade 1	Grade 2	Grade 3	Grade 4
Small/large intestine	Mild diarrhea; mild cramping; bowel movement five times daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement>5 times daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/perforation fistula
Bladder	Frequency of urination or nocturia twice pre-treatment habit/dysuria, urgency not requiring medication	Moderate frequency of urination/ nocturia that is less frequent than every hour, intermittent macroscopic hematuria	Severe frequency and dysuria hourly or more frequent , gross hematuria with or without clot passage	Ulceration/necrosis, severe hemorrhagic cystitis, hematuria requiring blood transfusion

RTOG – Radiation Therapy Oncology Group

Table 2: HDR brachytherapy with Co-60: Patient characteristics (*n*=70)

	N	%
Age (years)		
Range	25-69	
Average	45	
ECOG performance status		
0	52	74
1	15	22
2	3	4
FIGO stage		
1B	3	4
11A	9	13
11B	15	22
111A	22	31
111B	21	3

HDR – High-dose-rate; ECOG – Eastern Cooperative Oncology Group

Table 3: HDR brachytherapy with Co-60 — Treatment characteristics

	Median	Range
External beam radiation		
Therapy — whole pelvis (Gy)	45	-
High-dose-rate intracavity		
Brachytherapy (Gy/fr)	19.5/3	-
Point A biological effective dose		
(BED) (Gy10)	6.5	6.0 - 7.0
ICRU bladder point (Gy3)	5.6	4.2 - 6.0
ICRU rectal point (Gy3)	5.4	3.2 - 6.0
BED (Gy3) Rectum (External+HDR)	124.4	120 - 133
BED (Gy10) Tumor (External+HDR)	86.2	84.4 - 88.8
Chemotherapy 3 weekly×6		
Cisplatin 50 mg/m^2	55	50 - 60
5-FU 1000mg/m^2	1.2	1.0 - 1.4

HDR – High-dose-rate; BED – Biological Effective Dose; ICRU – International Commission on Radiation Units

Table 4: HDR brachytherapy with Co-60: Late complications

	Grade (%)			
	1	2	3	4
Bowel				
Rectal bleeding	6 (9)	4 (6)	1 (1)	1 (1)
Cramping	1 (1)	-	-	-
Diarrhoea	1 (1)	-	-	-
Bladder				
Dysuria	5 (7)	-	-	-
Fistula	-	-	-	1 (1)

HDR – High-dose-rate

The performance of the patients at evaluation, three years after treatment, is presented in Table 5. Those alive and without disease had a negative PAP smear done at least six months after treatment. One patient, with stage IIA disease, had a negative PAP smear six months post treatment, but died of pulmonary metastasis in the second year post treatment. The average duration of follow-up was three years (36-40 months).

Discussion

High-dose-rate brachytherapy (HDR) is a very useful treatment modality for several malignancies. These include gynecological malignancies, prostate cancer, esophageal cancer, and other interstitial applications. It enables larger number of patients to be treated per day compared to low-dose-rate brachytherapy. It also removes the need for inpatient care, especially in cervical cancer treatment.

Cobalt-60 emits gamma rays with an average energy of 1.25 MeV with a half-life of five years, while Iridium-192 emits gamma ray of 0.6 MeV, with a lower half-life of three months. This makes Co-60 less expensive, as source replacement expenditures are less. An average of 20 source replacements for Iridium-192 is needed for a corresponding single source replacement of a Co-60 source. At an average cost of about 15,000 USD per iridium source replacement, a total of about 300,000 USD will be spent in 20 months. It costs about 34,000 USD to change a Co-60 source during the same period. About 236,000 USD is saved if Co-60 radionuclide source is used for HDR brachytherapy every 20 months.

The available HDR Brachytherapy systems with Co-60 sources include the Ralston remote afterloader manufactured by Shimadzu Corporation of Japan and the BEBIG Multisource/Gyne Source remote afterloader manufactured by BEBIG GmbH of Germany.

The most successful application of HDR Brachytherapy has been for uterine cervical cancer and it has very high prevalence in developing countries. However, some of these countries have limited resources for sustainable radiation treatment facilities, while others do not have the facility at all. A majority of the patients in this study (83%) had a late disease (FIGO stages IIB-III), which is the common trend in developing countries, necessitating the use of concurrent chemoradiotherapy in their treatment.

