ACCELERATED PARTIAL BREAST IRRADIATION USING NON-INVASIVE IMAGE-GUIDED BREAST BRACHYTHERAPY (ACCUBOOST) FOR EARLY STAGE BREAST CANCERS: A TOXICITY ASSESSMENT

Principal Investigator
Jaroslaw T. Hepel, M.D.
Department of Radiation Oncology
Rhode Island Hospital

Co-Principal Investigator:
Theresa A. Graves, M.D.
Department of Surgery
Rhode Island Hospital

Sub Sites:
Dr Sandra Sha
Watson Clinic Lakeland FL

Dr Ann Pittier
Dr Dean Mastras
Tacoma/Valley Radiation Oncology Centers and Peninsula Radiation Oncology Centers

Coordinating Center
Kayla Rosati, EdM
BrUOG Manager of Operations
Brown University Oncology Research Group
233 Richmond Street
Providence RI 02903
401-863-3000
401-863-3820 (fax)
Kayla_Rosati@brown.edu

Mailing address:
Division of Biology & Medicine
Brown University
Box G-R001
Providence RI 02912

CONFIDENTIAL
The information contained in this document is regarded as confidential and, except to the extent necessary to obtain informed consent, may not be disclosed to another party unless law or regulations require such disclosure. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.
Protocol: 01/29/11

Treatment Schema

Breast conserving surgery

Eligibility Criteria

Ineligibility Criteria

Candidate for study?

YES

NO

AccuBoost APBI 34.0Gy

Standard Radiation therapy

Evaluation

Primary:

Acute and intermediate toxicity

Secondary:

Cosmesis

Local recurrence
## Table of Content

1. Purpose  
2. Objectives  
3. Introduction  
4. Background  
   4.1. Standard adjuvant whole breast radiotherapy  
   4.2. Accelerated Partial Breast Irradiation (APBI)  
      4.2.1. Rationale  
      4.2.2. Techniques  
      4.2.3. Expertise within the Brown University Oncology  
      4.2.4. Results and current status  
   4.3. AccuBoost: Non-invasive image-guided breast brachytherapy (NIBB)  
      4.3.1. Definition  
      4.3.2 Rationale  
      4.3.3. AccuBoost dosimetry and clinical results  
5. Study population  
   5.1. Eligibility criteria  
   5.2. Ineligibility criteria  
6. Treatment  
   6.1. CT simulation  
   6.2. Immobilization and imaging  
   6.3. Applicator selection and positioning  
   6.4. Dose and fractionation  
   6.5. Treatment Delivery  
7. Assessments and Toxicities  
   7.1. Endpoints  
      7.1.1. Primary endpoints  
      7.1.2. Secondary endpoints  
   7.2. Toxicity evaluation  
      7.2.1. Early and intermediate toxicity  
      7.2.2. Serious Adverse Event (SAE)  
      7.2.3. Cosmetic outcome  
8. Response Assessment  
   8.1. Methods of measurement  
   8.2. Breast recurrence  
   8.3. Regional recurrence  
   8.4. Metastases  
9. Schedule of Evaluations (Study Calendar) and Data Collection  
   9.1. Patient inclusion  
   9.2. Data entry  
      9.2.1. Data required at time of registration  
      9.2.2. Data required at completion of AccuBoost APBI treatment  
      9.2.3. Data required at each follow up visit  
      9.2.4. Photographs
10. Statistical consideration
11. Patient Registration
12. Adverse Reaction Reporting
   12.1. Definitions
   12.2. Monitoring of Adverse Events and Period of Observation
   12.2.1. Pregnancies
   12.3 BrUOG Adverse Event Reporting Requirements
   12.4 Reporting requirements and procedures
   12.5 Assessing Causality
   12.6 Types of Report
   12.7 BrUOG Responsibility Regarding Reporting
   12.8 Safety Reporting for IND Holders
13. Study withdrawal
   13.1. Patient withdrawal
   13.2. Lost to follow-up
   13.3. Withdrawal due to physician decision or medical reason
14. Regulatory and ethical issue
   14.1. Protection of Human Subjects
   14.2. Compliance with the Protocol and Protocol Revisions
   14.3. Protocol amendments or changes to study conduct
15. Data Monitoring/Quality Assurance/Record Retention
   15.1 Good Clinical Practice
   15.2 Patient Confidentiality
   15.3 Protocol Compliance
   15.4 On site Audits
   15.5 Premature closure of study
   15.6 Record Retention
   15.7 Data Protection
   15.8 Responsibilities of the Sponsor
   15.9 Source Documents Requirements
   15.10 Use and Completion of Case Report Forms(CRF’s) and additional Requests
16. Data Safety and Monitoring Board.
17. References
18. Appendices
1. Purpose
The purpose of this study is to evaluate the rate of early and intermediate toxicity related to the AccuBoost System for delivery of APBI in women with resected, early stage breast cancer.

2. Objectives
(1) The primary objective is to evaluate and report the rate of early and intermediate toxicity.
(2) The secondary objectives are to assess and report:
   - The rate of ipsilateral breast local recurrence;
   - The cosmetic outcome.

3. Introduction
Whole breast radiation is the standard technique for delivering adjuvant radiation following breast conservation surgery. Partial breast irradiation reduces the volume of breast tissue that receives radiation and decreases overall treatment time. The ongoing United States cooperative group study, NSABP B-39/RTOG-0413 is a randomized phase III of standard comparing adjuvant whole breast irradiation versus partial breast irradiation following breast conservation surgery. NSABP B-39/RTOG-0413 allows radiation oncologists to select one of the three conventional techniques for partial breast irradiation – multi-catheter brachytherapy, MammoSite® balloon catheter, or three-dimensional conformal external beam radiation (3D-CRT).

The conventional techniques for partial breast irradiation in NSABP-B-39/RTOG 0413 are unsatisfactory. Interstitial brachytherapy and intracavitary brachytherapy require placement of percutaneous catheters or applicator that need to be in place for the treatment duration which can be unacceptable for many patients. 3D-CRT requires a large PTV margin which has been associated with unacceptable cosmetic outcomes in some patients.

