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High Dose Rate Brachytherapy in the Treatment of Cervical Cancer: Preliminary Experience with Cobalt 60 Radionuclide Source—*A Prospective Study*

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Abstract: Iridium-192 is widely used for high-dose rate brachytherapy. Co-60 source with similar geometric and dosimetric properties are now available. It has a longer half life but higher energy than Iridium-192. *If Co-60 source can produce similar results, it will be more economical for low resource settings.*

Objective: To evaluate the acute gastrointestinal and genitourinary toxicity associated with Co-60 source in the brachytherapy of cervical cancer.

Methods: Seventy patients with cervical cancer received 45 Gy in 22 fractions of pelvic external beam radiotherapy and 19.5 Gy in 3 fractions of HDR with Co-60 source using tandem and ring applicators with 6 courses of cisplatin 50 mg/m^2 and 5 fluorouracil 1000 mg/m^2 every 3 weeks Toxicity was scored using NCI-CTC version 4.0.

Results: The median total BED (Gy_{10}) for tumor was 86.2 (84.4–88.8) while that for rectum (BED Gy_3) was 124.4 (120–133). Two patients (3%) had grade 3 gastrointestinal toxicity while all others had ≤grade 2 toxicity and this is comparable with previous results.

Conclusion: Co-60 as HDR brachytherapy source is tolerable and is economical for low resource settings.

Keywords: HDR brachytherapy, Co-60 source, cervical cancer, acute toxicity

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Introduction

Cancer of the uterine cervix is one of the malignancies that have been effectively treated with radiotherapy. A combination of external beam treatment with brachytherapy is used to increase the dose to the tumor with reduced dose to the organs at risk. High Dose Rate (HDR) brachytherapy is now accepted for cervical cancer treatment. One of its advantages over Low Dose Rate (LDR) treatment is the possibility to treat more patients which is better in centers with large turn out of patients but with limited facilities such as in low resource countries like Nigeria. Iridium 192 (Ir-192) radionuclide source is widely used for HDR brachytherapy. This is because it was easier to manufacture iridium-192 in smaller size for brachytherapy applications.

Cobalt-60 (Co-60) HDR source was available but unpopular because the earlier source sizes were larger than Ir-192.[1] It is now possible to produce miniaturized size of Co-60 radionuclide for HDR applications. This has been shown to have identical geometric and dosimetric properties with Ir-192.[2]

The advantage of Co-60 over Ir-192 is its longer half life of 5.2 years compared with 73.8 days for Ir-192. This implies that instead of changing the Ir-192 source every 3–4 months, Co-60 source can be changed every 6–8 years, which is a lot more economical and attractive for low resource settings. On the other hand, the higher energy of 1.25 MeV of Co-60 compared with 0.6 MeV for Ir-192 raises concerns of possible increase in toxicity to patients. This study was therefore carried out to assess the acute gastro intestinal and genito-urinary toxicity associated with Co-60 as HDR source compared with published results in patients with cancer of the uterine cervix with similar characteristics, treated with Ir-192 HDR brachytherapy. *Acute toxicity are acute reactions following treatment and are rapid in onset and typically reversible. These occur from day 1 of commencement of therapy to day 90 according to Radiation Therapy Oncology Group (RTOG) definition.*

Our center is equipped with a Cobalt-60 teletherapy machine. The International Atomic Energy Agency (IAEA) Vienna Austria, recently donated an HDR remote after loader brachytherapy unit (Gynesource) with Co-60 radionuclide source to our center. This is a replacement for our Caesium-132 low-dose rate equipment that was out of use. This machine is manufactured by BEBIG in Germany and it came with its Treatment Planning System (TPS)-HDR basic 2.2. The brachytherapy suite has a dedicated C-arm X-ray machine and all treatment procedures are completed within the room without the need to move the patients. This HDR brachytherapy unit, the first in Nigeria, became functional in July 2008. During the treatment of the patients evaluated in this study, the HDR source average activity was 60.09 GBq and the Air KERMA strength was 17.61 mGym^2/hr.

Adjuvant chemotherapy with cisplatin based regimen has been shown to improve local control and prolong disease progression time in cervical cancer patients.[3] This approach is still widely used in the treatment of cervical cancer.

Objective

To evaluate the acute gastrointestinal and genito-urinary toxicity following HDR brachytherapy with Co-60 radionuclide source.

