

CONCEPT, CHARACTERISTICS AND PERFORMANCE OF AN ELECTRONIC BRACHYTHERAPY SYSTEM FOR ACCELERATED PARTIAL BREAST IRRADIATION

Darius S Francescatti, MD ¹, John W Rieke, MD ², Mark J Rivard, PhD ³, Jacqueline P Williams, PhD ⁴, Steve Axelrod, PhD ⁵, Robert R Burnside, MS ⁵, Steven D Hansen, MS ⁵, and Thomas W Rusch, PhD ⁵.

¹ Surgery, Rush Medical School, Chicago, IL; ² Radiation Oncology, MultiCare Regional Cancer Center and University of Washington, Seattle, WA; ³ Radiation Oncology, Tufts-New England Medical Center, Boston, MA; ⁴ Radiation Oncology, University of Rochester Medical Center, Rochester, NY and ⁵ Xoft, Inc., Fremont, CA

ABSTRACT

• Purpose: To validate performance of the Xoft Axcent Electronic Brachytherapy System
• Materials and Methods: An electronic, non-radioactive high dose rate brachytherapy system has been designed to closely emulate conventional isotope sources previously used for accelerated partial breast irradiation. Pre-clinical medical physics measurements have verified the dosimetric similarities and have been used to establish treatment planning protocols. To verify performance the system has been tested in an animal model, utilizing the udders of Nubian milk goats. A breast surgeon and veterinarian performed bilateral balloon implants in multiple animals, each acting as its own control. Implantation and delivery was performed according to the conventional protocol of 10 treatments twice a day for five days. Balloon applicators were specially designed to improve seroma drainage, be readily imaged, and accommodate the water-cooled 40 kV X-ray source. Pre-treatment measurements included a check of balloon diameters and skin distances with ultrasound prior to 9 out of 10 fractions and with fluoroscopy prior to each afternoon fraction. Skin dose was measured using a Thomson-Nielsen MOSFET 20 Dose Verification System, and an external continuous dose rate measurement system verified stability of the source output.
• Results: Ten fractions were successfully delivered to each of four goats within five days. Drainage lumens allowed repeated removal of fluid (up to 40 cm) from the lumpectomy cavities surrounding the applicators. On ultrasound, applicator dimensions remained constant over the entire treatment period and with measurement uncertainties except for one exception where 5 cm of fluid was added. Controller hardware and software performed to specification. X-ray source performance and dose delivery were very stable during treatments and between different fractions. A flexible drapes radiation shield reduced radiation levels around the animals by at least 100x, safely allowing personnel presence in the treatment room. There were no radiochemical injuries or acute effects from the radiation treatments detected upon preliminary examination of the animals over the 14 days after treatment completion. Tissue analysis is being reported in another presentation at this meeting, but no unexpected findings or unusual toxicity was noted.
• Conclusions: The electronic brachytherapy system performed as expected with respect to applicator imaging, controller hardware and software operation, x-ray source lifetime and stability, and flexible shield radiation attenuation. This animal experience designed to emulate human treatment suggests that integration of electronic brachytherapy into clinical practice for APBI will likely be simpler than for isotope based systems. This is due to many factors we observed including ease of shielding the lower energy, non-radioactive source, portability, safety implications of active and control applicators were inserted in opposite udders by a veterinarian and ARC-approved outside surgeon.

INTRODUCTION

- External beam radiotherapy following breast conserving therapy (BCT) lasts 6 to 7 weeks. Many women elect mastectomy or omit post-operative radiotherapy because they cannot commit the required time or resources.
- Accelerated Partial Breast Irradiation (APBI) uses brachytherapy to deliver radiation to the breast. APBI is a treatment time but is labor intensive, requires a skilled operator, and can be uncomfortable for patients. Many radiation treatment centers cannot afford to maintain active isotopes or to build the shielded treatment room for HDR brachytherapy.
- Xoft has developed an electronic (non-isotopic) high dose rate brachytherapy device. The microTube Flexible X-ray Probe delivers light, conformal doses of x-radiation to the inner surface of a body cavity such as an excised tumor bed.
- The clinical application of the Xoft Axcent Electronic Brachytherapy System is to the conservative treatment of breast cancer utilizing balloon-based partial breast irradiation.
- The Axcent System is designed to shorten treatment time compared to external beam radiation. The Axcent System does not require a heavily shielded environment, making treatment potentially available for women without access to a facility with an HDR afterloader. This technology eliminates handling and disposal of isotope sources.