Non-invasive image-guided breast brachytherapy (NIBB), using advanced image-guided radiation technology, has the potential to eliminate the disadvantages of the conventional techniques of partial breast irradiation. NIBB would facilitate non-invasive breast partial breast irradiation without the use of catheters or implants and reduce non-target breast tissue within the irradiated field.

This pilot Brown University Oncology Research Group Study will assess toxicities associated with the AccuBoost Brachytherapy System (Advanced Radiation Therapy, Inc., Billerica, MA) in delivering NIBB. This system has been FDA approved to accurately target the lumpectomy cavity to provide tumor bed “boost” irradiation after standard whole breast radiation therapy. We hypothesize that NIBB will be more convenient, safe and effective modality to deliver partial breast irradiation.

4. Background
4.1. Standard adjuvant whole breast radiotherapy
With the wide-spread use of mammography, breast cancer is commonly diagnosed at an early stage (1-2). The standard treatment for early-stage disease is breast conserving surgery followed by adjuvant radiation therapy to the whole breast. This approach leads to low recurrence rates with good cosmesis and provides an effective alternative to mastectomy (3-10). However, half of
these women will develop significant acute skin toxicity following whole breast irradiation, most frequently in the infra-mammary fold (11). These acute reactions are associated with pain and with a reduction in health-related quality of life (11-12). Furthermore, standard whole breast radiotherapy involves daily treatments delivered over a period of 6 to 7 weeks which can be disruptive to the patient’s life (11-13).

4.2. Accelerated Partial Breast Irradiation (APBI)
4.2.1. Rationale for APBI
To address these drawbacks, the concept of accelerated partial breast irradiation has been proposed (14). It arose out of the realization that the majority of tumor recurrences occur at or near the region of the lumpectomy site, suggesting that for well selected patients only the breast tissue surrounding the tumor bed needs radiation treatment (15). In reducing the treatment volume, a higher dose of radiation can be delivered in each treatment session thus reducing the overall treatment time. Furthermore, the reduced volume of treated breast tissue has the potential for reduced acute and late toxicity with the added patient convenience of a shorter treatment schedule (16).

4.2.2. Techniques
Several accelerated partial breast irradiation techniques have been reported including brachytherapy techniques (17-20), external beam conformal techniques (21), and intra-operative techniques (22-23). Brachytherapy has been the most widely evaluated accelerated partial breast irradiation approach. Several techniques exists, the most widely employed are interstitial brachytherapy and intracavitary brachytherapy. Intersitial brachytherapy involves the insertion of multiple interstitial catheters that are then loaded with radioactive material. Intracavitary brachytherapy involved the placement of a balloon or cage-like applicator into the lumpectomy cavity. Several commercially available applicator systems are available (MammoSite, Contura, Savi). Radiation is delivered using a high-dose-rate (HDR) radioactive source (Ir-192) that is remotely afterloaded into the applicator to deliver the appropriate radiation dose and dose distribution. A dose of 34.0 Gy in 10 fractions, typically delivered twice daily, has been established as an appropriate dose in terms of efficacy and toxicity (24-26). The most commonly used external beam technique is three dimensional conformal radiation therapy (3D-CRT). This technique used multiple non-coplanar external beams to target the lumpectomy cavity with an appropriate clinical and planning target margin (21). Intra-operative radiation therapy is delivered at the time of lumpectomy using either electrons or low energy photons in a single treatment (22-23).

4.2.3. Expertise within the Brown University Oncology
The faculty in the department of Radiation Oncology at Rhode Island Hospital and Brown University is among international experts in partial breast irradiation and has had expertise in this field that spans several decades. The faculty has published extensively on treatment techniques, clinical outcomes, and treatment and dosimetric factors related to toxicity for a variety of APBI techniques. This includes interstitial multi-catheter brachytherapy (19, 41, 49-50), intracavitary balloon catheter brachytherapy (Mammosite) (26, 51-53), 3D conformal external beam radiation therapy (38, 54), and electronic brachytherapy (Xoft Axxent) (55-58). The faculty has also been involved in national committees establishing treatment related guidelines (59-61). This body of clinical investigation has been important in shaping the current practice of partial breast
irradiation. The aim of this protocol is to improve upon the shortcomings and limitations of existing techniques in the hopes to improve patient convenience and clinical outcomes.

4.2.4. Results and current status
Recent studies of APBI have demonstrated excellent local control rates in the breast with good/excellent cosmetic results in the majority of patients (16, 19, 24-30). Table 1 summarizes results of APBI. In a pair match analysis based on a cohort of 398 early stage breast cancers, half treated with accelerated partial breast brachytherapy and half with whole breast radiotherapy, Vicini reported the same rate of 1% of local recurrence at 5 years in both arms (16). To establish level I evidence of the equivalency of APBI to standard whole breast radiation therapy, several randomized trial have been commenced and are ongoing. These include APBI using brachytherapy (NSABP-B39/RTOG-0413 and GEC-ESTRO) and external beam irradiation (NSABP-B39/RTOG-0413 and NCIC). The results of these trials are not expected for several years. In the meantime based on favorable level II evidence, several professional societies including the American Society of Breast Surgeons (ASBS), the American Brachytherapy Society (ABS), and American Society of Radiation Oncology (ASTRO) have released consensus guidelines for appropriate patient selection for APBI (31-33). The ASTRO guidelines are the most complete and stringent, and therefore have been chosen for the development of this protocol. The ASTRO guidelines place patient into three categories “suitable”, “cautionary” and “unsuitable.” Several studies have shown good outcomes for APBI in “cautionary” and “unsuitable” patients (34-37). We have choice to restrict this protocol to those defined in the “suitable” category with the exception of including DCIS and age >50 yo as these factors have been shown to not increase the risk of recurrence with APBI (36, 62).