Patients and Methods

Seventy patients with cancer of the uterine cervix who were treated with concurrent chemo radiotherapy at the University College Hospital Ibadan Nigeria between July 2008 and March 2009 were selected for evaluation. These were among the first set of patients to be treated with HDR brachytherapy with Co-60 radionuclide source at the center. All the patients had histological confirmation of their diseases; FIGO stages included stages 1 to 111. Other selection criteria included Eastern Cooperative Oncology Group (ECOG) performance status of *not more than 2*, HIV sero negativity and haemoglobin level of at least 10 mg/dl maintained during the treatment. Tumor size measurement was not consistent in all the patients. All the patients had teletherapy, brachytherapy with ring and tandem applicators and chemotherapy.

Radiation therapy

External beam radiation treatment was 45 Gy in 22 daily fractions treated 5 days per week over 4–5 weeks using teletherapy Cobalt 60 machine. Antero- posterior and postero-anterior (AP/PA) fields were used. A four field box technique was used on 11 (16%) patients with antero-posterior diameter greater than 18 cm. The superior border of the pelvic field was L4/5 border and the inferior border was at

the lower border of the obturator foramen or 2 cm below the vaginal extent of the disease. The lateral border was 2 cm lateral to the widest true pelvic diameter. On the lateral field, the anterior border was placed anterior to the symphysis pubis while the posterior border was placed along the sacrum. Patients were treated to mid plane dose on AP/PA fields and at isocenter on four field box technique.

High Dose Rate brachytherapy was started not earlier than third week of external beam radiotherapy. The dose was 19.5 Gy in 3 weekly fractions. Twice a week treatment was allowed given that they were separated by at least 72 hours. Conscious sedation of patients was used for brachytherapy. Tandem and ring applicators were used for all the patients evaluated. A Foley's catheter was inserted into the urinary bladder and the balloon inflated with 7 cc of diluted Urografin to identify the bladder neck region. Barium soaked gauze was inserted in the posterior vagina to identify rectal point. The vagina was packed with gauze to further displace the bladder anteriorly and the rectum posteriorly to minimize the dose to these organs. AP and lateral semi orthogonal marker X-rays with the help of jig (reconstruction box) were taken with C-arm x ray machine at the same place for all insertions and digital pictures were obtained. The semi orthogonal pictures were reconstructed and treatment planning was done with BEBIG HDR basic 2.2. Dose prescription was to point "A" (a reference location 2 cm up from cervical os point of the uterine tandem and 2 cm lateral to the uterine source). Multiple points consistent with ICRU 38 were located and used for treatment planning and dose optimization to point A, point B, bladder, rectum and vaginal surface. A uniform dose of 6.5 Gy per fraction was used for all patients during this initial experience with the equipment. Bladder and rectum doses were optimized to ≤80% of prescribed point A dose. Teletherapy and brachytherapy sessions were completed within 8 weeks of patients' management.

Chemotherapy

All patients received concurrent chemotherapy. Chemotherapy was usually commenced as soon as possible after patient's presentation at the clinic because of the long waiting time for radiotherapy and is given every 3 weeks to a total of 6 courses. Most patients start radiotherapy after second course of chemotherapy and will continue while on radiotherapy. The chemotherapy regimen included cisplatin 50 mg/m^2 given in infusion after intravenous (iv) hydration and 5 fluorouracil 1 gm/m^2 administered as bolus i.v. injection. This regimen was adopted in the department when Caesium-137 low dose brachytherapy was used and was continued with the commencement of HDR brachytherapy. Acute gastro intestinal and urogenital toxicities were clinically assessed weekly during treatment, then 6 weeks and every 3 months after treatment using the NCI-Common Toxicity Criteria (NCI-CTC version 4.0). Regular follow up still continues after this initial evaluation. *The assessment of the patients for this report was done within 90 days of commencement of treatment*.

Results

A total number of 70 patients who met the study criteria were evaluated. All the patients were followed up for at least 3 months. The mean age of the patients was 45 years (range 25–69 years). Three patients were FIGO stage 1, while 24 and 43 patients were FIGO stages 11 and 111 respectively. The patient's characteristics are presented in Table 1.

Table 2 shows some of the treatment parameters of the patients. Biologically Equivalent Dose (BED) calculations were done using the linear quadratic formula assuming an alpha—beta ratio of 10 for tumors and 3 for normal tissues.[4] The mean BED (Gy_{10}) for tumors for both external and HDR radiotherapy was 86.2 (84.4–88.8) while that for the rectum (Gy_3) was 124.4 (120–133).

Table 3 shows the acute reactions experienced by the patients. Proctitis was the commonest acute reaction recorded with 35 (50%) patients having

Table 1. Patients characteristics (n = 70).

