

GLOBAL HEALTH

Implementation of a High-Dose-Rate Brachytherapy Program for Carcinoma of the Cervix in Senegal: A Pragmatic Model for the Developing World



John P. Einck, MD,* Alana Hudson, MSc,[†] Adam C. Shulman, MS,[‡] Catheryn M. Yashar, MD,* Mamadou M. Dieng, MD,[§] Magatte Diagne, PhD,[§] Latifatou Gueye, MSc,[§] Fama Gningue, MSc,[§] Pape M. Gaye, MD,[§] Brandon J. Fisher, DO,^{||} Arno J. Mundt, MD, FACRO, FASTRO,* and Derek W. Brown, PhD, FCCPM[†]

**Department of Radiation Medicine and Applied Sciences, University of California San Diego, San Diego, California; [†]Department of Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, Alberta, Canada; [‡]Overlook Medical Center, Summit, New Jersey; [§]Département de Radiothérapie, Institut Joliot-Curie, Hôpital Aristide Le Dantec, Dakar, Senegal; and ^{||}GammaWest Cancer Services, Salt Lake City, Utah*

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West Africa has one of the highest incidence rates of carcinoma of the cervix in the world. The vast majority of women do not have access to screening or disease treatment, leading to presentation at advanced stages and to high mortality rates. Compounding this problem is the lack of radiation treatment facilities in Senegal and many other parts of the African continent. Senegal, a country of 13 million people, had a single ⁶⁰Co teletherapy unit before our involvement and no brachytherapy capabilities. Radiating Hope, a nonprofit organization whose mission is to provide radiation therapy equipment to countries in the developing world, provided a high-dose-rate afterloading unit to the cancer center for curative cervical cancer treatment. Here we describe the implementation of high-dose-rate brachytherapy in Senegal requiring a nonstandard fractionation schedule and a novel treatment planning approach as a possible blueprint to providing this technology to other developing countries. © 2014 Elsevier Inc.

Introduction

Senegal, a country in West Africa with nearly 13 million people, has one of the highest incidence rates of cervical cancer in the world (1). The Institut Joliot-Curie Cancer

Center in Dakar, Senegal, is the only radiation therapy facility in the country, as well as a regional referral center for cervical cancer for Senegal and West Africa. Housing a ⁶⁰Co teletherapy unit and a conventional simulator, the clinic treats approximately 100 cervical cancer patients per year.

Reprint requests to: John P. Einck, MD, University of California, San Diego Moores Cancer Center, Department of Radiation Medicine and

Applied Sciences, 3960 Health Sciences Dr MC-0865, La Jolla, CA 92093-0865. Tel: (858) 246-1506; E-mail: jeinck@ucsd.edu
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Radiation therapy is given both as neoadjuvant treatment before definitive surgery and as palliative treatment but not definitively because there is no access to brachytherapy. Radiating Hope, a nonprofit organization whose mission is to provide radiation therapy equipment to countries in the developing world, provided a high-dose-rate (HDR) afterloading unit to the cancer center for curative cervical cancer treatment. Here we describe the implementation of HDR brachytherapy in Senegal requiring a nonstandard fractionation schedule and a novel treatment planning approach as a possible blueprint to providing this technology to other developing countries.

Background

Consisting of 2 radiation oncologists, 3 radiation physicists, a nurse, and 2 radiation therapists, the staff at the cancer center in Dakar treat approximately 30-40 patients per day with external beam radiation therapy using a ^{60}Co teletherapy unit. It is the only treatment facility within a 500-km radius and also serves several neighboring countries. There are a number of obstacles to a patient receiving radiation therapy in Senegal. A 4- to 5-week course of external beam radiation therapy typically costs the equivalent of US \$300, and the addition of 5-fluorouracil and cisplatin chemotherapy adds to the expense. Dakar is located on a peninsula in the far Western portion of Senegal, requiring patients from other parts of the country to travel hundreds of kilometers for treatment. Even patients able to travel and with sufficient resources to afford the treatment costs are eligible for either neoadjuvant chemoradiation therapy before radical surgery or palliative chemoradiation therapy but not curative chemoradiation therapy, secondary to the lack of brachytherapy. The paradigm for treatment of carcinoma of the cervix before March 2013 and the arrival of HDR is shown in [Table 1](#). Patients with early-stage disease undergo radical surgery, and those found to have high-risk features go on to receive

