DOSIMETRIC CHARACTERIZATION AND FEASIBILITY TESTING FOR A NEW ELECTRONIC HIGH DOSE RATE BRACHYTHERAPY SOURCE

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ABSTRACT

- **Purpose/Objective:** A new miniature x-ray source has been developed for electronically-controlled brachytherapy. This non-radioactive source is integrated with a flexible high voltage cable and enclosed in a cooling sheath which maintains the device surface temperature at or below 40 C. This study assessed the x-ray probe dose distribution and determined dosimetry parameters using the AAPM TG-43 protocol. Measured parameters, in conjunction with those determined by Monte Carlo modeling, were used with two commercially-available treatment planning systems to optimize the dose distribution around balloon-based brachytherapy applicators. A pilot animal study was performed to confirm the feasibility and tolerance of delivery of therapeutic dose in agreement with the treatment plans.
- **Materials/Methods**: Air ionization chambers, TLDs, an intrinsic germanium energy-dispersive x-ray spectrometer and radiochromic film were used to ascertain depth-dose curves in air and water, air kerma strength, angular dose distributions, x-ray energy spectra, and half-value layers. These measurements were compared with source output calculations employing the MCNP-4C radiation transport code. Source parameters were compiled for the MDS Nordion ABACUS and Varian BrachyVision™ treatment planning systems. These software packages were used for determining optimal dwell positions and times for a variety of spherical and ellipsoidal balloon applicators of different sizes. Device and applicator performance were then tested in a Nubian milk goat mammary model based on these treatment plans. A prototype dose optimization algorithm has also been demonstrated that can take advantage of the x-ray source operation with variable beam voltage, hence, variable depth-dose characteristics. This algorithm provides an additional degree of freedom for dose distribution optimization.
- **Results:** With the x-ray source operating at 40 kVp and 0.30 mA, the air kerma strength exceeded 800 Gy cm^2 h^{-1} or approximately twice that of a 10 Ci ^{192}Ir source. The depth-dose curve measured in a water phantom agreed with the Monte Carlo model to within 8% over a distance range from 0.5 to 3.0 cm from the source axis. TLD determination of the angular dose distribution in the water phantom agreed with the Monte Carlo model to within 15% over a 270 degree angular range. Five Nubian milk goats received a nominal 25 Gy in 10 fractions at a prescription point 1 cm from the balloon applicator surface. Based on a calibration in solid water and well ionization chamber readings of x-ray probe output before and after each fraction, the total doses delivered were 24.8±1.7 Gy. TLD and MOSFET skin measurements confirmed a surface dose less than the prescribed dose in all fractions. Procedure tolerance was good and no acute radiation or thermal complications were noted, grossly or in histologic post-mortem studies. (Update: After the trial, a dose rate correction factor was found to overestimate dose rate, so total dose delivered was less than intended.)
- **Conclusion:** A miniature x-ray probe for electronic brachytherapy has been characterized experimentally and with Monte Carlo modeling. Treatment plans were then incorporated in a pilot animal study using a Nubian milk goat mammary model which confirmed the delivery of therapeutic doses. Human clinical trials are scheduled to start later this year.

INTRODUCTION

"*… breast conserving surgery plus radiotherapy to the breast is an appropriate method of primary therapy for the majority of women with stage I and stage II breast cancer and is preferable to total mastectomy because it provides survival equivalence while preserving the breast …*"
J Natl Cancer Inst Monogr 1992; (11): 1-5.

"*Our findings at 20 years still show that lumpectomy and breast irradiation as compared to lumpectomy alone significantly decrease the incidence of a recurrence in the ipsilateral breast.*"
N Engl J Med Vol 347, No. 16; Oct. 17, 2002; 1240.

- 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.
- Brachytherapy can significantly shorten 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 (EHDRB) device. The Xoft microTube Flexible X-ray Probe delivers tight, conformal doses of x-radiation to the inner surface of a body cavity such as an excised tumor bed.
- The initial application of the Xoft microTube Flexible X-ray Probe has been to the conservative treatment of breast cancer utilizing a balloon-based Partial Breast Irradiation System. See Device Description and Figures 1-3.
- The Xoft Treatment System is designed to shorten treatment time while significantly reducing complications to the skin and surrounding healthy tissue. The Xoft Treatment 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.