Age (years)		
Median	45	
Range	25–69	
	n	**%**
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	30

Table 2. Treatment characteristics.

Cervical cancer 1B–111B (N = 70)	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) (Gy_{10})	6.5	6.0–7.0
ICRU bladder point (Gy_3)	5.6	4.2–6.0
ICRU rectal point (Gy_3)	5.4	3.2–6.0
BED (Gy_3) Rectum (External + HDR)	124.4	120–133
BED (Gy_{10}) Tumor (External + HDR)	86.2	84.4–88.8
Chemotherapy 3 weekly × 6		
Cisplatin 50 mg/m^2	55	50–60
5-FU 1 gm/m^2	1.2	1.0–1.4

grade 1 while 5 (7%) had grade 2 proctitis. Diarrhea was the second most common acute reaction experienced by the patients with 32 (46%) having grade 1 while 9 (13%) had grade 2. Grade 3 diarrhea was the worst reaction noted among all the patients and this occurred in 2 (3%) of the patients. These two patients had their treatments disrupted for one week due to the toxicity. Genitourinary toxicity were generally mild (grade 1) and did not disrupt treatment.

Table 4 describes acute toxicities greater or equal to grade 3 in some previous studies of chemo-radiation using Ir 192 as HDR radio nuclide source. In our study we observed ≥ grade 3 GI toxicity in 3% of patients. Low grade acute toxicities of less than or equal to grade 2 from the studies in Table 4 are presented in Table 5.

Discussion

The incidence of cancer of the uterine cervix is high in developing countries including Nigeria where about 75% of the patients present with locally advanced disease.[5] The combination of external beam radiotherapy and brachytherapy gives high cure rate especially with concurrent use of cisplatin based chemotherapy. HDR brachytherapy has been accepted as standard method of delivering brachytherapy. Cervical cancer is the most common indication for brachytherapy in most developing countries and HDR equipments are capable of treating large number of patients and hence recommended for developing countries with high incidence of the disease.[6]

Table 3. Acute toxicity during chemo-radiotherapy (n = 70).

Toxicity	Grade				
	0	1	2	3	4
Proctitis	30 (43%)	35 (50%)	5 (7%)	0	0
Diarrhea	27 (38%)	32 (46%)	9 (13%)	2 (3%)	0
Nausea	62 (89%)	5 (7%)	3 (4%)	0	0
Vomiting	63 (90%)	5 (7%)	2 (3%)	0	0
Cystitis	42 (60%)	28 (40%)	0	0	0
Urinary frequency	40 (60%)	28 (40%)	0	0	0
Urinary urgency	40 (60%)	28 (40%)	0	0	0

Iridium-192 is widely used as HDR source and is widely discussed in the literature. Reports on studies with Cobalt 60 HDR radionuclide source are very scanty especially with concomitant treatment with chemotherapy. All the patients analyzed in this study received uniform treatment and the treatment parameters were selected to be of benefit to both early and locally advanced diseases as well as taking into consideration the possible associable normal tissue toxicities. The total dose from both external beam and HDR brachytherapy in this study was 69.5 Gy with an average BED_{Gy10} of 86.2 (84.4–88.8) A total dose range of 65–71 Gy without chemotherapy using Ir-192 brachytherapy source has been previously prescribed by Jain VS. et al[7] with good local disease control. A BED_{Gy10} between 86–109 has been shown to result in acceptable pelvic disease control rate[8] though for stage 111 disease, $BED_{Gy10} > 84.5$ was noted to be associated with higher local control and 5 year survival rates than lower BED_{Gy10}.[9] In a report by Chen et al[10] BED_{Gy10} range between 82.6 and 101.1 (median 91.5) was associated with actuarial 5-year overall survival of 73% for stage 11B and 56% for stage 111 diseases and these rates were comparable with other studies with similar treatment parameters. The BED_{Gy10} of 86.2 (84.4–88.8) obtained in this study would be able to achieve comparable results.

An average BED_{Gy3} of 124.4 (120–133) was recorded for rectal point in this study. A rectal BED_{Gy3} between 110 and 125 has been shown to be associated with acceptable late rectal toxicity rate though with lower rate of 12% if ≤110 and 18% if >110.[11]

Our results have shown that HDR with Co-60 radionuclide source with concurrent chemotherapy is well tolerated in cervical cancer patients. Only 2 patients (3%) had grade 3 acute diarrhea that necessitated treatment suspension for one week. There was no grade 3 or 4 acute genitourinary toxicity among the patients. The acute toxicity rates found in this study are among the lowest when compared with those reported in studies

Table 4. Comparison of ≥grade 3 GI and GU acute toxicities in previous studies of chemo-radiation using Ir 192 as HDR source.