postoperative chemoradiation therapy. Patients with bulkier disease receive neoadjuvant chemoradiation therapy and with good response proceed to surgery. From January 2008 through December 2012, 48% of patients presented with stage III-IVA disease. (personal communication, Dr. M. Dieng, 11/2013) The vast majority of these patients are offered palliative hypofractionated chemoradiation therapy. These are the patients for whom the availability of HDR brachytherapy will make a major impact on the potential curability.

Program Design

There were a number of challenges to implementing HDR brachytherapy in Senegal. First, the HDR afterloader (Nucletron Microselectron; Elekta Medical Systems, Stockholm, Sweden) had to be located in the ^{60}Co treatment vault. Unfortunately applicator placement must be performed in the simulator, which is located at the opposite end of the center. With a full teletherapy schedule, the HDR procedures have to be coordinated with this schedule. Second, placement of the applicators is moderately painful, and immobilization is essential to quality brachytherapy. Moderate sedation with short-acting medications is usually adequate but requires monitoring of the patient's oxygen saturation and heart rate during the procedure. This capability would not initially be available. Because general anesthesia is also not possible, patient comfort and immobilization would be a challenge. Both of these limitations made it necessary to minimize the number of planned brachytherapy fractions. Finally, although an Oncentra treatment planning system (Nucletron, Elekta Medical Systems) was supplied with the afterloader, it could not be used to perform real-time treatment planning. There are 3 reasons for this. First, there was a lack of necessary infrastructure and equipment—it was not possible to acquire computed tomography (CT) images of the patient and applicator, no digitizer was available to reconstruct the applicator geometries from 2-dimensional orthogonal images, and there were connectivity issues between the treatment planning system and the afterloader that could not be resolved. Second, there is a large up-front training requirement for physics and radiation oncology staff and a significant additional per-case workload. Third, and importantly, there is a significant risk of misadministration of treatment when using a real-time treatment planning technique. In consideration of these factors, we developed a preplanned treatment technique involving design of an innovative system of fixed-geometry applicators (tandem and ring), preplanned dosimetry with a library of plans loaded directly into the afterloader control system, and isodose overlays (isodose curves printed on transparencies) for use with orthogonal simulator images to confirm that doses to International Commission on Radiation Units and Measurement (ICRU) rectal and bladder points were within tolerance. The radiation oncologists at the cancer center are well trained and experienced with low-dose-rate brachytherapy. Therefore, they are familiar with the

Table 1 Treatment paradigm for carcinoma of the cervix at Institut Joliot-Curie before implementation of high-dose-rate brachytherapy

Stage	Dose	Response	Surgery
I (nonbulky)	—	—	Yes
IB-2A (bulky)	4600 cGy in 23 fx (4-field box)	Any	Yes
IIB	4600 cGy in 23 fx (4-field box)	Good* Poor or none	Yes No
IIIB	3000 cGy in 10 fx AP/PA, then 1500 cGy in 5 fx Lats	Good or cCR* Less than good	Possible surgery No

Abbreviations: AP/PA = anterior–posterior/posterior–anterior; cCR = clinical complete response; fx = fractions. Lats = lateral fields.

* Patients not found to be surgical candidates but otherwise having a good response receive an additional 2000 cGy in 10 fractions using reduced 4-fields.

general technique of the placement of applicators and proper geometry to reduce toxicity but not with the idea of delivering multiple implants outside of the operating room and with the unique fractionation required with HDR. Therefore our chief aims were: (1) to design a treatment schema involving as few fractions of brachytherapy as possible to limit patient discomfort and staff workload without undue risk of rectal and bladder injury; (2) to use a fixed-geometry applicator and a library of treatment plans to safely deliver treatment without the requirement for computerized treatment planning; and (3) to show that the planned system can effectively and safely be used for patient treatments in the facility.

