EMERGING TECHNOLOGY COMMITTEE

Report on

Electronic Brachytherapy

Electronic Brachytherapy Working Group
Evaluation Subcommittee of ASTRO’s Emerging Technology Committee

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I. PROBLEM DEFINITION

The use of intraoperative radiotherapy has a long history in clinical radiation oncology. Its application has been to deliver single large fractions or a ‘boost’ dose directly in situ to the tumor and/or tumor bed to effectively increase local radiation dose delivery and decrease normal tissue exposure. Over time, there has been considerable experience with IORT in various clinical settings; a significant body of preclinical studies in animals combined with experience in humans has provided guidance for safe and effective use of this approach in general.

IORT using electrons has been the favored approach over orthovoltage beams due to better dose homogeneity, decreased treatment time and less bone absorption attributed to the photoelectric effect. However, orthovoltage IORT has advantages in certain clinical settings and is generally more cost-effective. Electronic brachytherapy devices have recently become commercially available. These devices utilize electronic brachytherapy sources instead of radioactive isotopes. The devices currently on the market produce low-energy radiation at a high dose rate. The major advantages are disposability of the source and applicator after each procedure and a lesser requirement for protective shielding during the procedure.

These devices are currently subject only to clearance by the Food and Drug Administration (FDA) but do not fall under the purview of the Nuclear Regulatory Commission (NRC). The regulatory requirements in individual states are undefined and may vary widely. Reports from the American Association of Physicists in Medicine (AAPM) address calibration and safety measures for radioactive isotopes but do not cover electronic sources. Therefore, there is a great interest in developing standardized dosimetric and regulatory standards for these new devices.

II. DESCRIPTION OF THE TECHNOLOGY

There are currently two devices that fit the category of electronic brachytherapy. The first, the Axxent® Electronic Brachytherapy System (Xoft Inc., Fremont, California), is a system of devices used for delivery of low-energy radiation at a high dose rate. Its primary components include an electronic controller, a miniature electronic X-ray source contained within a flexible probe, and a balloon applicator to apply radiation directly to a tumor bed within the body. The second, The Zeiss INTRABEAM® (Carl Zeiss Surgical Gmbh, Oberkochen, Germany), is a mobile photon Radiosurgery System that porcues a miniature electron beam driven X-ray source.
II. A. Xoft Device

II.A.1. Specifications

The Xoft controller, shown in Figure 1, delivers power to the electronic brachytherapy source and controls the source movement. The source is a disposable miniaturized X-ray tube that measures about 2.2 mm in diameter and has an operating potential of up to 50 kV. It is integrated into a water-cooled, flexible probe assembly, shown in Figure 2(a), measuring 250 mm in length and 5.4 mm in diameter. Details of the X-ray tube located at the tip of the source assembly are shown in Figures 2(b) and 2(c). The source assembly is connected to a high-voltage cable that is directed into the lumen of the applicator and enables the controller to step the source to preprogrammed dwell positions within the applicator. Power to the source reaches a maximum of 15 watts. When the source is active, the radiation output is 0.6 Gy/min at 3 cm from the source axis, as measured in water. During 50 kVp operation, the average of the bremsstrahlung photon spectrum ranges from 26.7 keV to 34.5 keV as the beam passes through 0 to 4 cm of water, respectively, with a maximum photon energy of 50 keV in each case. These energies are similar to those of iodine-125 (27.2-35.5 keV, mean 28.4 KeV). The controller can be set to operate at 50 kV, 45 kV, or 40 kV and has a maximum beam current of 300 μA.

The applicator, shown schematically in Figure 3(a), is a balloon with a radiolucent wall that can be visualized on plain films and computed tomography (CT). At present, spherical applicators with diameters ranging from 3 to 6 cm and a 5-6 by 7 cm elliptical applicator are available. The shaft of the applicator contains three separate lumens. Two ports are designated for inflation of the balloon and insertion of the radiation probe along the treatment pathway. The third port is connected to several drainage holes at the apex and base of the balloon which feed to extrusion lumens that provide clearance from the wound cavity in case of seroma. Figure 3(b) shows the complement of clinical applicators currently available.
Figure 1: Axxent® controller showing the source assembly (a) and the well-chamber (b) used for source calibration.

Figure 2(a): Axxent® source assembly.

Figure 2(b): Close-up of X-ray tube attached to the tip of the source assembly shown in Fig. 2(a).
Figure 2(c): Schematic diagram showing X-ray tube composition: cathode at the proximal end and conical tungsten anode at the distal end.

Figure 3(a): Schematic diagram showing balloon applicator. Three lumens are used: one each for balloon inflation and insertion of the source assembly, and the third for drainage of seroma through two holes on either end of the balloon.
II. A. 2. DEVICE OPERATION

When treatment is intended, a trocar is used to create a pathway for the applicator via a centimeter-sized lateral skin incision. The procedure can be performed at the time of surgery or under local anesthesia in an outpatient suite. A stiff metal obturator is placed into the balloon applicator to help guide it into the cavity. The applicator is then positioned within the breast cavity and inflated with sterile saline. Ultrasound, plain film or CT is used to verify the position of the applicator and ensure that the cavity is filled and the surgical margin conforms to the applicator. The applicator shaft is taped to the external skin of the breast for repeated access to the cavity.

Treatment planning is done in conjunction with CT images using a conventional brachytherapy treatment planning system incorporating parameters describing the electronic source data. Both Varian’s BrachyVision and Nucletron’s Plato treatment planning systems have been validated. Plan details, in the form of source dwell positions and dwell times, are downloaded directly to the controller. Based on the preset treatment plan, the controller manages source movement through the programmed dwell positions by stepping the source back along the shaft in millimeter increments accordingly. The cable can negotiate up to a 15 degree curve, but requires a fairly straight pathway within the treatment region (Turian et al., 2006).

Prior to each treatment, the probe containing the electronically activated source is advanced into the central lumen of the applicator shaft. Each patient is meant to be treated with an individualized source; thus, if more than one patient is under treatment at any given time there must be a system in place to ensure that sources are indexed to the appropriate patient. Once treatment is initiated, the controller moves the source to the
furthest distal point inside the shaft of the saline-filled balloon and stops it when the source comes in contact with the back wall of the lumen. A typical treatment plan requires the source to then be stepped through five-10 dwell positions. The source is encased in the cooling sheath through which water is pumped continuously during treatment to provide cooling. Any malfunction in either the high voltage circuit (including the X-ray tube) or the cooling system results in immediate treatment termination, and parameters of the treatment delivered thus far are recorded.

The treatment time for each fraction is usually less than 10 minutes. The controller contains a display showing the elapsed time, total planned time, time remaining at the current dwell position, and a visual display of the source position.

II. A. 3. SHIELDING

The Xoft device is used in much the same way that current high-dose-rate (HDR) brachytherapy afterloading systems are used in the treatment of early stage breast cancer. A major difference is that the procedure may be done in a minimally shielded room because of the low-energy nature of the x-ray source. A 15-inch flexible drape of 0.4 mm lead equivalent placed over the breast allows other personnel to be in the room with the patient with minimal exposure. A clinical application is shown in Figure 4.