METHODS

- **Objective**: This in vivo controlled study was designed to evaluate the Xoft microTube Flexible X-ray Probe with regard to delivery of therapeutic dose in therapeutic time.
- **GLP:** This study was conducted according to Good Laboratory Practices.
- **Subjects**: Five female Nubian milk goats completed the 10 fraction treatment
- **Treatments**:
  - Animals received bilateral applicator implants to both udders. One udder received active radiation treatment and the opposite udder served as a control.
  - Active treatment: 10 fractions of a nominal 2.5 Gy at 1 cm beyond the surgical margin over either five days (3 animals) or six days (two animals) with device operating conditions of 40 kVp and 300µA
- **Study Endpoints:**
  - Gross observation of adverse events
  - Histologic analysis at 1 hour, 24 hours and 14 days by standard light microscopic exam
    - Hematoxylin and eosin stain
    - Apoptosis stain (ApopTag; S7101 kit from Chemicon International)
    - Proliferation stain (PCNA; ARK Run kit from DAKO)
  - Device Performance – Thomson-Nielsen MOSFET 20 Patient Dose Verification System and LiF thermoluminescent detectors (TLDs)
  - Balloon conformance and stability
  - Electromechanical safety

DEVICE DESCRIPTION

- Electronic (non-isotopic) high dose rate brachytherapy (EHDRB) delivers HDR ionizing radiation to the tumor bed using a fully electronic system.
- The Xoft microTube Flexible X-ray Probe, an EHDRB device, consists of a disposable, micro-miniature x-ray source integrated into a cooled, flexible, disposable probe.

Figure 1. X-Ray Source

Figure 2. Activated x-ray probe operating with the cooling sheath removed.

- X-rays of 40-50 keV maximum energy are produced at the tip of the directable probe, which otherwise closely resembles current remote afterloading units.
- The x-ray source can be intensity modulated to mimic penetration and/or dose rate characteristics of many different isotopes, including HDR Ir-192, I-125 and Pd-103.
- Control variables are source operating voltage (penetration depth), beam current (dose rate), dwell time, and dwell position.
- The Xoft microTube Flexible X-ray Probe can be inserted directly into tissue or into one or more lumens of an intracavitary or interstitial brachytherapy applicator.
- This x-ray probe is potentially appropriate for any accessible body cavity or excised tumor bed such as with breast cancer or gynecologic cancers.
- The initial application of the Xoft microTube Flexible X-ray Probe will be for the conservative treatment of breast cancer utilizing a balloon-based Partial Breast Irradiation System (see Figure 3).
- The balloon applicator, a sterile, disposable, single use device, is designed for the water-cooled x-ray probe and functions as its guide.

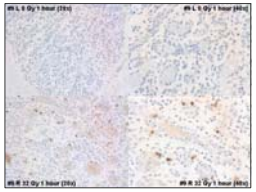
Figure 3. Xoft Treatment System

RESULTS: HISTOLOGY

- In all early irradiated sections (1 hour – 5 days post-radiation), there was a small increase in apoptosis (ApopTag). This increase in apoptotic levels was no longer present in the later (13-14 day post-radiation) samples. These findings support the literature that shows that apoptosis, as a primary event, occurs from a few to more than 12 hours post-radiation. See Figure 4.
- An increase in proliferation (PCNA) was observed at the later time points (13-14 days post-radiation) and was confined to the ductal epithelium. The wide spread nature of the PCNA positive reaction suggests that the proliferation is part of a normal wound healing response to the radiation and/or the catheter stimulation. See Fig. 5.

Apoptosis

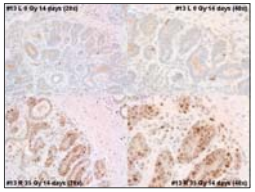
Figure 4. One hour after dosing with 0 Gy (top) and 23 Gy (bottom)



- The top panel illustrates a typical lobule from a control breast. The normal terminal duct-lobular units are evident. No apoptotic cells are evident.
- The bottom panel shows the contralateral irradiated breast with positive apoptotic cells, indicated by the brown nuclear stains.

Proliferation

Figure 5. 14 days after dosing with 0 Gy (top) and 25 Gy (bottom)



- The top panel illustrates a typical lobule from a control breast. There is a relatively low rate of proliferation, indicated by the scattered brown stained nuclei in the cells.
- The bottom panel shows the contralateral irradiated breast. Although the architecture of the lobule terminal ducts appears normal, the proliferation rate is significantly higher.