Table 1: Select results of APBI experience

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Technique</th>
<th>Median Follow-up (mo)</th>
<th>Local Recurrence (%)</th>
<th>Cosmetic Outcome (% Excellent/Good)</th>
</tr>
</thead>
<tbody>
<tr>
<td>William Beaumont Hospital (27)</td>
<td>199</td>
<td>Interstitial Brachytherapy</td>
<td>65</td>
<td>1% at 5yrs</td>
<td>99</td>
</tr>
<tr>
<td>National Institute of Oncology-Budapest (28)</td>
<td>45</td>
<td>Interstitial Brachytherapy</td>
<td>133</td>
<td>9.3% at 12yrs</td>
<td>77.8</td>
</tr>
<tr>
<td>Tufts Medical Center (19)</td>
<td>32</td>
<td>Interstitial Brachytherapy</td>
<td>33</td>
<td>3% at 4yrs</td>
<td>91</td>
</tr>
<tr>
<td>Mammosite Registry Trial (24)</td>
<td>1440</td>
<td>Intracavitary Brachytherapy</td>
<td>54</td>
<td>3.8% at 5yrs</td>
<td>90.6</td>
</tr>
<tr>
<td>William Beaumont Hospital (25)</td>
<td>43</td>
<td>Intracavitary Brachytherapy</td>
<td>66</td>
<td>0%</td>
<td>83.3</td>
</tr>
<tr>
<td>Multi-institutional (26)</td>
<td>483</td>
<td>Intracavitary Brachytherapy</td>
<td>24</td>
<td>1.2%</td>
<td>91</td>
</tr>
<tr>
<td>RTOG 0319 (29)</td>
<td>52</td>
<td>3D-CRT</td>
<td>54</td>
<td>6% at 4yrs</td>
<td>NR</td>
</tr>
<tr>
<td>William Beaumont Hospital (30)</td>
<td>94</td>
<td>3D-CRT</td>
<td>50</td>
<td>1% at 4yrs</td>
<td>89</td>
</tr>
<tr>
<td>Tufts Medical Center/Rhode Island Hospital (38)</td>
<td>64</td>
<td>3D-CRT</td>
<td>15</td>
<td>0 %</td>
<td>81.7</td>
</tr>
<tr>
<td>Targit A Trial (39)</td>
<td>1113</td>
<td>Intra-op</td>
<td>NR</td>
<td>1.2% at 4yrs</td>
<td>NR</td>
</tr>
</tbody>
</table>
4.3. AccuBoost: Non-invasive image-guided breast brachytherapy (NIBB)

4.3.1. Definition

Non-invasive image-guided breast brachytherapy (NIBB) is an APBI technique utilizing the AccuBoost Brachytherapy System (Advanced Radiation Therapy, Inc., Billerica, MA) (Figure 1). This technique consists of a three step process: breast immobilization, imaged-guided target delineation, and treatment with collimated photon emission using Ir-192 high-dose-rate (HDR) brachytherapy. Breast immobilization is performed via moderate compression between two mammography paddles. This technique achieved stable position of the breast and lumpectomy cavity for imaging and treatment. Imaging is then performed using 30 kVp x-rays in the immobilized position and in the treatment plane. The lumpectomy cavity is delineated, usually with the assistance of radio-opaque clips placed at the time of lumpectomy. Using a target localization grid the appropriate applicator size and position is selected to cover the lumpectomy cavity with an appropriately margin. Tungsten alloy applicators mounted on the mammography paddles are centered on the target. Treatment is then delivered using directed Ir-192 HDR photons. The process is then repeated along a second intersecting orthogonal axis in a sequential manner.

4.3.2 Rationale

Advantages of NIBB for APBI:

1. Completely non-invasive.
2. Breast and target immobilization irrespective of patient or respiratory motion.
4. Reduced non-target breast tissue within the irradiated field.

Studies of APBI using interstitial brachytherapy (ISB) and intracavitary brachytherapy (ICB) have shown high levels of local control and good cosmetic outcomes as discussed above. These brachytherapy techniques have the advantage of delivering radiation directly to the tumor bed. A typical clinical tumor volume (CTV) expansion of 1cm beyond the lumpectomy cavity is used to account for subclinical disease. There is no need for additional margins expansion, i.e. planning tumor volume (PTV), to account for set up errors or motion related to the breast, patient or respiration. The disadvantage of ISB and ICB is that these techniques are invasive requiring the percutaneous placement of catheters or applicator. This is not acceptable to many patients. In addition, these catheters or applicator need to be in place for the entire treatment duration typically about 1 week, and even longer if place at the time of initial surgery. Instrumentation related infection is a known complication that can deleteriously affect cosmetic outcome (40). A second disadvantage to ISB and ICB is the steep dose gradients seen with these techniques. Portions of breast tissue receive doses of 150% and even 200% of the prescription dose. The volume of these high dose regions has been associated with late tissue toxicity (41). Similar to ISB and ICB, NIBB has the advantage of delivering radiation directly to the tumor bed. By using breast immobilization and image guidance for each fraction of radiation, there is no need for additional expansion of treatment margins beyond the CTV to account for set up errors or motion related to the breast, patient or respiration. Unlike ISB or ICB, NIBB is completely non-invasive and is thus more acceptable to patients and carries no additional risk of infection. The dose distribution of NIBB does not have the same step dose gradients of ISB or ICB with no regions of dose exceeding 150% (42).
APBI using three dimensional conformal radiation therapy (3D-CRT) was designed as a non-invasive alternative to APBI using ISB and ICB, and gained rapid popularity. The disadvantage of 3D-CRT APBI is the need for large PTV margin expansion of 1.5 cm beyond the 1cm CTV expansion. This additional PTV margin is necessary to account for inter- and intra-fraction inaccuracies due to daily set up inaccuracy, breast and patient motion, and respiratory motion. This large PTV expansion, however, results in substantially more volume of non-target normal breast issue within the irradiated volume. Two studies have been published that have shown a higher rate of late tissue toxicity using this technique. Toxicity was correlated with volume of irradiated breast tissue (38, 43). NIBB has the advantage of being non-invasive but also does not needing a PTV expansion by using precise breast immobilization and image guidance.

Intra-operative techniques are being studied but concerns regarding efficacy and late toxicity of these large single fraction radiation treatment limits its widespread applicability until more clinical information becomes available.