Figure 4: Clinical application of the Axxent® device showing the controller, x-ray source assembly placed into an implanted balloon, and flexible drape used for shielding. A standard wall outlet powers the system.
Measurements have shown that during treatment the radiation exposure is on the order of 15 mR/hour at a typical operator’s location. As an additional safety feature, the device also has the ability to pause or stop treatment at any time since power to the source can be halted via the controller, thus instantly interrupting X-ray production.

II. A. 4. SOURCE CALIBRATION

There is currently no standard from the National Institute of Standards and Technology (NIST) for the electronic source. The Radiation Calibration Laboratory (RCL) at the University of Wisconsin has developed a secondary standard based on measurements from exposure of the source to a free-air ionization chamber and provides calibration certificates for re-entrant well chambers that can be used for field measurements of source air-kerma strength. A calibrated well chamber (HDR-1000, Standard Imaging, Middleton, WI) coupled with a calibrated electrometer (MAX 4000, Standard Imaging, Middleton, WI) are provided with the system and are used to calibrate each source prior to clinical use. Since sources are specific to each patient, the clinic calibration procedure is repeated at least once for each patient that is treated.

II. A. 5. SAFETY AND REGULATORY CONSIDERATIONS

The low-energy radiation aspect of these devices obviates the need for special room shielding and personnel can wear lead aprons and/or patients draped with lead sheets, allowing much less radiation exposure to staff and family. However, the device, which does employ radiation therapy, is not currently subject to regulation by the Nuclear Regulatory Commission (NRC), or state departments of public health. The Conference of Radiation Control Program Directors (CRCPD) is actively considering development of a set of template regulations for consideration by its members for local presentation and possible adoption. Because the device contains no radioactive source, a radioactive materials license is not required. Concepts from AAPM reports have been proposed to guide usage and quality assurance, but there are no reports specifically addressing electronic brachytherapy. There are also no reporting or consequence provisions for adverse medical events.

In states slated for human studies, Xoft is currently working with regulators to determine reporting requirements. In Florida, for example, the company is in discussions with the State of Florida’s Advisory Council on Radiation Protection. Each preclinical testing site will most likely need to provide radiation exposure data to relevant state agencies as part of the license application.
II. A. 6. DOSIMETRIC GUIDELINES AND QUALITY ASSURANCE

The relevant AAPM brachytherapy reports covering operational use of the system include:

- Calibration Laboratory Accreditation (CLA) Subcommittee on source calibration (2004)
- TG-61: Protocol for calibration of kV beams

According to AAPM TG-56, a high-dose-rate remote afterloading system should be subjected to quality assurance measures including: mechanical and radiological safety, positional accuracy to within 2 mm, temporal accuracy and timer linearity, and accuracy of dose delivery within a margin of less than 2 percent.

TG-56 also specifies quality assurance measures for the source calibration and dose distribution. It is recommended that the frequency be based on the radioisotope’s half-life, but this provision is not applicable to electronic sources. The margin of error for source calibration should be less than 3 percent. The dose distribution may be characterized for a single source in water.

AAPM TG-59 outlines the training and responsibilities of the staff, as well as the responsibility for documenting written procedures for applicator preparation, insertion, and localization, treatment plan documentation and approval, and quality assurance procedures and checklists as well as emergency procedures.

Xoft has developed a proposed quality assurance checklist that incorporates some provisions of the TG-56 and TG-59 reports. The CRCPD has formed a task force and a report is being drafted for review.

II. B. ZEISS DEVICE

II.B.1 SPECIFICATIONS.

The second system, The Zeiss INTRABEAM® (Carl Zeiss Surgical Gmbh, Oberkochen, Germany) system is a mobile photon Radiosurgery System (PRS) that produces a miniature electron beam driven X-ray source, Figure 5. The electrons are generated and accelerated in the main unit (Figure 6) and travel via the electron beam drift tube which is surrounded by the conical applicator sheath such that its tip lies at the
epicenter of the applicator sphere (Figure 7). It provides a point source of low energy X-rays (50 kV maximum) at the tip of a 3.2 mm diameter drift tube with a target at the tip emitting a nearly isotropic field of low energy photons (Figure 8).

Figure 5: Miniature X-ray generator INTRABEAM®
II.B.2. DEVICE OPERATION

There are a series of spherical applicators that range in size from 1.5 to 5 cm diameter. The applicators are reusable and biocompatible made of polyetherimide (C37H24O6N2). This has a glass transition temperature of 216 C, a density of 1.27 g/cm³, is biocompatible and radiation resistant. They are cleaned and sterilized prior to use in a patient using a pre-
vacuum steam sterilization process at 132-135 C for 3-4 minutes. Each spherical applicator consists of an applicator ball at the distal end attached to a cylindrical shank, which is open at the proximal end. The Applicator Transfer Function (ATF) takes into account the attenuation and scatter due to a given applicator size. The ATF values have been characterized and tabulated as a function of depth.

Once the applicator size has been selected, the X-ray device is mounted on its stand and inserted in the applicator. An optical interlock system detects the type of applicator attached to the X-ray unit and indicates its proper positioning. The stand and the X-ray device are wrapped in a sterile clear plastic cover per routine sterile surgical techniques, leaving only the already sterile applicator exposed.

The device is inserted into the surgical cavity and the tumor bed is conformed around the applicator sphere. An intraoperative ultrasound is performed to determine the distance of the applicator surface to the skin, to avoid significant skin doses that occur with distances of < 1 cm. The applicator is secured into place by the surgeon using subcutaneous sutures around the neck of the sphere. To measure skin dose, a strip of dosimetric film (Gafchromic) placed in sterile plastic is taped onto the skin where the device is most superficial. Before the X-ray device is turned ON, everyone except the anesthesiologist and the physicist leave the operating room. The radiation received is proportional to the time the machine is switched on and left in situ. The irradiation time is approximately 20-35 minutes.

II.B.3. SHIELDING

As the device emits X-ray quasi-isotropically, any person present in the room when the X-ray is switched ON should be behind a shielded screen. However, the quick attenuation of exposure rate allows treatment to be carried in a standard operating room. No additional shielding is required.

Measurements have shown that during treatment the radiation exposure is on the order of 12-15 mR/hour at about 2 meters from the source. A mobile shielded panel and/or a leaded apron is sufficient to bring the exposure to background level. This allows the anesthesiologist and physicist to stay in the room during the entire procedure. As an additional safety feature, the device also has the ability to pause or stop treatment at any time since power to the source can be halted via the controller, thus instantly interrupting X-ray production.
II.B.4. SOURCE CALIBRATION

A pretreatment verification is carried out within 24 hours of the IORT equipment being required in the operating room. The procedure is based on the manufacturer’s recommendations. The same calibration can be used if two deliveries are scheduled on the same day. The precise dose rate depends on the diameter of the applicator and the beam energy and current. The main items are the X-ray source itself, two ion-chamber measuring devices and an X-ray needle alignment tool. The applicator spheres are kept in the operating room areas. The operating room personnel are responsible for the sterilization and the availability of the applicators for a treatment procedure. The proper balancing of the stand should be verified prior each procedure. The stand must be balanced using the proper procedure if any resistance is felt while holding the device with the break released.