Aim 1: Determining fractionation schedules

In December 2012, a team from the United States consisting of radiation oncologists, radiation oncology residents, physicists, nurses, and others traveled to Senegal and held a number of working sessions with the staff at Institut Joliot-Curie. We discussed the current treatment schema at the center, treatment techniques, and dose/fractionation issues, with an eye toward minimizing the number of brachytherapy fractions.

We reviewed the American Brachytherapy Society recommendations for the use of HDR brachytherapy published in both 2000 and 2012 (2, 3), suggesting limiting fraction size to <7.5 Gy and listing common fractionation schedules that generally include 4 or 5 fractions of HDR after 45 Gy of external beam irradiation. A recent review of brachytherapy practice patterns across the Gynecologic Cancer Intergroup, however, showed wide variability across cooperative groups in Australia, New Zealand, United States, and Europe, but these commonly resulted in an equivalent dose in 2-Gy fractions (EQD2) to tumor of approximately 80 Gy (4). We reviewed the literature and found a number of published experiences using 3 or fewer fractions of HDR brachytherapy, and these are listed in Table 2 with the institution, fractionation scheme, EQD2, control rates, and toxicity if published. The majority of reports on hypofractionated brachytherapy are from centers in the developing world. Whole-pelvis doses of 40-50 Gy are common, with HDR fractionation ranging from 2 fractions of 7.5-9 Gy to 3 fractions of 6.5-10 Gy. Corresponding EQD2 ($\alpha/\beta = 10$) values range from 68.5 to 90 Gy. There does not seem to be a strong correlation between EQD2 values and pelvic control or toxicity in Table 2, but this is difficult

Table 2 Published results of treatment schema involving external beam radiation therapy (EBRT) with/without chemotherapy and 3 or fewer fractions of HDR brachytherapy

First author, year (reference)	Country	N	EBRT (Gy)	Chemotherapy?	HDR schedule (Gy × fx)	EQD2 (Gy) ($\alpha/\beta = 10$)	Local control (%), time point	Grade 3+ late GI/GU toxicity (%)
Shigematsu, 1983 (7)	Japan	249	20, WP 30, MLB	No	10 × 3	74	90, 1 y	36, rectal bleeding (not scored)
Sood, 2002 (5)	United States	54	45, WP	Yes (81%)	9 × 2	72.6	84, 3 y	5
Okkan, 2003 (8)	Turkey	293	50-54	No	8 × 3	86-90	73, 5 y	14
Lertsanguansinchai, 2004 (9)	Thailand	112	40 50	No	7.5 × 3 8.3 × 2	73 75.3	86, 3 y	4.5
Souhami, 2005 (10)	Canada	282	45	No	8 × 3	80	75, 15 y	6.3 GI 3.5 GU
Patel, 2005 (11)	India	121	40 46	No	9 × 2 9 × 2	68.5 74.5	74.5, 5 y	3.31
Jain, 2007 (12)	India	214	50-54	No	7.5 × 2	72-76	42, 5 y	1 GI 0.5 GU
Verma, 2009 (13)	India	36	50	Yes	7.5 × 3	82.8	70, 1 mo	10
Tan, 2009 (14)	UK	28	45	Yes	7 × 3	74.4	96, 3 y	14
Das, 2010 (15)	India	286	40, WP 10-20, MLB	No	7 × 3	70	75, 2 y	1.8 GI 0.7 GU
Azad, 2010 (16)	India	342	46	No	6.5 × 3	72.8	47 Median f/u 36 mo	<1
Kumar, 2012 (17)	India	50	50	No	5.2 × 5 7.5 × 3	82.9 82.8	80 cCR 68 cCR	Not reported
Tharavichitkul, 2012 (18)	Thailand	337	40, WP 10, MLB	Yes	7.2 × 3 6 × 4	70.9 72	80.7, 3 y 86.1, 3 y	3.5 GI 0 GU 10.1 GI 5.3 GU