Study	Radiotherapy Gy/fr			GI toxicity	GU toxicity
	Regimen	Ext	HDR	%	%
Chung Y et al 2005	4 weekly CP	45/25	25/5	2	0
Chen S et al 2006	Weekly CP	45/25	24/4	4.3	0
Nyongesa C et al 2006	Weekly CP	46/23	26/4	0	0
Shakespeare et al 2006	Weekly CP	45/25	31.8/6	0	0
Kim Y et al 2008					
Group 1	4 weekly CP/5FU	41.4/23	30/6	8	3
Group 2	Weekly CP	41.4/23	30/6	0	0
Current study *(with Co-60)*	4 weekly CP/5FU	45/22	19.5/6	3	0

Abbreviations: Ext, External beam radiotherapy; GI, gastro intestinal; GU, genitourinary; CP, cisplatin; 5FU, 5- fluorouracil.

using Ir-192 HDR radionuclide source. In these studies, the reported rates of acute toxicity ≥ grade 3 ranged from 0%–8% for gastrointestinal and 0%–3% for genitourinary toxicities (Table 4). Other studies with low –dose rate brachytherapy reported acute toxicity ≥ grade 3 range from 0%–15% for gastrointestinal and 1%–8% for genitourinary toxicities. It was also observed that the influence of chemotherapy regimen on gastrointestinal and genitourinary toxicities was less apparent.[12] The early (≤grade 2) gastrointestinal and genitourinary toxicities experienced by patients in this study are similar to outcomes from other studies though comparison is difficult because most authors ignore these mild symptoms hence they are not reported and if reported, consistent scoring criteria are not used (Table 5).

The acute genito-urinary toxicity in this study is relatively low though the risk of late treatment related toxicity is yet to be evaluated but this, together with effectiveness of treatment, are expected to be similar to previous reports. In a 20 year retrospective analysis of Co-60 HDR brachytherapy in Iran, Mosalaei A. et al[13] reported a 10-year overall and disease free survival rate of 62.4% with about 6% severe genito- urinary and/or gastrointestinal toxicity. In that analysis, a uniform external beam dose of 50 Gy in 5–5.5 weeks using Co-60 machine was used and brachytherapy was 30 Gy in 3 fractions using Co-60 remote after-loading equipment. Treatment planning was done manually and chemotherapy was not given. These were assessed to be comparable with reported brachytherapy results in the literature.

As this initial evaluation of HDR brachytherapy practice in our centre with other studies are favorable, the use of adjusted treatment schedules with differential radiotherapy doses for early and late stage diseases as recommended by the American Brachytherapy Society and adopted in some earlier reports using Ir-192 HDR source[14,15] could be adopted for Co-60 radionuclide. In the adjustment treatment schedules, chemotherapy regimen would be changed to weekly cisplatin with a dose range of 25–30 mg/m^2, as this has been shown to be more tolerable and equally effective when compared with 40 mg/m^2 dosage. The use of 5-fluorouracil would also be discontinued as it

Table 5. Comparison of some early (≤grade 2) GI and GU acute toxicities in the previous studies cited in Table 4.

Study	Toxicity (%)						
	Proctitis	Diarrhea	Nausea	Vomiting	Cystitis	GU	GI
Chung Y et al 2005[15]	–	77	44	–	–	22	–
Chen S et al 2006[10]	–	–	–	–	–	5.7	51.4
Nyongesa C et al 2006[16]	–	58	92	58	–	–	–
Shakespeare et al 2006[3]	4.8	–	–	–	23.8	–	47.6
Kim Y et al 2008[17]							
Group 1	–	–	–	–	–	10	26
Group 2	–	–	–	–	–	9	26
Current study *(with Co-60)*	57	59	11	10	–	40	–

has been shown to be of no added advantage to the treatment outcome but rather leads to increased acute hematological toxicity.[16,17]

Conclusion

This study shows that acute gastrointestinal and genitourinary toxicity following high-dose-rate brachytherapy with Co-60 radionuclide source in chemoradiation treatment of cervical cancer is low and comparable with those reported for Iridium-192 HDR source. Cobalt 60 has lots of economic advantages over Ir-192 and hence suitable for low resource radiotherapy settings.