The calibration procedures are described in the PRS400 Radiosurgery Treatment System Operator’s Manual (PN 99200001 Rev: B).

The calibration procedures must include the following steps:

- XRS Probe Straightening: Verification and correction (if required) of the needle alignment.
- Measurements with the Internal Radiation Monitor (IRM) of a count rate.
- Current with the ion-chamber. This value should be corrected for temperature and pressure and compared with the factory ion chamber measurement. The comparison provides the Ion Chamber ratio (IC ratio).
- Measurement of dose rate with the Secondary Dose Monitor.
- The system is put is Standby mode and then turned off.

In the event that the needle is bumped during transport or in the operating room all steps described above must be performed again. Therefore, all pieces of equipment required for those steps must be carried along to the operating room.

The values of the IRM count rate, Ion chamber current, and secondary ion-chamber dose rate should be printed out and included in the patient dose plan. These values will be required for dose planning purpose.

Before each treatment, the performance of the X-ray source must be verified. A medical physicist typically spends 2 hours in the procedure room and the pre-treatment verification requires 1 hour; this amounts to 3 physics-hours per procedure.
II.B.5. DOSE DISTRIBUTION CHARACTERISTICS

The dose is generated by a single source position. The dose distribution is therefore mostly spherical. The radiation has the typical inverse square law behavior \((1/r^2)\). Attenuation in the tissue introduces an additional attenuation factor governed by an approximate inverse linear law \((1/r)\). Therefore the radial dose attenuation decreases as the inverse cubic law \((1/r^3)\).

The Dose Rate in water \(D_o\), in Gy per minute, is calculated by correcting the reference dose rate (provided by the company) using the Ion Chamber ratio \(\text{IC}_{\text{ratio}}\) obtained during the calibration process. The radial dose rate distribution in tissue is calculated from the dose rate distribution obtained in a water phantom without the applicator by multiplication with the so-called applicator transfer functions \(\text{ATF}\), defined as the ratio between the dose rates in the presence and in the absence of the applicator as a function of the radius, \(r\) (distance from the target). For a given Prescribed dose \(D_{px}\) in Gy, the Run-time (in minutes) is obtained with the following equation:

\[
\text{Run-Time} = D_{px} / (D_o \times \text{IC}_{\text{ratio}} \times \text{ATF})
\]

Typical Run-Times vary from 16 to 33 minutes for 2.5 cm and 5 applicators, respectively. The same dose of 5 Gy at 1 cm depth is prescribed for each patient receiving INTRABEAM® for breast cancer treatment.

II.B.6. TECHNICAL CHARACTERISTICS

- X-ray source is outside of the body
- 50 kV peak X-rays emitted from a Gold target (Xoft uses Tungsten resulting in a different spectrum and depth dose curve)
- Max. current 40 µA
- Probe diameter 3.2 mm, length 10 cm
- Fixed dose rate
- Dose rate is monitored online with an Internal Radiation Monitor, i.e. actual dose delivered is always available in case of issues like power breakdown (unlike Xoft)
- High voltage is outside the body (No high voltage cable in the patient)
- Calibration of the device is required before each intervention
- Applicator and source are manually inserted
- Single dose delivery
- Single source position
- Quasi-Spherical dose distribution only: Anisotropy is higher towards the proximal direction due to increased filtration within the model S700 Source.
- Quasi isotropic dose distribution around the tip of the probe due to Automated Beam Centering that ensures that the electron beam spins always in the center of the Gold target
- Dose fall-off more pronounced than any radioactive source currently used clinically.
- Planning does not require imaging
- Variable (discrete) sizes of applicators (diameters from 2.5 to 5 cm in 0.5 cm increment)
- Applicators are re-usable
- Dose prescription: 5 Gy at 1 cm from the surface of the applicator
- Typical treatment last approximately 25 minutes

II.B.7. SAFETY AND REGULATORY CONSIDERATIONS

Similar to the Axxent® device, this device is not regulated by the Nuclear Regulatory Commission (NRC), or state departments of public health. The American Association of Physicists in Medicine (AAPM) has proposed guidelines for similar intraoperative radiotherapy devices, which appear to be relevant here:


The AAPM TG-72 report comprehensively describes and recommends the basic components and expertise necessary for the implementation of an IORT program within the operating room environment. It provides guidelines for radiation protection issues, machine commissioning of items that are specific to mobile electron linear accelerators, and design and recommend an efficient quality assurance program for mobile systems.

The concepts put forth by TG-72 specifically refers to the linac Mobetron® unit, Novac 7®, however, “in general, apply to the installation of new IORT programs using mobile linacs, regardless of manufacturer”. Most of the recommendations regarding procedures are similar to what was followed in practice for installation and use of the Zeiss Intrabeam™ system at the University of California, San Francisco.
III. POTENTIAL FUTURE DEVELOPMENT

III.A.1. PRESENT SCOPE OF USE (Xoft Axxent®)

The date of approval for marketing of the device by the FDA was 12/22/2005 (K050843). At this time, the scope of the FDA’s approved usage has been restricted to postoperative breast cancer treatment. As stated by the FDA: “The Xoft Axxent® Electronic Brachytherapy System is intended to provide brachytherapy when the physician chooses to deliver intracavitary or interstitial radiation to the surgical margins following lumpectomy for breast cancer.”

Following FDA approval, Xoft initiated a 40-patient post-marketing study which will likely finish accrual by the end of 2008. A voluntary registry has also been established by Xoft in coordination with the American College of Radiation Oncology (ACRO) and the American Society of Breast Surgery (ASBS). The registry is planned to include 1,300 patients. According to current projections released by Xoft, at least four sites are now treating patients and at least nine sites will have started treatment by the end of 2007. These sites are or will be utilizing the device to deliver breast brachytherapy treatment.

III.A.2. ANTICIPATED CLINICAL IMPLEMENTATION

Electronic brachytherapy can be delivered in one or multiple fractions. Currently, the fractionation schedule being used in practice resembles that developed for other post-surgical breast brachytherapy applicators that use high-dose-rate radioactive isotopes as sources. The fractionation schedule, modeled after that of the B-39 trial of National Surgical Adjuvant Breast and Bowel Project (NSABP), is comprised of ten fractions of 340 cGy. Two fractions are delivered daily. Confirmatory radiographic imaging is performed at the time of each fraction.

III.A.3. FUTURE POTENTIAL CLINICAL APPLICATIONS

Other indications for the system are currently being investigated. Xoft is currently developing vaginal applicators for use with the electronic controller and source.