Abbreviations: EQD2 = equivalent dose in 2-Gy fractions; f/u = follow-up; fx = fractions; GI = gastrointestinal; GU = genitourinary; HDR = high-dose-rate; MLB = lymph node/parametrial irradiation with a central block; WP = whole-pelvis radiation.

to evaluate between centers treating patients with different stages, comorbidities, techniques, and follow-up schedules. The majority of centers in these series treated patients with 2-dimensional treatment planning and no chemotherapy. An exception is the report from New York Hospital Medical Center (5), where patients received an HDR dose of 18 Gy in 2 fractions using 2-dimensional treatment planning techniques, with 81% of patients receiving systemic chemotherapy and a low incidence of reported late toxicity.

Although 2 fractions of HDR is desirable in a high-volume center with limited resources, and the literature suggests low toxicity with 2 fractions of 9 Gy, we believed a more conservative fractionation scheme was appropriate given the challenges of starting a new cervical cancer program in a center without prior HDR experience. Because the center was already accustomed to treating the whole pelvis to 46 Gy in 23 fractions using a 4-field technique with concurrent 5-fluorouracil and cisplatin chemotherapy, we favored this fractionation added to a conservative brachytherapy approach of 3 fractions of 7.5 Gy to point A, providing an EQD2 of 78.8 Gy to tumor for patients with nonbulky disease or a good response to chemoradiation therapy. An additional fraction of 7.5 Gy could be added to the poor responders, for a cumulative EQD2 of 89.75 Gy, only if implant geometry and cumulative dose to rectal and bladder points were acceptable. Although a “one size fits all” option is attractive in designing a new program, we believed it is important to have an option for dose escalation in poor responders given the evidence of significantly improved local control with higher dose to the high-risk clinical target volume (6). This brachytherapy could be either interdigitated into the external beam radiation for early-stage patients or more commonly performed twice weekly at the end of external beam treatment. Concurrent chemotherapy would not be given on the day of

brachytherapy. Once substantial experience is gained using this dose fractionation the clinic could consider moving to 8 Gy × 3 or even a 2-fraction regimen, but we favored a conservative, methodical approach with ongoing reassessments of local control and toxicity before any modification.

Aim 2: Applicator selection and treatment planning design

Without real-time treatment planning, we designed a process based on a combination of fixed geometry applicators and a library of preplans created for each applicator. Nucletron CT/MRI-Tandem and Ring Applicators (Elekta, Stockholm, Sweden) were donated to Radiating Hope for the Senegal project (Fig. 1). The applicators have a number of configurations, with tandem lengths of 20, 40, and 60 mm, tandem/ring angles of 30°, 45°, and 60°, and ring diameters of 26, 30, and 34 mm. Given the variation in ring size and tandem length there are 27 possible geometric configurations for which a library of plans was created. All applicators were assembled, CT scans of each performed, and preplanning completed before shipment to Senegal.

We used a standard low-dose-rate configuration of 15-10-10/15/15 to determine relative dwell times at positions throughout the applicator for a 6-cm tandem length; 15-10/15/15 was used for a 4-cm tandem length; and 15/15/15 was used for a 2-cm tandem length. Five-millimeter dwell spacing was used in the tandem, and we chose 3 dwell positions on each side of the ring separated by 5 mm at the 9 o’clock and 3 o’clock positions. We did not vary the relative dwell times in the ring according to ring diameter. Point A was determined by measuring 2 cm superior to the plane of the ring along the tandem length and then 2 cm lateral to the tandem on both sides and prescribed 7.5 Gy. When completed, these treatment plans were prepared for loading directly into the HDR afterloader and coded according to the 3 variables of applicator angle, tandem length, and ring diameter. Transparent isodose overlays were generated with the applicator position and



Fig. 1. Nucletron CT/MRI-compatible tandem and ring applicators with rectal retractors in place.