4.3.3. AccuBoost dosimetry and clinical results

The AccuBoost Shielded Breast Applicators have undergone rigorous dosimetric characterization using Monte Carlo simulation and direct dosimetric measurement (44-45). Based on detailed characterization of the AccuBoost Shielded Breast Applicators, a treatment nomogram has been designed to deliver the prescription dose using parallel opposed applicators along a single axis. This nomogram takes into account the size and type of applicator, breast separation and source strength. Treatment is typically delivered over two orthogonal axes, (Figure 2). This is usually performed in cranio-caudal and medio-lateral orientation so that pre-surgical mammography can be used to further assist and ensure appropriate target coverage. Although 3D dosimetric planning has been a challenge given the marked tissue deformity between treatment planes, composited dose distribution taking into account both orthogonal treatment axes has been performed (42). Dosimetric comparison with 3D-CRT APBI technique has also been performed (42). This comparison showed good target coverage with the prescription dose for both AccuBoost and 3D-CRT, V90 of 96% and 100%, respectively. However, the doses delivered to normal tissues were significantly lower with AccuBoost as compared with 3D-CRT. PTV volumes were 50% smaller with AccuBoost. The maximum skin dose (Dmax) was 10% lower. The chest wall and lung Dmax were lower by factors of 3.0 and 4.8, respectively. Dose distribution was more heterogeneous for AccuBoost compared with 3D-CRT, Dmax 118% vs. 104% respectively. However, AccuBoost has a less heterogeneous dose distribution compared with other brachytherapy techniques.

Initial clinical experience using AccuBoost in delivering tumor bed boost in conjunction with whole breast radiation therapy (WBRT) has thus far shown excellent results (46). One hundred and ten patients received a boost dose to the tumor bed of 10-14 Gy in 5-7 fractions in conjunction with 45-50Gy WBRT. Boost was performed before, during or after WBRT in 57%, 39% or 4% of patients. No grade 3 or greater toxicity has been seen. Grade 1-2 acute skin reaction was seen in 18% of patients. This compares favorably with WBRT followed by electron or photon boost where a rate of moist desquamation of 38-48% has been reported (47-48). Cosmesis was excellent, good, and fair/poor in 52%, 48%, and 0%, respectively, at a median follow up of 6 months (range 1-17 months).
5. Study population

5.1. Eligibility criteria

Patients referred for adjuvant radiation therapy with:

1) A confirmed histological diagnosis of invasive breast carcinoma or DCIS;
2) Age greater or equal to 50 years old;
3) Life expectancy > 6 months;
4) Treated by breast conserving surgery;
5) Pathologic tumor size less than or equal to 2 cm for invasive carcinoma and less than or equal to 3 cm for DCIS;
6) Estrogen receptor positive for invasive disease (DCIS can be ER negative).
7) Unifocal/unicentric disease;
8) Negative surgical margins greater than or equal to 2 mm. Margins at natural tissue boundaries such as skin or posterior fascia can be < 2 mm;
9) Pathologic lymph node negative, which includes(PN0 i-, i+);
   Patients, who are at very low risk for sentinel node involvement and have elected to forgo sentinel node biopsy, are eligible if clinically lymph nodes negative (cN0). These patients include:
   - Microinvasion only
   - Pure tubular or mucinous histology
   - Patients ≥ 70yo with T1a-b; estrogen receptor +
   - Patients ≥ 70yo with T1c; grade 1-2: estrogen receptor +
   - Patients ≥ 75 with T1c; estrogen receptor +
   - DCIS
10) No evidence of lymphovascular invasion;
11) ECOG performance status of 0 or 1 (Appendix 1);
12) Informed consent signed.

5.2. Ineligibility criteria

1) Known BRCA 1/2 Mutation; (BRCA 1 and 2 testing is not required)
2) Active Lupus or Scleroderma
3) Pregnancy;
4) Breast implants;
5) Psychiatric or addictive disorder that would preclude attending follow-up;
6) Neoadjuvant chemotherapy (adjuvant chemotherapy is permitted);
7) Suspicious remaining microcalcification on post-surgery mammogram (unless biopsy proven benign);
8) Node positive on axillary dissection or in the sentinel lymph node biopsy;
9) Multicentric or multifocal disease;
10) Paget’s disease of the nipple;
11) Distant metastases;
12) Lumpectomy cavity not well visualized on AccuBoost imaging;
13) Lumpectomy cavity with 1cm margin (PTV) not adequately encompassed by any applicator
14) Breast separation with compression > 8cm.
15) Overlap of skin between orthogonal treatment axes.
6. Treatment
6.1. CT simulation
Patients should undergo CT simulation in standard position for whole breast irradiation; supine on a breast board with the ipsilateral arm abducted at or beyond 90 degrees. The gross tumor volume (GTV) is to be delineated on each CT image. The GTV is defined as the lumpectomy cavity and should encompass the seroma cavity, postsurgical changes, and surgical clips. The clinical tumor volume (CTV) is defined as a 1.0 cm circumferential expansion of the GTV limited by the chest wall and 0.5 cm from the skin surface. The planning tumor volume (PTV) is defined to equal the CTV without additional expansion. The GTV and CTV/PTV volumes are to be recorded. Initial assessment about the suitability of AccuBoost APBI should be made. The CTV/PTV needs to be encompassed by one of the available applicators. The position of the CTV/PTV should be appropriate for delivery of two orthogonal axes of treatment without skin overlap between each axis. Surgical clips that define the lumpectomy cavity need to be identified and counted to ensure that all are visualized and accounted for at the time of AccuBoost imaging. CT simulation with breast compression mimicking the treatment position is not required but can also be obtained to assist in three-dimensional dosimetry.

6.2. Immobilization and imaging
The patient’s breast will be immobilized and compressed between the imaging paddles in the desired orientation axis; typically crano-caudal follow by medio-lateral. Maximum compression is based on patient tolerance but is typically less compression than used with screening mammography. Patients who are unable to achieve a maximum breast separation with compression of less than or equal to 8.0 cm are not candidates for this study. Once immobilized and compressed, imaging of the breast is obtained using 30 kVp x-rays. These images are used to guide targeting and applicator selection.