Manually controlled variables are the operating voltage of the anode (penetration depth), beam current (dose rate), dwell positions within the applicator, and time at each dwell point. Therefore, the electronic source can be intensity-modulated to mimic the penetration and dose rate characteristics of several isotopes, including iodine-125, iridium-192, and palladium-103. However, the limited penetration of the beam may
contribute to greater dose conformity and higher dose inhomogeneity between surface and depth.

III.B.1.

The INTRABEAM® System was first approved for use by the FDA for intracranial tumors in 1999 and was subsequently approved for whole body use in 2005. The INTRABEAM® Spherical Applicators are indicated for use with the INTRABEAM® System to deliver a prescribed dose of radiation to the treatment margin or tumor bed during intracavity or intraoperative radiotherapy treatments.

The cumulative reported experience worldwide using the INTRABEAM® system to date includes 1,100 patients with brain tumors (primary and metastatic), 1,200 patients with primary breast cancer, and more than 100 cases of varying indications including colorectal cancer, soft tissue sarcomas, head and neck tumors and liver tumors (numbers provided by Zeiss).

The routine application of IORT using INTRABEAM® has included:
1) breast cancer: boost treatment, recurrences in the setting of prior irradiation;
2) brain cancer: boost treatment for primary and metastatic lesions;
3) colorectal cancer: treatment for recurrent tumor;
4) soft tissue sarcomas: boost treatment.

Future plans by Zeiss are reported to expand the clinical applications for this device to include liver lesions, spine tumors and vaginal and skin cancers.

IV. DESCRIPTION OF IMPACT

IV.A.1. PRESENT STATUS OF PRODUCT MARKETING

A survey was commissioned by Xoft at a satellite technology symposium of the annual ASTRO meeting in Denver in 2005. The survey measured radiation oncology professionals’ anticipated acceptance of electronic brachytherapy. About 90 percent of the symposium attendees who responded agreed that electronic brachytherapy is an exciting new technology, and a majority said that once electronic brachytherapy received clearance from the FDA they would be likely to incorporate the technology into their practice.

Philip Z. Israel, M.D., director of The Breast Center in Marietta, Ga., was the first to utilize the Xoft Axxent® brachytherapy system to treat patients at the WellStar Kennestone Hospital in Marietta. Other physicians have
adopted the technology and are serving in educational roles with the company. Peter Beitsch, M.D., director of the Dallas Breast Center, led an industry-sponsored symposium entitled “The Role of the Surgeon in Electronic Brachytherapy of the Breast” at the annual ASBS meeting in Phoenix in May 2007, to discuss best practices for implementation. He is also participating in development of the planned patient registry, which will be administered by ASBS to track patient data and outcomes. Vivek Mehta, M.D., led a satellite symposium at the annual ASTRO meeting in Los Angeles in October 2007, entitled “Electronic Brachytherapy: Putting the Accent on Access.”

IV.A.2. COMPETING COMMERCIALY AVAILABLE PRODUCTS

The Xoft system has multiple components. Similar products can therefore be grouped into 3 main categories:

- Controllers – The closest comparisons would be to high-dose-rate afterloaders produced by Varian and Nucletron Corp.

- Radiation Sources – The best comparisons would be to HDR Ir-192 (as delivered by an HDR afterloader) and the Zeiss/PhotoElectron Corporation Intrabeam™ device.

- Applicators – For the breast cancer indication, there are a number of new applicators on the market, namely Cytyc’s MammoSite®, North American Scientific’s ClearPath™, Cianna’s Strut-Adjusted Volume Implant (SAVI)™, and SenoRx’s Contura™.

IV.A.3. REPORTED PLANS FOR EXPANSION OF CLINICAL USE

Xoft states that a 40-patient post-marketing study in human subjects was initiated by the company following FDA approval, entitled “Post Market Clinical Study to Evaluate the Safety and Performance of the Xoft Radiation Treatment System in Women with Resected, Early Stage Breast Cancer.” Four sites are currently treating patients: Rush University in Chicago; WellStar Kennestone Hospital in Marietta, Ga.; Swedish Hospital in Seattle; and Rhode Island Hospital in Providence, R.I. At least another five sites were expected to have begun treatment with the device by the end of 2007: Mills Health Center in San Mateo, Calif.; the University of Oklahoma; the University of Maryland; Beth Israel Hospital in New York; and Dickstein Cancer Center in White Plains, N.Y. All of these sites are or will be utilizing the Xoft device to deliver breast brachytherapy treatment. The company’s projections are that by the end of the 2007, the 9 clinical sites will have treated approximately 40 patients and accrual to the post-marketing study should be complete.
Additional negotiations with at least ten to fifteen sites are reported to be in progress. A patient treatment registry has also been established by Xoft for 1,300 patients and will include the patients from these additional sites. The plan is to follow a larger number of patients in the registry to assess long-term outcomes.

IV.A.4. REPORTED PRICING (Axxent®)

Multiple patents extend to the controller, source, and balloon. The list price of the basic device, including the controller, one source, and balloon applicator is $196,500. Varian’s BrachyVision™ Treatment Planning System, preloaded with the electronic source characteristics, is distributed with the Xoft system. The BrachyVision™ treatment planning system costs an additional $91,500. Several other accessory items, such as a flexible silicone-based drape for radiation shielding and physics quality assurance tool kit are available. Appendix 1 shows detailed pricing for the individual components of the device.

PRODUCT SUMMARY AND PRICE LIST

Effective June 14, 2007 – Courtesy of Xoft Inc.

- Axxent® Controller with Physics Accessories Kit $189,000
- Axxent® HDR X-Ray Source $5,000
- Axxent® Physics Accessories Kit $25,000
- Axxent® Flexishield $250
- Axxent® Cooling Tubing Set $100
- Axxent® Balloon Applicator Kits:
  - 3-4cm Spherical (30-45 cc) $2,500
  - 4-5cm Spherical (45-75 cc) $2,500
  - 5-6cm Spherical (65-130 cc) $2,500
  - 5x7cm Elliptical (90-125 cc) $2,500
  - 6x7cm Elliptical (120-160 cc) $2,500
- Varian BrachyVision™ Treatment Planning System $91,500
- Axxent® Controller Service Platinum Comprehensive Coverage
  - Point of sale 2-year contract $18,590/year
IV.B.1. SIMILAR PRODUCTS (Zeiss)

Other IORT devices that have some similar features with the Zeiss INTRABEAM® are compared in Table 1.

IV.B.2 Pricing (Zeiss) – courtesy of Zeiss, Inc.

The present cost for the entire operational unit is $400,000 USD.