- The early indications appear to restrict any toxic side effects to being epithelial in nature and, therefore, probably benign. Histologic evaluation showed tissue coagulation, reactive fibroplasia and neovascularization, damaged lobules, acinar degeneration and/or squamous cell metaplasia, and reactive epithelial changes. The depth of consistent total penetration was not more than 900 microns, even in the most severely represented sections. This tissue damage is felt to be thermal necrosis resulting from the cautery unit used in creating the simulated lumpectomy site.

RESULTS: SAFETY

OVERALL

- Evaluation of the clinical pathology data revealed no major abnormalities. None of the changes during the experimental period could be attributed to device complications.
- There were no telangiectasias, fibrosis, or necrosis observed on any section at any time point.
- All acceptance criteria for the gross and histologic evaluation of the mammary sections were met.

ADVERSE EVENTS

- Mastitis was detected in one goat. While it is possible this occurred due to the procedure, there is reason to think there may have been pre-existing subclinical infection in this animal.
- Two goats showed signs of dorsally located, pulmonary hypostatic congestion and one goat had signs of slight pulmonary edema, both of which are consistent with extended dorsally recumbent anesthetic events.

ELECTROMECHANICAL SAFETY

- High voltage transient events, traditionally called 'arcs', are random occurrences in high voltage, high vacuum electronic devices. The arcing of the x-ray sources did not result in any unacceptable or untoward effects in the animals.
- To evaluate the physiologic impact of a catastrophic failure *in vivo*, an x-ray source was purposefully damaged and used to create a catastrophic event (high voltage exposure external to the device). These mock catastrophic failures did not result in any unacceptable or untoward effects in the two animals subjected to such an event because of energy limits designed into the console.

Study Funded by Xoft

The Xoft microTube Flexible X-ray Probe is for investigational use only. FDA clearance pending.

RESULTS: DEVICE PERFORMANCE

OVERALL

- There were no untoward effects directly related or linked to the balloon applicator, source, or radiation treatment in general.

BALLOON CONFORMANCE

- All applicator balloons (test and control) conformed to the resection cavities as expected. Figure 6 shows the treatment and control balloons implanted in one animal.
- No evidence of seroma, hematoma, balloon failure or migration was observed.
- The x-ray probe is shown in four different positions within an implanted balloon during pullback in Figure 7.

Figure 6. X-Ray image of two 3-4 cm spherical balloons prior to delivery of the first fraction.

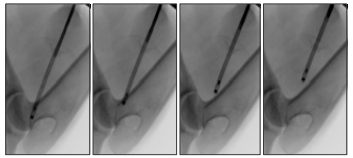


Figure 7. Sequence of x-ray images showing the x-ray probe in four positions within an implanted balloon during pullback.

DOSIMETRY

- Well chamber readings had a broad distribution (Figure 8) reflecting a variation in x-ray source output. The mean value of these individual readings is 74.5 nA. These data with dose delivery time, dose measured in solid water, and tissue results from a prior study were used to estimate the nominal dose per fraction and total dose.
- The total dose delivered was 23, 25, 25, 25 and 26 Gy in the five animals.

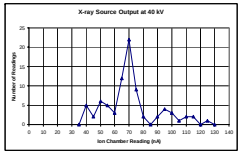


Figure 8. Well chamber readings from each x-ray catheter for each fraction

SUMMARY

- The Xoft microTube balloon applicator with accompanying sources and equipment appears to be safe when implanted in a caprine breast tissue model.
- The imaging demonstrated conformity and satisfactory inflation performance of the device with no evident untoward tissue effects in the surrounding area.
- There were no gross or specific untoward clinical effects during application of radiation or the remainder of the animal's lives.
- The histopathology showed evidence for cell death in all cases that was limited to a small fraction of tissue directly surrounding the applicator. Penetration of tissue damage was within a safe range (below 900 microns). This damage is felt to result from the use of a cautery instrument during tissue resection.

CONCLUSIONS

- Performance of the Xoft microTube Flexible X-ray Probe, balloon conformance and electromechanical safety were satisfactory.
- Procedure tolerance was good. No acute radiation or thermal complications were noted, grossly or histologically.
- The Xoft microTube Flexible X-ray Probe delivered the dose to mammary tissue as predicted from preclinical studies.