DEVICE DESCRIPTION

- The Xoft Axcent Electronic Brachytherapy System, consists of the X-ray Source, the Balloon Applicator and the Controller.
- The X-ray Source comprises an X-ray tube in a multi-lumen catheter that allows cooling fluid to circulate over the tube. The X-ray tube is ~2.25mm in diameter x 15mm long and is attached to a high voltage cable and encapsulated within an electrical ground.
- The Disposable Balloon Applicator Kit contains one of five balloon sizes/shapes: three spherical and two ellipsoidal. The balloon applicator, a sterile, disposable, single use device, is designed for the water-cooled x-ray source and functions as its guide. The balloon material is radiopaque to facilitate imaging.
- The Axcent System Controller provides power to the X-ray Source as well as allows the X-ray Source, positioned within the Applicator, to be translated. The translation or pullback movement of the X-ray Source within the balloon is designed to provide a predictable dose of radiation in the tissue surrounding the balloon. It also provides a user interface with a control panel. It houses all safety and interlock circuitry and manages coolant pump activity.
- Disposable accessories for placement of the applicator as well as an optional radiation shield and system controller accessories are available.



OBJECTIVES

- Objective: To further validate performance of the Xoft Axcent Electronic Brachytherapy System in a Nubian milk goat animal model. The endpoints were:
 - Ability to implant applicators and obtain confirmatory images.
 - Delivery of a total of 34 Gy in 10 fractions to within ±20%.
 - Confirmation of lack of adverse tissue effects by evaluation of tissue histopathology ~ 14 days post-radiation and Applicator explant including identification of untoward tissue effects.
 - No unanticipated adverse events due to the device during implant or delivery of radiation.

METHODS

- Day 1: Eight balloon applicators were inserted percutaneously into simulated lumpectomy cavities created in the udders of four healthy adult Nubian milk goats under anesthesia; active and control applicators were inserted in opposite udders by a veterinarian and ARC-approved outside surgeon.
- Two goats received spherical applicators inflated (90-25 cm) to a nominal diameter of 3.4 cm, and two goats received 5x7 cm ellipsoidal applicators inflated (90-100 cm³) to a nominal diameter of 4.5 cm. The balloons were filled with saline.
- Days 4-8: Radiation treatment using 40 or 50 kV was delivered to one udder of each goat. The prescription dose was 34 Gy to a point 1 cm from the applicator surface (transverse-plane) to be delivered in 10 fractions BID for 5 days as for conventional APBI.
- Source output was measured before and after each fraction using a Standard Imaging Model HDR 1000 well ionization chamber and Standard Imaging Model MAX-4000 electron detector and used with existing bench-top measurements to calculate dose delivered.
- Treatment planning was performed with BrachyVision software (Varian, v6.5) following AAPM TG-43 formalism for source definition. Balloon diameters and skin distances were measured with ultrasound prior to 9 out of 10 fractions and with fluoroscopy prior to each afternoon fraction. Skin dose was measured using a Thomson-Nielsen MOSFET 20 Dose Verification System.
- Day 8: Applicators were removed by a radiation oncologist after final treatment. The 4 goats were survived for 14 additional days. All udders (control & active) were resected. All surrounding tissue (abdominal muscles, large intestine, kidneys, urinary bladder, uterus, and ovaries) was grossly observed for collateral damage, and samples were collected and stained with hematoxylin & eosin (H&E) and for apoptosis (TUNEL) or proliferation (PCNA).

Figure 1. Animal #65 with applicators implanted in each udder. In this animal the right udder was the treatment udder.

RESULTS

First Endpoint: Successful Implantation

- The applicators were implanted successfully in all four goats.
 - Each goat was implanted with one applicator in each udder as shown in Figure 1 (below-left).
 - Confirmatory images were obtained and include the fluoroscopic images of the pelvic region (Goat #65) with applicator implanted in the ure. See Figure 2 (right).
 - Drainage lumens allowed removal of fluid (up to 40 cm) from the lumpectomy cavities surrounding the applicators.
 - With the exception of one ellipsoidal balloon that required one 5 cm³ supplement, applicator integrity as measured by balloon diameter consistency was acceptable within measurement error over the entire treatment period.
 - Ultrasound imaging was used to confirm minimum distance from skin to the applicator and the diameter of the balloon. The fluoroscopic images were used to confirm the shape and symmetry of the balloon.

Figure 2. Fluoroscopic image of an implanted ellipsoidal applicator.

Second Endpoint: Accurate Delivery of Radiation

- Ten fractions were successfully delivered to each goat within five days.
- All treatments were delivered on the scheduled days, and each animal received two fractions per day, with approximately 6 hours between fractions.
- X-ray source performance and dose delivery were very stable during treatments and between different fractions. Six sources were used to deliver treatment.
- The controller hardware and software performed to specification.
- A flexible radiation shield reduced radiation levels around the animals by at least 100x, safely allowing personnel presence in the treatment room.
- The average distances (SD) from the applicator to the skin as measured by ultrasound were 12.2 mm (0.7), 14.0 mm (1.7), 9.8 mm (1.4) and 12.0 mm (1.0) in the four goats. The average balloon applicator diameters as measured by ultrasound were 3.8 mm (0.4), 4.9 mm (0.4), 4.9 mm (0.5), 3.3 mm (0.4) in the four goats. The dose delivered to the skin was less than 3 Gy during each fraction. Based on the clinical data from the experience with delivering similar doses with ¹⁹²Ir sources for accelerated partial breast irradiation, this level of dose to the skin is acceptable.