Table 1. Comparison of IORT units and Brachytherapy Devices

<table>
<thead>
<tr>
<th>Issues</th>
<th>Zeiss INTRABEAM® IORT</th>
<th>Mabetron® IORT</th>
<th>Novac-7® IORT</th>
<th>Mammosite®</th>
<th>XOFT Axxent®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost Per Unit</td>
<td>$400,000</td>
<td>$1,200,000</td>
<td>N/A</td>
<td>$400,000 (includes afterloader), $2500 for disposable catheter, does not include cost for seeds</td>
<td>$160,000 for Generator, $2500 for disposable source, $2500 for disposable catheter</td>
</tr>
<tr>
<td>O.R. Set Up Time</td>
<td>10 min.</td>
<td>45 min.</td>
<td>One Day</td>
<td>not used in OR</td>
<td>not used in OR</td>
</tr>
<tr>
<td>Shielding (people)</td>
<td>Aprons - Screen</td>
<td>Must Leave Room</td>
<td>Must Leave Room</td>
<td>O.R.- none/requires Brachy room with aprons</td>
<td>aprons - screen</td>
</tr>
<tr>
<td>Capital Expense - Install</td>
<td>None</td>
<td>$25,000 per O.R.</td>
<td>$200,000 per O.R.</td>
<td>HDR Shielded Room Expense</td>
<td>TBD</td>
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<tr>
<td>Energy Source</td>
<td>50KVP Xrays</td>
<td>LINAC electrons 4-12 MeV</td>
<td>LINAC electrons 3-9 MeV</td>
<td>Irridium Ribbon</td>
<td>50 KVp x-rays</td>
</tr>
<tr>
<td>Delivery of Treatment Time, incl procedure set up</td>
<td>1 Session up to 45 minutes during surgery</td>
<td>1 Session up to 45 minutes during surgery</td>
<td>1 Session up to 45 minutes during surgery</td>
<td>10 Fractions of 30 Min. over 5 days Post-Op Fractions</td>
<td>10 Fractions of 30 Min. over 5 days Post-Op Fractions</td>
</tr>
<tr>
<td>Installed Units World Wide</td>
<td>20</td>
<td>24</td>
<td>7</td>
<td>na</td>
<td>None</td>
</tr>
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<td>Installed Units U.S.</td>
<td>5</td>
<td>8</td>
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<td>na</td>
<td>None</td>
</tr>
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<td>Applicators</td>
<td>Yes(8) Reusable</td>
<td>Yes (3) (Circular 3 to 12 cm in 0.5 cm increments with flat, 15 and 30 degree bevels; rectangular 8x15 cm)</td>
<td>None</td>
<td>Catheter Balloons</td>
<td>Disposable</td>
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<td>Treatment Sites</td>
<td>brain, skin, colorectal, vaginal wall, spine, breast, prostate</td>
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<td>skin, colorectal, vaginal wall, spine, breast, abdominal cavity, pelvis, stomach, pancreas, head &amp; neck</td>
<td>Breast</td>
<td>Breast and Cervix only</td>
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<tr>
<td>FDA/CE Mark</td>
<td>Yes - whole body</td>
<td>Yes -</td>
<td>Yes -</td>
<td>Yes</td>
<td>YES</td>
</tr>
<tr>
<td>Issues</td>
<td>INTRABEAM® IORT</td>
<td>Mobetron® IORT</td>
<td>Novac-7® IORT</td>
<td>Mammosite®</td>
<td>XOFT Axxent®</td>
</tr>
<tr>
<td>Disposables</td>
<td>drapes, shields</td>
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<td>none</td>
<td>Catheter</td>
<td>Yes, Catheter, Source</td>
</tr>
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<td>Single Field Treatment Size</td>
<td>1 up to 6cm volume</td>
<td>5cm up to 10 x10 cm field; 12 cm circular, 8x15 cm rectangular</td>
<td>5cm up to 10 x 10 cm field</td>
<td>3 to 5 cm volume</td>
<td>1 up to 6cm volume</td>
</tr>
<tr>
<td>Applicator or Catheter Displacement</td>
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<td>None</td>
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V. EVALUATION/SUMMARY OF RESULTS OF EXISTING STUDIES

PRECLINICAL DATA

Mature clinical data has not been published using the Xoft device. However, a number of small-scale industry-sponsored studies have addressed the characteristics of the produced radiation, safety considerations related to the device, and the feasibility of the device for clinical use.

V.A.1. Relative biological effectiveness of radiation of a high dose-rate and low energy

Brenner et al. first investigated the relative biological effectiveness (RBE) of the low-energy, high-dose-rate radiation produced by miniaturized electronic sources. This group determined that the RBE could be considerably above unity compared to cobalt or iridium sources, based on an $\alpha/\beta$ ratio of 8 Gy to assess early responding endpoints. The group cautioned that dose rate, total dose, and depth could produce clinically relevant effects in the RBE and should be taken into account in treatment planning (Brenner, 1999). However, Fowler et al. re-examined this question specifically addressing the scenario of the Xoft device, assuming an $\alpha/\beta$ ratio of 3 Gy to account for late reactions such as breast fibrosis. The effective RBE was calculated for a range of fraction sizes comparing high-energy to low-energy radiation and accounting for changes in the dose rate. The group estimated the RBE to be approximately 1.3. The Fowler group also proposed that the steep dose gradient with distance would allow changes of 1-2 mm in the surface prescription dose that would obviate changes of 10-20 percent in RBE (Fowler, 2004).
V.A.2. Dose distributions obtained with variable energy of the source

Unlike radioisotopes, the kVp of the anode within the electronic brachytherapy source must be specified, and small changes in the kVp will alter the produced energy spectrum. Therefore, brachytherapy treatment planning is more complex, because of the need to specify the operating kVp and dwell time at each dwell position. This greater complexity may offer dosimetric advantages in achieving improved conformity of the dose distribution.

Silvern et al. (2004) authored two computer programs, one calculating reference point doses achieved with a set of defined kVp and dwell time parameters, and the other determining an optimized kVp and dwell time at each dwell position to achieve the desired reference point doses while respecting priority-weighted constraint points set under tolerance doses input by the user. These programs were used to evaluate the Xoft source and dosimetrically compared to plans developed using a Varian CadPlanBT RTP system with a VariSource Ir-192 source. Superior dose conformity was noted for a linearly stepped source, a gynecologic implant, and a three catheter planar implant. The effect was primarily due to the higher energy of the Ir-192 source, resulting in greater penetration compared to the electronic source. However, the group noted that for achieving homogeneity between proximal and distal dose points separated by greater depth, Ir-192 could provide a better result than the electronic source.

V.A.3. Application of TG-43 formalism to the Xoft brachytherapy source

Rusch and Rivard (2004) evaluated the dosimetric parameters of the Xoft brachytherapy source and concluded that it may be characterized within the updated TG-43 protocol with minor modifications. Measured source performance agreed with predictions to better than 30% for operation at 40 kVp. The measured microTube X-ray source operating at 40 kVp had an air kerma strength of approximately 810 Gy·cm²·h⁻¹ when scaled to a beam current of 0.3 mA, which is twice that of a 10 Ci Ir-192 source. The measured dose rate constant at 40 kVp was 0.53 cGy·cm²·h⁻¹.

Rivard et al. (2006) published their characterization of the in-water dosimetry parameters using the Xoft source. Using a high-purity germanium detector to measure photon spectra, these doses were compared to spectra derived using Monte Carlo simulations. The conclusion was that for operating voltages of 40 kV, 45 kV, and 50 kV, agreement of measurements with calculated Monte Carlo values was within 2 percent. The source exhibited depth dose behavior similar to
established low-energy photon sources such as iodine-125 and palladium-103 but with capability for variable rates and penetration.