6.3. Applicator selection and positioning
Using imaging obtained in the immobilized treatment position, the target lumpectomy cavity is identified and delineated. The assistance of surgical clips placed at the time of lumpectomy can help define the tumor bed. Alternatively radio-opaque contrast can be injection directly into the seroma cavity to help identify the tumor bed. Patients whose tumor bed cannot be clearly identified are not candidates for this study. The tumor bed constitutes the gross tumor volume (GTV). The clinical tumor volume (CTV) to account for subclinical disease will include the tumor bed with at 1.0 cm radial margin limited by the chest wall and 0.5cm from the skin. No additional expansion is needed for the planning tumor volume (PTV). Thus the CTV will also be the PTV. An appropriate sized applicator will be selected that encompasses the entire CTV/PTV. No margin between the applicator edge and the CTV/PTV volume is required. Using the localization grid, the appropriate position of the selected applicator is chosen. The selected AccuBoost Shielded Breast Applicator is then position in the corresponding locations on the compression paddles. Patients with CTV/PTV volumes that are not encompassed by any of the available applicator sizes are excluded for this study. After treatment of one parallel opposed axis the immobilization, imaging, targeting, applicator selection and applicator placement process is repeated for the orthogonal treatment axis. Careful attention is needed to ensure that there is no overlap of skin between the two orthogonal treatment axes. The breast should be
compressed so as to achieve breast immobilization. Compression should be tailored to patient comfort and should not cause significant pain. Breast compression should ideally be ≤ 8cm which should be achieved at the time of initial simulation to ensure the patient is a good candidate for this approach. As breast compression varies for fraction to fraction and treatment related edema may increase separation during treatment, separation up to 8.5cm is considered acceptable, 8.6-10.0 cm is considered a minor deviation, and >10cm is considered a major deviation.

Any deviations must be recorded on the treatment form and a formal memo to file with documentation must be sent to the BrUOG office. Guidance on reporting of deviations will be provided by BrUOG upon receipt of deviations.

6.4. Dose and fractionation
Patients will receive a total dose of 34.0Gy delivered in 10 fractions. Fraction will be either twice daily separated by at least 6 hours over 5 to 8 days or daily over 12 to 15 days based on patient preference. Both the cranio-caudal and medio-lateral axes are to be treated for each fraction. For twice daily fractionation, every effort should be made to ensure a minimum intra-fraction interval of 6 hours. An intra-fraction interval of less than 4.5 hours is considered a major deviation.

6.5. Treatment Delivery
Treatment is delivered using Iridium-192 high-dose-rate (HDR) source using a remote afterloading system. The AccuBoost System is designed to be compatible Nucletron and Varian HDR afterloading system. Source dwell position and treatment times are determined by the AccuBoost nomograms.

7. Assessment and Toxicities
7.1. Endpoints
7.1.1. Primary endpoints:
Evaluate and report the rate of early and intermediate toxicity.

7.1.2. Secondary endpoints:
1) The rate of ipsilateral breast local recurrence;
2) The cosmetic outcome.
3) Provide preliminary data for testing NIBB in a Phase III or IV trial.

7.2. Toxicity evaluation
7.2.1. Early and intermediate toxicity
Any toxicity related to the radiation treatment will be scored and graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (Appendix 4). Acute side effects are any side effects occurring within 3 months of treatment. Intermediate side effects are any side effects occurring between 3 months and 2 years.

7.2.2. Serious Adverse Event (SAE)
Serious Adverse Event (SAE) is an unintended sign, symptom, or syndrome illness that occurs during the period of observation in the clinical study and that is life threatening or result in death.
SAE will be coded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0 scale and corresponds to grade 4 or 5 signs or symptoms.

7.2.3. Cosmetic outcome
Cosmetic results will be evaluated at each follow-up visit by the treating radiation oncologist using the Harvard criteria (Appendix 4). An excellent cosmetic result score is assigned when the treated breast looked essentially the same as the contralateral breast (as it relates to radiation effects). A good cosmetic score is assigned for minimal but identifiable radiation effects of the treated breast. A fair score means significant radiation effects were readily observable. A poor score is used for severe sequelae of breast tissue secondary to radiation effects. Photographs of bilateral breast will be taken for independent validation of cosmetic assessment.

8. Response Assessment
8.1. Methods of measurement
Physical breast exam and annual mammogram +/- ultrasound +/- breast MRI will be utilized to assess for breast recurrence. Clinical examination and appropriate imaging based on signs or symptoms will be used to assess regional and metastatic recurrence.

8.2. Breast recurrence
Ipsilateral in-breast or chest wall recurrence is defined as evidence of invasive or in situ breast cancer (excluding LCIS) in the ipsilateral breast. Suspicious lesion should undergo a biopsy to confirm the diagnosis.

8.3. Regional recurrence
Regional recurrence is defined as the development of tumor in regional nodes or the soft tissue of the ipsilateral axilla after axillary dissection. Regional lymph nodes include the ipsilateral axillary, supraclavicular, internal mammary nodes. Suspected recurrence should be documented with biopsy or fine needle aspiration.

8.4. Metastases
Distant recurrence is defined as evidence of tumor in any area of the body aside from the breast or regional lymph nodes. The metastasis recurrence should undergo appropriate imaging and/or biopsy.

9. Schedule of Evaluations (Study Calendar) and Data Collection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-study</th>
<th>During Treatment</th>
<th>Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>X</td>
<td></td>
<td>Each Follow Up</td>
</tr>
<tr>
<td>Physical examination</td>
<td>X</td>
<td>Weekly</td>
<td>Each Follow Up</td>
</tr>
<tr>
<td>Cosmetic Assessment</td>
<td>X</td>
<td>Weekly</td>
<td>Each Follow Up</td>
</tr>
<tr>
<td>Breast Photographs</td>
<td>X</td>
<td></td>
<td>Each Follow Up</td>
</tr>
</tbody>
</table>
9.1. Patient inclusion
Patients eligible based on medical history and tumor pathology features will be offered the study. Signed informed consent will be obtained. Patients will then undergo CT simulation and then breast compression and imaging on the AccuBoost system. If they do not meet the technique related inclusion criteria, they are not candidates for AccuBoost APBI and will be excluded from this study. Patients not eligible for this study will be offered standard adjuvant radiation treatment options. Eligible patients will be enrolled.