A comparison of the late complications observed in this study with other studies is presented in Table 6. Although the studies had some variations in combination therapy and dosages, yet they still provide a reasonable basis for comparison.

As seen in Table 5, Ferrigno *et al*., used radiotherapy alone with an Ir-192 HDR Brachytherapy source, while Chung *et al*., Chen *et al*., and Kim *et al.* used cisplatin-based chemotherapy, with an Ir-192 HDR brachytherapy source. The studies reported by Mosalaei *et al.* and Pesee *et al.* used the Co-60 HDR brachytherapy source, without concurrent chemotherapy, and the treatment planning by Mosalaei *et al*. was done manually.

The high rate of late complications reported by Mosalaei could be due to high-dose-per-fraction of HDR brachytherapy (10 Gy weekly x3) after 50 Gy of external beam therapy, in addition to the manual HDR treatment planning employed.

Despite these factors, the severe complications (grades 3 and 4) were less than 6%. The report by Pesee *et al.*, who also used the Co-60 HDR source, showed higher complications, but severe (grades 3 and 4) late bowel complications were only 1.4%. The present study has severe late complications (grades 3 and 4) of about 3% in the bowel and 1.3% in the bladder. The late complications recorded are close to those reported in studies using Ir-192 HDR brachytherapy sources. The outcome of treatment is an important aspect to be considered in this treatment modality. A comparison of the treatment outcome reported for patients treated with the Ir-192 HDR brachytherapy source in Table 5 is presented in Table 7.

The treatment outcome in our report is still comparable with other studies that used the Iridium-192 HDR source. In this study, 40% of the patients are alive without disease. This seemingly low value may be due to the fact that most of our patients presented for treatment in the late stage. Another reason may be due to the fact that this group of patients constituted our initial experience of HDR brachytherapy with the Co-60 radionuclide source and we prescribed an equal dose for all the patients, irrespective of the stage of the disease. We have since adopted the 2012 American Brachytherapy Society dose recommendations for HDR Brachytherapy[13] in our practice and we hope the subsequent outcomes, with respect to adequate dosing, will be better. We also recorded a high percentage of cases that were not evaluated. These patients were lost to follow up and this also affected our data. We have also taken steps to improve the attendance of patients at follow-up clinics so as to have a better evaluation of their response to treatment, for future study.

Conclusion

The use of radioactive Cobalt-60 as a HDR Brachytherapy source gives an effective and acceptable treatment outcome. The late complications associated with its use in the setting of concurrent treatment with cisplatin-based chemotherapy are comparable with the use of the radioactive Ir-192 HDR brachytherapy source. The effectiveness in terms of disease control is also comparable if recommended dose schedules are used. The economic advantages of Cobalt -60, makes it suitable in low resource settings. The deployment of three-dimensional (3D) treatment planning with these radioactive sources will greatly improve the treatment outcome.

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Table 5: HDR brachytherapy with Co-60: Patients status at time of analysis

Status	No. of patients (%)
Alive without disease (ds)	28 (40)
Alive with disease	7 (10)
Died of persistent/recurrent ds	7 (10)
Died of metastatic disease	4 (6)
Lost to follow-up	24 (34)
Total	70 (100)

HDR – High-dose-rate

Table 6: HDR Brachytherapy with Co-60: Record of late toxicities

Study	HDR Source	Rectum (%)	Bladder (%)	Small intestine (%)
Ferrigno *et al*. (2001)[7]	^{192}Ir	12.3	7.9	10.1
Chung *et al* (2005)[8]	^{192} Ir+CTH*	26	19	-
Chen *et al*. (2006)[9]	^{192}Ir+CTH	24.2	10	-
Kim *et al* (2008)[10]	^{192}Ir+CTH	6	7	-
Mosalaei *et al* (2006)[11]	^{60}Co	34.6	-	-
Pesee *et al* (2010[12]	^{60}Co	37.6	3	-
This study	^{60}Co+CTH	15	7	-

*CTH – Chemotherapy; HDR – High-dose-rate

Table 7: HDR Brachytherapy with Co-60- status of patients after three years

Status	Ferrigno[6] %	Chung[7] %	Chen[8] %	Kim[9] %	This study %
Alive without disease	44	81	68	59	40
Alive with disease	6.2	2	8.6	9	10
Alive with metastasis	9.4	-	-	21	-
Dead	40	17	20	-	16
Not evaluated	9.4	-	-	11	34

HDR – High-dose-rate

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