Chiu-Tsao et al. (2004) established a methodology for measuring dose distributions using radiochromic film dosimetry. A series of calibration films was irradiated with doses ranging from 1 to 60 Gy. The source was set to operate at 40 kVp and 100 μA. Net optical density was related to dose based on miniature ion chamber measurements and Monte Carlo simulations. The dose distribution of the Xoft source was then evaluated using the calibration curve. Subsequent experiments (Chiu-Tsao et al., 2007) demonstrated that two-dimensional dosimetry using the radiochromic film could be used to determine reproducibility of dose distributions and compatibility with TG-parameters.

Three-dimensional volumetric analysis has been performed by Axelrod et al. (2006) using point-by-point comparisons to determine absolute and percent dose differences. Histogram-based error analysis was carried out on a per-source basis and as an average.

Monte Carlo modeling of the Xoft source radiation has been validated by Rusch et al. (2005). Monte Carlo results agree with measured results for radial dose and anisotropy functions to within 10 percent.

V.A.4. In vivo clinical feasibility in a Nubian milk goat mammary model

Rieke et al. (2004) conducted an in vivo test of the Xoft device using five Nubian milk goats. Each animal had applicators placed bilaterally in each udder; one udder served as a control and the other received 10 fractions of 3.4 Gy at 1 cm depth over the surgical margin, delivered over 5 to 6 days. The device was set at 40 kVp and 300 μA. Histologic analysis showed increased apoptosis (ApopTag S7101 kit, Chemicon International) at 1 hour to 5 days after irradiation and increased proliferation (PCNA, ARK Run kit, DAKO) confined to the ductal epithelium at 13-14 days after irradiation. Histologic evaluation showed a depth of consistent total penetration of not more than 900 microns, consistent with thermal necrosis from surgical electrocautery. Device performance was assessed by LiF thermoluminescent detectors and MOSFET (Thomson-Nielsen MOSFET 20 Patient Dose Verification System). Well chamber readings showed a broad distribution reflecting variation in source output, with a total dose to the five animals ranging from 31.6 to 36.9 Gy. Satisfactory balloon conformance was judged by sequential x-ray images with no evidence of seroma, balloon failure, or migration. No acute radiation or thermal complications were noted, although one goat developed mastitis and three goats developed mild pulmonary congestion and edema related to the dorsally recumbent position during anesthesia. Safety was further assessed.
by intentional damage resulting in a high voltage exposure in two animals; the energy limits of the console prevented untoward effects in the animals.

The effect of thin lead shielding was assessed in the in vivo study performed by Rusch et al. (2005). Goats were used as test subjects for the 0.4 mm lead equivalent drape. Without shielding, the exposure rate operating at 50 kV was 2270 mR/hour for all averaged in-plane and above-plane readings. A properly installed flexible shield lowered the maximum exposure at any point to 43 mR/hour, and readings behind the portable operator’s shield had a maximum of 0.13 mR/hour. At 40 kV operation, the maximum exposure was 3.7 mR/hour using the shield with an average of 1.3 mR/hour. At this energy, all readings behind the portable operator shield were undistinguishable from the background.

This experiment was repeated by Francescatti et al. (2006) in four additional goats. Two goats received ellipsoidal balloon applicators. One balloon required a 5 cm³ supplemental filling. A flexible lead shield was used over the treatment area and was found to reduce the radiation levels around the animals by at least 100-fold. Utilizing the proposed method of Axelrod et al. (2006) to determine skin dose using MOSFET, skin dose was measured at less than 3 Gy during each fraction. Minor infections were treated in two goats with antibiotics.

V.A.5. Stability of X-ray exposure during simulated device operation

Burnside et al. (2007) evaluated the stability of the Xoft device’s output using a simulated breast brachytherapy treatment in a supine female body phantom. During each fraction, exposure rate was monitored using a calibrated Victoreen Model 451B ion chamber survey meter positioned 10 cm below the phantom. Exposure rates varied from 0.1 to 0.55 R/hour. Standard deviations from the average exposure rates ranged from 0.5 percent to 2.9 percent with an average over 50 fractions of 0.9 percent.

Stability of the source output was also evaluated in the Nubian goat model by Rieke et al. (2005) using a similar ion chamber method. Four goats received implants and were treated to a prescription dose of 34 Gy in 10 fractions at 1 cm past the cavity margin. Radiation levels were recorded at 1 second intervals during the treatments and were analyzed for dose rate fluctuations. The standard deviations from the average dose rates varied by 1.2 percent for the shortest treatments at 50 kV to 3.7 percent for the longest treatments at 40 kV.

V.A.6. Manufacturing standards for commercial source production

Axelrod et al. (2007) outlined the testing that will be used by Xoft in production of the sources. The specifications include: azimuthal
asymmetry $\leq 7$ percent, normalized polar anisotropy in two orthogonal planes $\leq 0.10$ of the TG-43 reference, and depth-dose behavior within 0.03 of the TG-43 reference. In addition, when cycled on and off, all sources must reproduce their previous output within 2 percent, with an average standard deviation of $\leq 2$ percent during the “on” portion of the short cycles. During the 20 minute “on” period, the drift (maximum deviation from start) measured over four 5-minute intervals is $\leq 3$ percent, and the noise (standard deviation of 0.5 second readings) at 10 second intervals is $\leq 0.25$ percent.

V.A.7. Design deficiencies identified in preclinical studies

In the course of preclinical testing, several issues were raised about possible design deficiencies by investigators at Rush University (Turian et al., 2006). A redesigned X6 system will be ready to release early next year and will address several concerns. In the X6 version, a redesigned arm will prevent the source from being displaced from its nest, and the source attachment clip will be less fragile. The source travel distance remains a maximum of 7.5 cm; this travel distance will be lengthened by Xoft only should other medical indications for the device arise necessitating such a modification. One episode was reported in which there was an interlock failure, resulting in X-ray generation but no water flow in cooling tube; this failure has not been observed again and the company considers it a non-reproducible error.

Further market research will determine the need for pressure and temperature gauges to be installed on the device. The company is not ready to release a physics-based mode of operation, in part due to the required negotiations that would take place with third-party vendors. In response to this feedback, the displayed pressure measurement has been amended to show units of mmHg, and a physics kit is available including a shielded test fixture and 2 marker catheters, to allow for a variety of tests and measurements.

V.A.8. Inaccuracies in turn-on dose time when starting treatment

Rusch et al. (2007) reported a proposed means for adjusting for inaccuracy in dose calculation due to turn-on time. At the first dwell position, the treatment timer starts after the source has ramped-up to full operating voltage and beam current (50 kV, 300 $\mu$A), so planned dose-delivery time does not account for a small “turn-on” dose. For subsequent dwell positions, the timer starts when the source begins moving to the next dwell position so elapsed time includes the transit time. The source remains on during the time between dwell positions, typically 0.7 seconds for a 0.5 cm step. Dose contribution during transit was estimated using Varian BrachyVision™ by subtracting the transit time from the second and
subsequent dwell positions, then adding extra dwell positions at midpoints between original positions with times equal to the transit time. The composite turn-on dose profile from Monte Carlo results was equivalent to 5 seconds of additional time at the first dwell position with source operation at 38 kVp or approximately 2 seconds of additional time at 50 kVp. This corresponds to < 0.5 percent of a typical treatment time.