Table 1. Dose delivery accuracy to each animal

Fraction	#65	#66	#67	#69
1	101.2%	96.1%	103.7%	100.3%
2	100.6%	95.6%	99.2%	100.7%
3	100.8%	96.9%	100.2%	101.5%
4	104.4%	96.9%	98.3%	99.9%
5	101.5%	97.1%	99.2%	100.2%
6	101.0%	98.5%	99.4%	99.8%
7	101.2%	104.8%	99.7%	100.8%
8	100.8%	100.2%	102.8%	100.2%
9	100.3%	101.3%	98.8%	100.3%
10	101.7%	101.0%	101.5%	100.1%
Average	101.0%	98.8%	100.3%	100.4%
SD	0.4%	2.8%	1.7%	0.5%

- The protocol called for the source to be calibrated both before and after each fraction was administered. Normal operation will consist of a calibration before the radiation is delivered to the patient.
- Table 1 shows a summary of the consistency between the pre- and post-treatment measurements by calculating the ratio of the average of the two values to the initial value.
- The sources were sufficiently stable, as determined by this measurement, that there was no correction applied to the dose delivered due to any variations in the source output over the course of the treatment.

RESULTS

Third Endpoint: No Adverse Tissue Effects

- The PCNA analysis showed a low level (1-5%) of proliferation in the lobular epithelium in 3 of 4 control samples and 2 of 4 irradiated mammary samples. These levels were consistent across samples, proximal to distal. The increased proliferation levels seen in animal #66 may have been due to the active (facing) condition of many of the lobules. The most significant levels of proliferation were seen in areas of active inflammation; these were observed in both control and irradiated tissues. In general, higher levels of inflammation were seen in the irradiated samples, although, apart from focal increases immediately adjacent to the lesion, there was no significant gradient with respect to the irradiated field. I.e. infiltrations were distributed throughout the tissues. Of note, increased levels of proliferation were not seen in the interlobular connective tissue or fatty areas in any sample. See Figures 3-6 (right).
- The apoptosis analysis revealed little or no difference between control and irradiated mammary tissue in all cases. In general, apoptosis was distributed evenly across all sections of tissues, proximal to distal, with the exception of some increases seen in active areas of inflammation. Therefore, irradiation appeared to have no effect on levels of apoptosis at this time point using the stated dosing schedule.
- Results of the hematoxylin & eosin stains showed localized necrosis on both the control and treatment side consistent with caustery-induced cavities.

PCNA Images (20x)

A. #65 control B. #65 irradiated

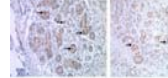


Figure 3. The images (magnified 20x) show PCNA staining in control tissue (A) and irradiated tissue (B) from the same animal (solid arrows indicating positive cells).

A. #66 irradiated B. #66 irradiated

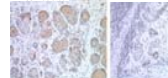


Figure 4. The images (magnified 20x) show PCNA staining in irradiated tissue showing (A) increased levels associated with the thickened lobular epithelium in active lobules (B) increased levels in areas of high inflammatory infiltration.

A. #65 irradiated B. #69 irradiated

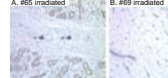


Figure 5. The images (magnified 20x) show PCNA staining in (A) irradiated connective tissue (broken arrows indicating blood vessels) and (B) irradiated fatty tissue.

Fourth Endpoint: No Adverse Events

- Overall, no unanticipated adverse events were noted during the study.
- The applicators were implanted successfully in all four goats with no difficulty.
- All 4 animals tolerated the treatment well and were healthy at the end of the treatment.
- Some minor infection was noted on 2 goats and treated with antibiotics during the 14 day survival time.
- The eight applicators were explanted with no difficulty; the hub was removed from one applicator prior to explantation.

SUMMARY

- These results demonstrate that all four primary endpoints were met.
 1. Implantations of applicators were performed without complications. Ultrasound and fluoroscopic imaging modalities were effective.
 2. Delivered doses were well within the goal of 34 Gy ±20% as calculated from the laboratory-based treatment plan validation and source stability measurements.
 3. There were no adverse tissue effects. Pathologic changes induced in tissue surrounding lumpectomy cavities of the Nubian milk goats were similar to those described for whole breast external beam radiation therapy.
 4. There were no adverse events.

CONCLUSIONS

- The Xoft Axcent Electronic Brachytherapy System performed as expected with respect to applicator imaging, controller hardware and software operation, x-ray source lifetime and stability, and flexible shield radiation attenuation.
- The system was able to safely deliver the required dose, and no adverse effects were associated with treatment or the implantation/removal of the applicator.

Study Funded by Xoft