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Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

References

1. Chao KS, Perez CA, Brady LW. Physics and Dosimetry of High-Dose-Rate Brachytherapy in Radiation Oncology Management Decisions (2nd Edition). Lippincott Williams & Wilkins. *Philadelphia*. 2002;89–94.
2. Ballester F, Granero D, Perez-Calatyud J, Casal E, Agramunt S, Cases R. Monte Carlo dosimetric study of the BEBIG Co-60 HDR source. *Phys Med Biol.* 2005;50:N309–16.
3. Shakespeare TP, Lim KHC, Lee KM, Back MF, Mukherjee R, Lu JD. Phase 11 study of the American Brachytherapy Association guidelines for the use of high-dose rate brachytherapy in the treatment of cervical carcinoma: is 45–50.4 Gy radiochemotherapy plus 31.8 Gy in six fractions high-dose rate brachytherapy tolerable? *Int J of Gynecologic Cancer.* 2006;16:277–82.
4. Cho JH, Kim HC, Sur CO, et al. Optimum Radiotherapy Schedule for Uterine Cervical Cancer based-on the Detailed Information of Dose Fractionation and Radiotherapy Technique. *J of Korean Soc of Ther Radiology and Oncology.* 2005;23(3):143–56.
5. Campbell OB, Akinlade IB, Arowojolu A, Babarinsa IA, Agwimah R, Adewole IF. Comparative evaluation of hypofractionation radiotherapy and conventional fractionation radiotherapy in the management of carcinoma of the uterine cervix in Ibadan Nigeria. *African J Med and Med Sciences*. 2000;29:253–5.
6. Nas S, Dally M, Torre M. Recommendations for implementation of high dose rate 192 Iridium brachytherapy in developing countries by the advisory group of IAEA. *Radiotherapy and Oncology*. 2002;64:297–308.
7. Jain VS, Sarje MB, Singh KK, Umberka R, Shrivastava R, Jain SM. High-dose-rate-intracavitary brachytherapy applications and the difference in the bladder and rectum doses: A study from rural center of Maharashatra, India. *J of Cancer Res and Ther*. 2007;3(2):116–20.
8. Petereit D, Fowler JF. High-dose-rate brachytherapy—high-dose, high-tech, and high results. *Int J Radiation Oncology Biol Phys*. 2003;55(5): 1159–61.
9. Mandal A, Asthana AK, Aggarwal LM. Clinical significance of cumulative biological effective dose and overall treatment time in the treatment of carcinoma cervix. *J of Med Phys*. 2007;32(2):68–72.
10. Chen S-W, Liang J-N, Hung Y-C, et al. Concurrent wekly cisplatin plus external beam radiotherapy and high-dose rate brachytherapy for advanced cervical cancer: A control cohort comparison with radiation alone on treatment outcome and complications. *Int J Radiation Oncology Biol Phys*. 2006;66(5):1370–7.
11. Ferrigno R, Novaes ER, Pellizzon AC, et al. High-dose-rate brachytherapy in the treatment of uterine cervix cancer. Analysis of dose effectiveness and late complications. *Int J Radiation Oncology Biol Phys*. 2001;50(5):1123–35.
12. Tan LT, Rusel S, Burgess L. Acute Toxicity of Chemo-radiotherapy for Cervical Cancer: The Addenbrooke's Experience. *Clinical Oncology*. 2004;16:255–60.
13. Mosalaei M, Mohammadianpanah M, Omidvari S, Ahmadloo N. High-dose rate brachytherapy in the treatment of carcinoma of uterine cervix: twenty-year experience with cobalt after-loading system. *Int J Gynecol Cancer*. 2006;16:1101–5.
14. Nag S, Erickson B, Thomadsen B. The American Brachytherapy Society Recommendation for High-Dose-Rate Brachytherapy for Carcinoma of The Cervix. *Int J Radiation Oncology Biol Phys*. 2000;48(1):201–11.
15. Chung Y-L, Jian J, Cheng S, et al. Extended-field radiotherapy and high-dose-rate brachytherapy with concurrent and adjuvant cisplatin-based chemotherapy for locally advanced cervical cancer: a phase 1/11 study. *Gynecologic Oncology*. 2005;97:126–35.
16. Nyongesa C, Ruff P, Donde B, Kotzen J. A phase 1study of concurrent cisplatin chemotherapy in patients with carcinoma of the cervix receiving pelvic radiotherapy. *Int J Gynecol Cancer*. 2006;16:1614–9.
17. Kim YS, Shin SS, Nam J-H, et al. Prospective randomized comparison of monthly fluorouracil and cisplatin versus weekly cisplatin concurrent with pelvic radiotherapy and high-dose rate brachytherapy for locally advanced cervical cancer. *Gynecologic Oncology*. 2008;108:195–200.