Whether or not transit time is accounted for, the planned doses at prescription points 1 cm outside of a typical balloon agree to within an average of 0.1 percent with a standard deviation of 0.2 percent. The authors suggest that turn-on dose may be approximated in treatment planning by adding two seconds to the first dwell time and that dose during source transit may be ignored when using a balloon applicator for APBI.

V.A.9. Dosimetric comparisons of Xoft Axxent® to other forms of breast brachytherapy

Dickler et al. (2007) published a comparison of the accelerated partial breast irradiation devices. The study population consisted of 15 Rush University Medical Center patients who were treated with MammoSite® balloon brachytherapy based on iridium-192. These patients’ computed tomography scans were used to replan the treatment using physics parameters specific to the Xoft x-ray source. Plan optimization was carried out on PLATO software (Nucleotron, Netherlands). In the Xoft plans, an additional dwell position was placed at the proximal end of the catheter to compensate for the decreased dose along the axis of the catheter.

In target volume coverage, the systems seemed similar; the volumes of the planning treatment volume that received 90 percent (V90, 3060 cGy) or 100 percent (V100, 3400 cGy) of the dose were not statistically different. However, a significant difference was found in the volume of high-dose regions. Significantly less volume received 150 percent, 200 percent, and 300 percent of the dose in the MammoSite® plans as opposed to the Xoft plans. The mean doses for MammoSite® and Xoft, respectively, were: V150 (5100 cGy), 41.8 percent versus 59.4 percent; V200 (6800 cGy), 11.3 percent versus 32.0 percent; V300 (10,200 cGy), 0.4 percent versus 6.7 percent. The authors caution that the hot spots resulting in the Xoft plans could pose an increased risk of fat necrosis. The Xoft plans also resulted in significantly greater dose to normal tissue structures, particularly to the normal ipsilateral breast tissue and the heart.

Smitt et al. (2007) published a description of dose-volume data comparing coverage of the planning target volume (PTV) achieved with the Xoft source compared to the published data for iridium-192 source delivered within the MammoSite® device or as an interstitial multicatheter implant.
In order to achieve 90 percent coverage of the PTV using the smaller Xoft applicator sizes, the volume receiving 200 percent of prescribed dose (V200) was close to that reported to be at increased risk of fat necrosis in a previous study of multicatheter interstitial iridium-192 implant (Wazer et al., 2006). The authors concluded that higher doses may be delivered to the tissues near the surface of the balloon in comparison with iridium-192.

V.B.1. RADIobiological considerations

There is a significant body of literature that addresses the clinical efficacy of single large fraction radiotherapy delivered via IORT for various organ sites. The central radiobiologic considerations of IORT have been: 1) single fraction vs. multiple fractionation schedules and early and late reacting tissues; 2) dose-rate effects; 3) organ tolerance. This literature is beyond the scope of the present report, however, provides basic clinical guidelines in terms of organs and tolerance doses for the safe application of IORT in general.

With respect to the Zeiss PRS system, there have at this time been two published studies that address specific aspects of the radiobiology of this device. Both are by Herskind et al. The first (2005) provides a model of the distribution of RBE around the spherical applicators for single dose treatment. It addresses specific features associated with using PRS that influence radiobiologic considerations including 1) the radiation quality of 50 kv source (RBE increases with decreasing photon energy), 2) the steep dose gradient around the source 2) prolonged radiation delivery associated with the PRS system (20-35 minutes). The authors used a modification of the linear-quadratic formalism used to calculate RBE as a function of dose for different low-energy X-ray spectra (Brenner, 1999) to calculate RBE values as a function of dose and treatment time. Their main findings were that radial depth-dose curves became shallower with increasing applicator size, and that the RBE varied between the surface and 20 mm depth according to applicator size and treatment time. Assuming a half-life of 15 minutes for recovery from sublethal damage, the RBE ranged from 1.28-2.21 for the 3 cm applicator and 1.20-1.98 for the 5.0 cm applicator.

In a subsequent study, Herskind et al studied the effect of simultaneous induction and repair of sublethal damage associated with prolonged treatment time. They used the linear quadratic model, which accounted for treatment time by multiplying the quadratic coefficient with the Lea-Cathcheside time factor. Based on these models and clonogenic assay experiments in hamster fibroblast cell line v79, they conclude that simultaneous radiation damage and repair occurred with protracted treatment time for radiation qualities with RBE’s greater than 1, and that half-time of repair was approximately 15 minutes.
V.B.2. TOXICITY

To date, only acute toxicity and efficacy data associated with INTRABEAM® as a boost treatment for breast cancer has been published. One report describes acute toxicity in 84 patients at a single institution who received lumpectomy and immediate 20 Gy IORT prescribed at the applicator surface (Krause-Tiefenbacher et al, Onkologie 2006). Toxicities were prospectively documented using EORTC criteria. In general, treatment was well tolerated without any grade 3-4 toxicity. 

Acute effects 1 week after IORT included wound healing problems (2 percent), grade 1-2 erythema (3 percent), palpable seroma (6 percent) and mastitis (2-4 percent). At four weeks after IORT, there was grade 1 erythema (6 percent), induration at the tumor bed (5 percent), mastitis (4 percent) and hematoseroma (14 percent). 

Another published report summarized local recurrence data from five institutions comprising 321 patients who received IORT as a boost using INTRABEAM® followed by whole breast irradiation (Vaidya et al, IJROBP 2006). The patients had mostly T1-2 tumors, and 29 percent had axillary node positive disease. After primary surgery, IORT was delivered to 5-7 Gy at 1 cm depth, followed by whole breast external beam radiotherapy. One hundred sixty four patients had a minimum of 2 years of follow-up (range 3-80 months). The estimated five year Kaplan-Meier actuarial local recurrence rate was 2.6 percent.

Two studies describing experience treating patients with brain tumors using INTRABEAM® have been published. Takakura and Kubo (2000) treated 76 brain tumors (55 malignant gliomas, 11 metastases) with the INTRABEAM® device following biopsy or excision. They report 2-year survival rates of 89 percent among 18 patients with anaplastic astrocytoma and 42 percent among 19 cases of GBM, which compared favorably to the results reported by the Japanese Brain Tumor Registry (77 percent and 21 percent, respectively. Another group from Massachusetts General Hospital (Curry et al 2005) described experience after treating 72 metastatic brain tumors treated in 60 patients. They report local control of 81 percent of lesions at a median of six months follow-up, which was comparable to results achieved with resection and stereotactic radiosurgery.