9.2. Data entry
9.2.1. Data required at time of registration are (see Form 2):
1) Patient’s first and last initial, and date of birth;
2) Height and weight to calculate the body mass index;
3) Bra size;
4) ECOG performance status (Appendix 1);
5) Past medical history;
6) Menopausal Status;
7) Date of surgery or surgeries;
8) Adjuvant systemic treatment: chemotherapy, anti-estrogen therapy;
9) Date of the last cycle of chemotherapy if any;
10) Laterality and breast quadrant;
11) AJCC TNM staging (Appendix 2);
12) Pathology report with detailed tumor characteristics (size, histologic type, MSBR grade, margin status and minimal microscopic size, nodal status, hormone receptor status, Her-2-nue status, and presence of LVI, DCIS, EIC, or multicentricity/multifocality);
13) Metastasis work-up if any;
14) Baseline cosmetic assessment and photographs;
15) Mammogram (if subject had a post-surgical mammogram please send that as well)
16) Signed informed consent.

9.2.2. Data required at completion of AccuBoost APBI treatment (see Form 3 and 4):
1) GTV and CTV/PTV volumes from CT simulation.
2) Total dose received and number of fractions
3) For each fraction:
   a) Dose;
   b) Date and time;
   c) Axis orientations;
   d) Applicator size and type;
   e) Breast separation;
4) Acute toxicity assessment (Form 4).

<table>
<thead>
<tr>
<th>Performance status (ECOG)</th>
<th>X</th>
<th>Each Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammogram</td>
<td>X</td>
<td>Annually</td>
</tr>
</tbody>
</table>

^ Following the 1-2 week treatment course, follow-up at 2, 6 weeks and at 3, 6, 12, 18, 24 months after completion of radiation (+/- 2 weeks).
9.2.3. Data required at each follow up visit (Form 5):
Patients should have follow up visits at 2, 6 weeks and at 3, 6, 12, 18, 24 months.

1) Patient and disease status:
   a. Ipsilateral breast recurrence; quadrant and date of recurrence if applicable.
   b. Regional lymph node recurrence; region and date of recurrence if applicable.
   c. Distant recurrence; date of recurrence if applicable.
   d. Survival; date and cause of death if applicable.

2) Toxicity assessment

3) Cosmetic assessment and photographs

9.2.4. Photographs
Breast photographs for cosmetic assessment will be taken at baseline and at each follow up visit. Photographs will include both ipsilateral breast as well as contralateral breast for comparison. Photographs should not include patient identifiers such as the patients face but should have patients BrUOG ID # and patient initials written on all submitted photographs.

10. Statistical consideration
Sample size: 40 patients

Unacceptable Rate of Toxicity: To address the safety of NIBB, the rate of unacceptable acute adverse events (defined as grade 3+ or higher cutaneous toxicity occurring during or within 120 days from the end of treatment). The Brown University Oncology Research Group have determined that a rate of 35% or greater will be considered to be unacceptable. According to Flemming’s method (49) with a maximum overall significance level of 0.05 if there are:

16 or more patients with unacceptable adverse events out of the first 40 evaluable patients,

The study will have exceeded the limit for unacceptable adverse events. If the number of unacceptable adverse events crosses a boundary, as described in the rules above, then the conclusion will be that the treatment-related unacceptable adverse event rate is greater than 35%. These toxicity rules provide 85% power for concluding that the unacceptable adverse event rate is equal to or exceeds 35% when in fact that is the true rate.

11. Patient Registration

All patients will be registered through the Brown University Oncology Research Group Central Office. Eligibility Checklist with supporting documentation, On Study Form must be faxed to the BrUOG Central Office, Fax: (401) 863-3820, at the time of registration and prior to patient treatment.

Details of patient’s study participation should be documented in clinic/file notes. The Brown University Oncology Research Group will provide case report forms, included in the appendix, for the recording and collection of data. In the event of corrections, each correction will be initialed and dated by the person making the correction. The investigator will sign the case reports to indicate that, to his/her knowledge, they are complete and accurate. Case report forms,
flow sheets, off-study forms and follow-up forms should be emailed / faxed or scanned to:

Brown University Oncology Research Group  
Phone: (401) 863-3000, Fax: (401) 863-3820  
Email: Kayla_rosati@brown.edu

All support data must be sent in with the corresponding BrUOG forms.

It is the treating physician’s responsibility to review all data submitted to the BrUOG Central Office for accuracy and completeness

12. Adverse Reaction Reporting

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject after or during treatment and does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of non-invasive image-guided breast brachytherapy (AccuBoost).

During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.)

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication. All AEs considered related to trial radiation therapy will be followed until resolution even if this occurs post-trial.

12.1. Definitions

An adverse event is any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered treatment-related.

Serious adverse event (SAE)  
An adverse event occurring at any dose that results in any of the following outcomes (CFR 312.32):

- Death
- Life-threatening adverse reaction
- Inpatient hospitalization or prolongation of existing hospitalization excluding those for study drug administration, transfusional support, disease staging/re-staging procedures, concomitant radiotherapy, thoracentesis / paracentesis, or placement of an indwelling catheter, unless associated with other serious events.
- Persistent or significant disability or incapacity,
- Congenital anomaly / birth defect.
The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. A new diagnosis of cancer during the course of treatment should be considered an important medical event.

The definition of “related” being that there is a reasonable possibility that the drug caused the adverse experience.

**Unexpected adverse event**
An adverse event that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

**Life-threatening**
Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

**12.2. Monitoring of Adverse Events and Period of Observation**
Adverse events, both serious and non-serious, and deaths that occur during the patient’s study participation will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient’s stable or chronic condition or intercurrent illness(es).

**12.2.1. Pregnancies**
Pregnancies occurring while the subject is on treatment com are considered expedited reportable events. The treatment is to be immediately discontinued.

