

# PERFORMANCE OF AN ELECTRONIC BRACHYTHERAPY SYSTEM FOR ACCELERATED PARTIAL BREAST IRRADIATION IN A GOAT MAMMARY MODEL

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## ABSTRACT

• Purpose: This study was conducted to further validate performance of the Xoft Axcent Electronic Brachytherapy System using a Nubian milk goat animal model.

• Materials and Methods: Eight balloon applicators were inserted percutaneously into simulated lumpectomy cavities created in the udders of four Nubian milk goats; active and control applicators were inserted in opposite udders. Two goats received spherical applicators inflated (20-25 cm) to a nominal diameter of 4.7 cm elliptical applicators inflated (90-100 cm) to a nominal diameter of 4.8 cm. Treatment planning was performed with BrachyVision software. Radiation treatment using 40 or 80 kV commenced three days after implantation. Prescription doses were 34 Gy to a point on the surface transverse-plane to be delivered in 10 fractions BID for 5 days as for conventional APBI. 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 2D Dose Verification System.

• Results: Ten fractions were successfully delivered to each goat within five days. Drainage lumens allowed removal of fluid (up to 40 cm) from the lumpectomy cavities surrounding the applicators. With the exception of one elliptical balloon that required a 5 cm supplement, applicator integrity as measured by balloon diameter was maintained with measurement error over the entire treatment period. The 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 radiation shield reduced radiation levels around the animals by at least 10x, safely allowing personnel presence in the treatment room. There were no electrochemical 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 performed and will be reported upon.

• Conclusions: The Electronic Brachytherapy System performed as expected with respect to applicator integrity, controller hardware and software operation, x-ray source lifetime and stability, and flexible shield radiation attenuation.

• This study was funded by Xoft, Inc. Financial Disclosure: Drs. Rieke, Francescatti, Rivard and Williams are paid consultants of Xoft, Inc. Dr. Axelrod (Disclosure: The Xoft Axcent system is currently under FDA) reviewed the FDA.

## 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) using brachytherapy can significantly shorten treatment time but is labor intensive, requires skilled operators, and can be difficult to perform 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 Xoft microTube Flexible X-ray probe delivers tight, conformal external irradiation to the inner surface of a body cavity such as an excised tumor bed.

• The initial 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 ~225mm 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 elliptical. 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 25%.
- 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 AARC-approved outside surgeon.

• Two goats received spherical applicators inflated (20-25 cm) to a nominal diameter of 3.4 cm, and two goats received 8x7 cm elliptical applicators inflated (90-100 cm) to a nominal diameter of 4.8 cm. The balloons were filled with saline.

• Days 4-8: Radiation treatment using 40 or 80 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 electrometer and used with existing bench-top measurements to calculate dose delivered. (See poster by S Axelrod, ABS 2005 Annual Meeting, for validation of dose delivered from the Axcent system.)

• Treatment planning was performed with BrachyVision software (Varian, v5.5) following TG-23 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 2D Dose Verification System. (See oral presentation by M.J. Rivard, ABS 2005 Annual Meeting, for TG-23 dosimetry parameters.)

• Day 9: 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 intestines, 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 #66 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 image of the pelvic region (GOAT #66) with applicator implanted in the udder. (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 elliptical balloon that required one 5 cm supplement, applicator integrity as measured by balloon diameter constancy 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.

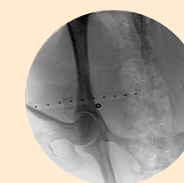


Figure 2. Fluoroscopic image of an implanted elliptical applicator.

### 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 (1.5) in the four goats. The average balloon applicator diameters as measured by ultrasound were 48.8 mm (0.4), 34.0 mm (0.4), 49.3 mm (0.5), 33.7 mm (0.4) in the four goats. The dose delivered to the skin was less than 1 Gy during each fraction. Based on the clinical data from the experience with delivering similar doses with <sup>192</sup>Ir 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%	95.8%	99.2%	100.7%
3	100.8%	96.9%	100.2%	101.5%
4	100.4%	96.9%	98.3%	99.8%
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%	0.8%

• 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.

Study Funded by Xoft The Xoft Axcent System is for investigational use only. FDA clearance pending.

## 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 level in the irradiated animal was due to the active (lactating) 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 lobules, immediately adjacent to the lesion, there was no significant gradation with respect to the irradiated field. In 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 3-5 (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 caustic-induced cavities.

### PCNA Images (20x)

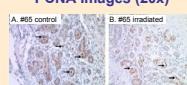


Figure 3. The images (magnified 20X) show PCNA staining in control tissue (A) and irradiated tissue (B) from the same animal (bold arrows indicating positive cells).

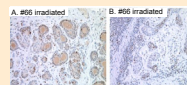


Figure 4. The images (magnified 20X) show PCNA staining in irradiated tissue showing (A) increased levels associated with the thickened lobular epithelium in active lobules (B) increased levels in areas of active inflammatory infiltration.

### 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 period.

• 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.

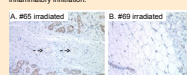


Figure 5. The images (magnified 20X) show PCNA staining in (A) irradiated connective tissue (black arrows indicating blood vessels) and (B) irradiated blood vessels.

## 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 integrity, 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.