Finally, Algur et al provided a preliminary report (abstract only) from experience in 24 patients with locally advanced or recurrent colorectal cancer treated with INTRABEAM® at the Cleveland Clinic. Eleven patients had adherent tumor. They concluded that use of INTRABEAM® IORT was relatively safe and did not increase the length of hospital stay in these difficult cases.

Ongoing clinical trials using the INTRABEAM® system include:
1) A randomized international multicenter trial, ‘TARGIT’, designed to determine whether a single dose of IORT delivered using INTRABEAM® is equivalent to conventional fractionated whole breast irradiation for highly selected patients with relatively low risk early stage invasive breast cancer. Currently, 17 sites have enrolled more than 900 of the target accrual goal of 2,200 patients.

2) A dose-escalation study of pediatric gliomas is ongoing at the Chicago Children's Hospital.

VI. IDENTIFICATION, ANALYSIS AND EVALUATION OF CONSEQUENCES OF NON-USE

Advantages of EBT over existing technologies are as yet unproven in terms of efficacy or patient outcomes. Viable and tested treatment methods are available for the intraoperative environment and include electron beam IORT and HDR. Additionally, treatment for accelerated partial breast irradiation is also currently available in the form of external beam radiotherapy and via HDR (MammoSite®). The aforementioned modalities require licensed, qualified, authorized individuals to oversee the process and deliver the treatments. Additionally, use of these modalities requires a properly shielded facility.

VII. POSSIBLE IMPACT

The impact of clinical use of electronic brachytherapy (EBT) could be far-reaching and if used improperly, potentially harmful to patients. As was noted in the technical sections of this report, EBT is currently an unregulated treatment delivery modality for cancer therapy, with minimal clinical data available from small single institution studies, none with any significant follow-up. The EBT devices currently commercially available propose usages analogous to the still investigational HDR accelerated partial breast irradiation (APBI) technique. EBT is currently subject only to medical device review by the FDA, which reviews the safety and effectiveness of the device per a standard that does not assess efficacy, outcomes, or potential clinical applications. As the devices do not contain any radioactive source, they are not subject to regulation by, or user standards for radioactive devices, as overseen by the NRC. Neither are the devices regulated by state public health departments. Inappropriate use of these devices by a medical practitioner, or potentially non-medical personnel, who is not properly trained in their use or who uses them in inappropriate circumstances may lead to patient harm.

The doses for various EBT applications used are typically hypofractionated (single large fraction or several large dose fractions), as extrapolated from other radioactive source applications, which may or may not be appropriate. Although the source is low energy, the radiation dose per fraction is very high and with a corresponding high dose rate, there is potential for patient injury similar to the
types of injury that can occur with HDR radioisotope brachytherapy. There is also the potential for electrical or heat injury to patients that is not inherent in HDR therapy. As with HDR isotopic brachytherapy, the application of EBT leaves little room for error as only one or very few fractions are delivered, so precision and accuracy are critical.

There are currently no accepted calibration standards for EBT. Therefore, there can be large uncertainties associated with absorbed dose measurement at low energies. This means that different centers could potentially deliver different doses of radiation, even if the prescriptions are the same. Moreover, the impact of tissue composition heterogeneities on absorbed dose can easily add 20-30 percent uncertainties to absorbed dose estimates. In addition, the dose rates can vary between and during applications. Accepted quality assurance standards do not yet exist, so individual centers could inadvertently admit systematic errors in calibration or treatment delivery processes. While the AAPM has published task group reports on the recommended procedures for brachytherapy dosimetry, high dose rate treatment delivery and calibration and use of intraoperative devices, there is no state or federal requirement that these guidelines be adhered to when using EBT devices. In the few theoretical studies evaluating RBE (radio-biologic equivalence) for these devices, described earlier in this report, the RBE varied widely between 1.20 and 2.21 depending on applicator size and other factors. Dose fractionation schemes have varied widely. The clinical impact of the rapid dose fall off is unknown. Finally, the effects of EBT on tumor and normal tissues are not well understood, given the paucity of clinical studies.

The Xoft device is currently solely approved for partial breast brachytherapy, which is analogous to Ir-192 HDR brachytherapy techniques that have been available only since 2002. Accelerated partial breast irradiation (APBI) with HDR brachytherapy itself is an experimental modality that is currently the subject of ongoing randomized trials, such as the RTOG 0413/NSABP B39 trial and the TARGIT trial, comparing its efficacy to conventional whole breast irradiation. It will be several years before any results of these phase III studies are published.

As APBI is itself an investigational technique, using EBT to deliver APBI could also be considered as investigational. The RBE calculations for these devices suggest the RBE may be only 1.3, and dose comparisons to HDR sources are not as yet validated. Such calculations are theoretical, and must be validated by clinical studies. Since the kVp must be specified, unlike a fixed energy for any given day of treatment with HDR sources, the energy spectrum, and ultimately the dose calculation, may be altered by small changes in kVp, increasing the complexity of brachytherapy treatment with EBT relative to HDR.

The **Zeiss INTRABEAM®** device is currently used for intraoperative brachytherapy (IORT) applications for low energy treatment, primarily postoperatively for intracranial tumors and after lumpectomy for breast cancer, but also a variety of other body applications. In small published reports,
intraoperative doses have varied widely, between 5 and 20 Gy per single fraction at different depths. In some jurisdictions no user regulations are in place, so there is no requirement for a radiation oncologist to be involved in the procedure, although a physicist is typically required to perform pre-treatment calibrations and intraoperative monitoring. Therefore, intraoperative EBT could potentially be performed by a surgeon or other personnel who have limited or no expertise in radiation treatment of cancer, brachytherapy principles, dose delivery principles or normal tissue tolerances. The complexities of dose gradient, RBE and fractionation principles may be unfamiliar to professionals outside of the field of Radiation Oncology. This situation could lead to inappropriate patient selection, inaccurate or technically inadequate treatment delivery and poor patient outcomes; both in terms of added toxicity and poorer cancer control.

The manufacturers of these devices have plans to expand the sites for treatment. INTRABEAM® already has approval for all body applications, and is developing applicators for liver, spine, skin and gynecologic cancers. Xoft only currently has approval for breast applications, and is developing applicators for gynecologic cancers. Many of these new sites require special expertise in brachytherapy techniques, especially gynecologic cancers. Hypofractionated treatment of many sites, but in particular brain and spine, require detailed knowledge of normal tissue toxicity in order to avoid potentially debilitating or life-threatening treat-related toxicity.

There are potential therapeutic advantages inherent in the low energy EBT device compared to HDR sources. The primary advantage is the low energy obviates the need for special room shielding and personnel can wear lead aprons, or patients can be draped with lead sheets, allowing much less exposure to staff and family and less expense to the facility for special shielding in the clinic. There is greater potential for dose modulation due the ability to specify kVp. The dose intensity may be modulated to mimic a variety of HDR sources, although the beam has more limited penetration characteristics. EBT may provide less anisotropy than single dwell HDR devices. However, properly trained professionals are best able to take advantage of any potential treatment planning advantages and to assure appropriate administration in a safe manner.

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