The Investigator will follow the subject until completion of the pregnancy. The Investigator will provide this information as a follow-up to the initial SAE. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs.

The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs.
12.3 BRUOG ADVERSE EVENT REPORTING REQUIREMENTS

Investigators are required by Federal Regulation to report adverse drug reactions.

Question regarding drugs as used in this study should be directed to the Brown University Oncology Research Group (BrUOG) Central Office, Phone: (401) 863-3000 Fax (401) 863-3820, which will in turn notify the Principal Investigator.

Intensity for each adverse event will be scored using CTCAE Version 3.0. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTCAE Version 3.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient’s outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

12.4 Reporting requirements and procedures depend upon:

- Whether investigational agents are suspected of causing toxicity;
- Whether the possibility of such a toxicity was reported in the protocol, consent form, or manufacturer’s literature (Expected toxicity); and
- The severity of grade of the toxicity. All reactions in a “reportable” category must be reported unless it is documented on flow sheets and/or follow-up forms that the treatment is definitely not responsible for the toxicity.

12.5 Assessing Causality:

Investigators are required to assess whether there is a reasonable possibility that treatment caused or contributed to an adverse event. The following general guidance may be used.

Yes: if the temporal relationship of the clinical event to treatment administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: if the temporal relationship of the clinical event to treatment administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

12.6 Types of Report:

Telephone report: For SAEs contact BrUOG Central Office (401) 863-3000 immediately upon learning of the event.

Written report: Send the copy of the Medwatch 3500 form within 10 days of the event to the BrUOG Central Office by e-mail, scan or Fax:

Brown University Oncology Research Group
Phone: (401) 863-3000, Fax: (401) 863-3820
Email: Kayla_rosati@brown.edu
MedWatch 3500 Reporting Guidelines:
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500 form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator’s assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:
Additional Info maybe added to a previously submitted report by any of the following methods.
- Adding to the original MedWatch 3500 report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500 form

Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report).

12.7 BrUOG Responsibility Regarding Reporting:
The BrUOG Central Office will notify by phone and/or fax all drug reaction reports to the FDA, the Principal Investigator, and the participating sites (who will in turn notify their local IRBs) as soon as possible but no later that 7 calendar days after the sponsors initial receipt of the information. Serious unexpected adverse events will be reported as an amendment to the IND within 15 days of sponsor notification. They will all receive a simultaneous copy via facsimile of all adverse events filed with the FDA. A copy of the form will be kept by the BrUOG Central Office.

Medwatch
5600 Fischers Lane
Rockville, MD  20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
(sent to Center Drug Evaluation and Research or product review division for Center for Biologics Evaluation and Research that has responsibility for review of IND)

12.8 Safety Reporting for IND Holders
In accordance with 21 CFR 212.32, Sponsor-Investigator of the study conducted under an IND must comply with following safety-reporting requirements:

a. Expedited IND Safety Reports:
7 Day calendar Telephone or Fax Report: The Sponsor-Investigator is required to notify the FDA of any that is serious, unlisted/unexpected and assessed by the investigator to be possibly
related to the use of study drug(s). An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be telephoned or faxed to the FDA as soon as possible but no later than 7 calendar days of first learning of the event. Each telephone call or fax transmission (see fax number below) should be directed to the FDA new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever is responsible for the review of the IND.

FDA fax number for IND Safety Reports: 1 (800) FDA - 0178

AND: Report of Adverse Events to the Institutional Review Board

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

13. Study withdrawal
13.1 Patient withdrawal
At any time, a patient may voluntarily withdraw from the study. The withdrawal will not affect their future medical treatments or benefits.

13.2 Lost to follow-up
Should a patient be lost to follow-up, efforts to contact the patient should be made.

13.3 Withdrawal due to physician decision or medical reason
Should a physician decide or a patient’s condition deteriorates such that the constraints of the protocol are detrimental to the health and welfare of the patient, the patient may be terminated from the study.

14.0 REGULATORY CONSIDERATIONS
14.1 Protection of Human Subjects
The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

14.2 Compliance with the Protocol and Protocol Revisions:
The study must be conducted as described in this approved protocol. All revisions to the protocol must be provided to Brown University Oncology Research Group, and Advanced Radiation Therapy Inc (ART). The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the
IRB/IEC and ART except where necessary to eliminate an immediate hazard(s) to study patients.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Brown University Oncology Research Group, and ART. If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

14.3 Protocol amendments or changes in study conduct:

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by ART and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to ART.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by ART in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons ART must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

1. changes in the staff used to monitor trials (ART. considers a change in Principal Investigator or the addition of sub-site(s) to be substantial and requires ART approval prior to implementation)

15.0 DATA MONITORING / QUALITY ASSURANCE/ RECORD RETENTION

15.1 Good Clinical Practice: The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator’s Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.
15.2 Patient Confidentiality: In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from ART or its designees and regulatory authority (ies) access to the patient’s original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient’s confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the Clinical Trial, including, but not limited to, the Clinical Trial Protocol, the CRFs, the Investigator's Brochure and the results obtained during the course of the Clinical Trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor. However, the submission of this Clinical Trial Protocol and other necessary documentation to the Ethics Committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the Clinical Trial. The Investigator and the Sub-Investigators shall use the information solely for the purposes of the Clinical Trial, to the exclusion of any use for their own or for a third party's account. Furthermore, the Investigator and the Sponsor agree to adhere to the principles of personal data confidentiality in relation to the patients, Investigator and its collaborators involved in the study.

15.3 Protocol Compliance: The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority (ies). Changes to the protocol will require approval from ART and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority (ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to ART and the regulatory authority (ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

15.4 On-site Audits: Regulatory authorities, the IEC/IRB and/or ART clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor. The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found.
during the audit or inspections

15.5 Premature Closure of the Study: This study may be prematurely terminated, if in the opinion of the investigator or ART there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or ART by the terminating party.