Table 3 EQD2 for normal tissues comparing common fractionation regimens in use with Senegal HDR fractionation regimen

EBRT dose	HDR fractionation (Gy × fx)	EQD2 with 90% to bladder (α/β = 3) (Gy)	EQD2 with 70% to rectum (α/β = 3) (Gy)
46 Gy in 2-Gy fx	7 × 4	92.8	77
46 Gy in 2-Gy fx	6 × 5	91.3	76
46 Gy in 2-Gy fx	7.5 × 3	85.5	72

Abbreviations: EBRT = external beam radiation therapy; EQD2 = equivalent dose in 2-Gy fractions; fx = fractions; HDR = high-dose-rate.

Note that using 90% and 70% of point A dose for bladder and rectum, respectively, results in acceptable cumulative EQD2 doses.

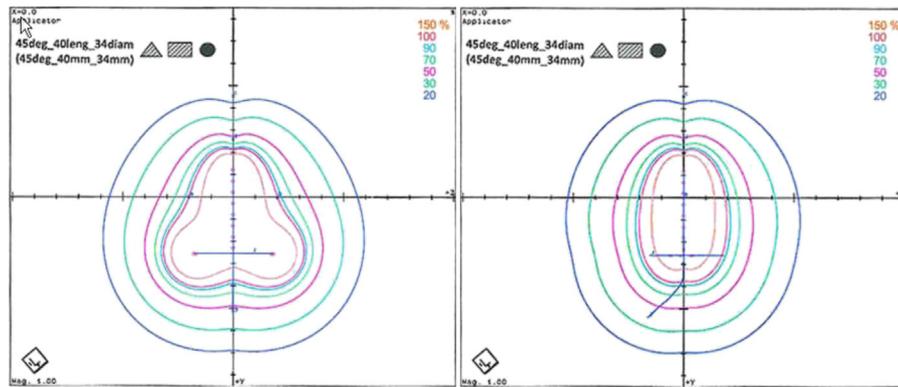


Fig. 2. Isodose overlay transparencies coded for applicator angle, tandem length, and ring diameter.

clearly marked with the 150%, 100%, 90%, 70%, 50%, 30%, and 10% isodose curves. The 100% represented point A, the 90% represented the maximum bladder point dose, the 70% represented the maximum rectal point dose, and 30% and 10% were to estimate pelvic side wall dose. The maximum point doses to bladder and rectum were chosen so that the combined EQD2 ($\alpha/\beta = 3$) for both the external beam and brachytherapy doses to these structures was within a tolerable range (Table 3). These overlays were also coded with the 3 geometric variables of the applicators (Fig. 2). Therefore, the applicator could be matched to the overlay and be used to confirm the proper plan at the treatment console. The basic implant procedure included placement of a Foley catheter with 7 cm³ of radio-opaque contrast in the Foley balloon. Pain control is managed with the use of intravenous paracetamol and paracervical injections of local anesthetic. Applicators are placed along with a beaded marker in the rectum, and anterior–posterior and left lateral radiographs are taken. An aluminum ring of known diameter is placed on the patient at the time the radiographs are taken. This enables the radiographs to be scaled to the magnification of the overlays. The ICRU bladder and rectal points are then determined and drawn onto the radiographs. Dosimetric estimations of bladder, rectal, and pelvic sidewall doses are done by matching the overlay to the radiograph and viewing the isodose lines. An

acceptable implant is one for which the ICRU bladder point is outside of the 90% line and rectal point is outside of the 70% line. If the points are thought to be receiving higher than acceptable doses, then repacking is performed and images are repeated.

Aim 3: Successful treatment

In March 2013, a team of 2 radiation oncologists, 2 physicists, a radiation oncology resident, and a radiation oncology nurse traveled to Senegal. Before our arrival patients were identified by the local radiation oncologists as candidates for curative therapy, and consent was obtained for brachytherapy. Our goal was to treat patients according to protocol while initially providing substantial assistance to the clinic staff, with graduated independence throughout the week.

The patients were brought to the simulator and the procedure performed as outlined above. Although the use of intravenous paracetamol and intracervical injections of lidocaine were somewhat effective, there was moderate patient discomfort with applicator placement. Vaginal packing was performed with betadine-soaked gauze instead of the rectal retractor to minimize patient discomfort. The correct transparency overlay was chosen, and confirmation

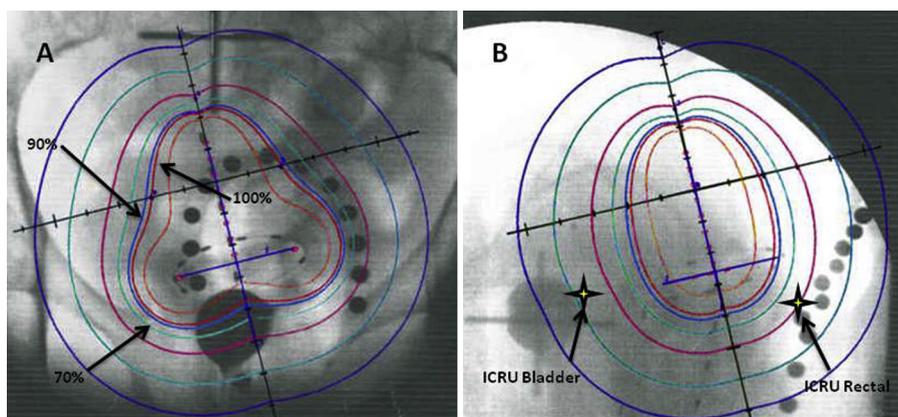


Fig. 3. Transparency isodose overlays over anterior–posterior (A) and left lateral (B) simulation films. (B) International Commission on Radiation Units and Measurement bladder and rectal points falling outside of the 90% (blue) and 70% (green) isodose curves, respectively. The tandem and ring devices can be seen as dummy seeds with 1-cm spacing.

was obtained that the rectal and bladder points were within their respective tolerances. A patient radiograph with overlays is shown in Figure 3. When the radiographs were approved, the patients were taken by gurney to the treatment room. The guide tubes were attached to the appropriate applicator and verified by 2 physicists. The proper preplan was chosen from the afterloader control system library, and treatment was delivered. A total of 10 implants were performed on 6 patients over 5 days, with none of the implants requiring repacking due to inadequate dosimetry.

Conclusions

High-dose-rate brachytherapy can be implemented in Senegal and other developing countries with the use of fixed-geometry applicators and a library of plans. What began as a “work-around” to our desire to not perform real-time treatment planning evolved into an efficient, accurate, and simple HDR treatment system. Although daily imaging is required to verify acceptable doses to the bladder and rectal points, this requires little time and resources compared with real-time treatment planning. Unfortunately we do not yet have efficacy and toxicity data, but this will be quite important in the future to determine whether this dose/fractionation regimen and dosimetry system are adequate for the ongoing needs of the center. However, it is based on published fractionation schema and treatment planning techniques that should result in an acceptable outcome.

Despite our ability to design a treatment program that allows Senegalese patients to have curative chemoradiation therapy for cervical cancer using only an HDR afterloader, tandem and ring applicators, and a preloaded library of plans, there remain several obstacles toward a sustainable HDR brachytherapy program there. First, patient comfort is extremely important and will affect compliance to this form of treatment. Acquisition of equipment and medications to allow moderate sedation will be a priority. Second, brachytherapy is an additional expense to the patient after chemoradiation therapy, and this is necessary to pay for the continued maintenance and source changes for the afterloader. This cost may be prohibitive for some patients, and it remains unclear whether patient revenue alone will be sufficient to support the cost of equipment upkeep. Third, the construction of an HDR-dedicated room, or renovation of an existing room to make it HDR compatible, would alleviate scheduling conflicts between external-beam and HDR treatments and would increase treatment capacity at the center. Finally, making this treatment available to the majority of patients with cervical cancer treated at Institut Joliot-Curie would require substantial additional physician and staff resources, adding expense and pressure on a clinic that is already extremely busy. Given the potential for converting a substantial number of patients from palliative to curative intent with HDR brachytherapy, these challenges are worth solving. Our support for the program in Senegal is ongoing, and we believe that the system we have

designed could be a model for building HDR programs in other developing countries.

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