Circumstances that may warrant termination include, but are not limited to:
- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug

15.6 Record Retention: The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

The Brown University Oncology Research Group, as coordinator of this study, is responsible for ensuring proper conduct of the study with regard to protocol adherence and the validity of the data recorded on the case report forms. The Principle Investigator (Jaroslaw Hepel, M.D.) and Brown University Oncology Research Group Manager of Operations (Kayla Rosati) will monitor this study. The case report forms will be monitored against the submitted documents on a regular basis for accuracy, completeness, adherence to the protocol and regulatory compliance.

15.7 Data protection:
- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

U.S. FDA regulations (21CFR312.62[c]) require all records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consents forms, laboratory test results and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the FDA and the applicable local health authorities are notified. CTI will notify the Principle Investigator if an application is filed.

15.8 Responsibilities of the Sponsor
The Sponsor of this Clinical Trial is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the Clinical Trial Protocol as regards ethics, Clinical Trial Protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main
duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the Clinical Trial.

At regular intervals during the Clinical Trial, the site will be contacted, through monitoring visits, letters or telephone calls to review study progress, Investigator and patient compliance with Clinical Trial Protocol requirements and any emergent problems. These monitoring visits, will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AEs with pre-specified monitoring documentation and reporting, AE documentation, IP allocation, patient compliance with the IP regimen, IP accountability, concomitant therapy use and quality of data.

15.9 Source Document Requirements
According to the ICH guidelines for Good Clinical Practice, the Monitoring Team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The Informed Consent Form will include a statement by which the patient allows the Sponsor’s duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (e.g., patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

15.10 USE AND COMPLETION OF CASE REPORT FORMS (CRFs) AND ADDITIONAL REQUEST
It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation. All CRFs should be completed in their entirety to ensure accurate interpretation of data. Should a correction be made, the corrected information will be entered on the CRF overwriting the initial information. An audit trail will allows identifying the modification.

16.0 DATA SAFETY AND MONITORING BOARDS
All trials initiated by the Brown University Oncology Research Group (BrUOG) are subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets three times per year with any additional meetings scheduled when needed. The responsibilities are as follows:
• Familiarize themselves with the research protocol (s)
• Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
• The DSMB reviews trial performance information such as accrual information.
• The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
• All adverse events are reviewed by the committee, with assurances that these have been in fact sent for review to all pertinent IRBs.
• Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
• Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).

Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial. The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRB’s.
17. References

31. www.breastsurgeons.org/apbi.shtml
32. www.americanbrachytherapy.org/resources/abs_breast_brachytherapy_taskgroup.pdf

18. Appendices

Appendix 1

<table>
<thead>
<tr>
<th>Affiliate</th>
<th>Rhode Island Hospital</th>
<th>The Miriam Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bradley Hospital</td>
<td>Newport Hospital</td>
</tr>
</tbody>
</table>

Agreement to Participate in a Research Study
And Authorization for Use and Disclosure of Information

<table>
<thead>
<tr>
<th>Committee #</th>
<th>Name of Study Volunteer</th>
</tr>
</thead>
</table>

ACCELERATED PARTIAL BREAST IRRADIATION USING NON-INVASIVE IMAGE-GUIDED BREAST BRACHYTHERAPY (ACCUBOOST) FOR EARLY STAGE BREAST CANCERS: A TOXICITY ASSESSMENT

You are being asked to take part in a research study. All research studies carried out at Lifespan institutions are covered by rules of the Federal government as well as rules of the State of Rhode Island and Lifespan. Under these rules, the researcher will first explain the study, and then he or she will ask you to participate. You will be asked to sign this agreement which states that the study has been explained, that your questions have been answered, and that you agree to participate.

The researcher will explain the purpose of the study. He or she will explain how the study will be carried out and what you will be expected to do. The researcher will also explain the possible risks and possible benefits of being in the study. You should ask the researcher any questions you have about any of these things before you decide whether you wish to take part in the study. This process is called informed consent.

This form also explains the research study. Please read the form and talk to the researcher about any questions you may have. Then, if you decide to be in the study, please sign and date this form in front of the person who explained the study to you. You will be given a copy of this form to keep.

1. Nature and Purpose of the Study
Your doctors are participating in this research study sponsored by the Principal Investigator, Dr. Jaroslaw T. Hepel, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study. This study is financially supported by Advanced Radiation Therapy (the makers of the AccuBoost treatment machine).
You are being asked to take part in a research project because you have early stage breast cancer and are a good candidate for partial breast radiation therapy based on currently accepted national guidelines. This study is evaluating the use of a partial breast radiation treatment that hopes to improve upon the currently used techniques. This technique is called non-invasive image-guided breast brachytherapy or NIBB. It is delivered using an AccuBoost treatment machine. Unlike some techniques, NIBB is non-invasive, meaning that it does not require any surgical placement of catheters or devices. NIBB also allows for better targeting by immobilizing or holding the breast in a fixed position and imaging the breast before each treatment. This study will evaluate 40 patients over a 2 year period.

2. **Explanation of Procedures**

If you take part in this study, you will receive partial breast irradiation using NIBB. You will undergo standard radiation planning using a planning CT scan to make sure you are a good candidate for this technique based on your anatomy and lumpectomy cavity. You will then undergo imaging on the NIBB treatment machine to make sure your lumpectomy cavity can be seen and targeted. If your breast cannot be appropriately immobilized, your lumpectomy cavity cannot be seen on imaging, or the cavity is too large for the available treatment applicators, you are not a good candidate for this study and you will be offered standard radiation treatment. If you meet these criteria, you will then undergo treatment with NIBB. This will include 10 treatments over approximately 1-2 weeks. If the 10 treatments are given over 1 week, the treatments are administered twice daily about 6 hours apart. Most other partial breast irradiation techniques have used 10 treatments given over 1 week. Alternatively, you may choose to have one treatment per day over 2 weeks for a total of 10 treatments. It is not known whether it is better to have 10 treatments, with treatments given twice a day over 1 week, or 10 treatments administered as 1 treatment per day over 2 weeks. You may choose which treatment schedule you prefer. Each treatment session will consist of targeting and treatment via two different angles. For each treatment angle, the breast will be immobilized between two mammography paddles, images of the lumpectomy cavity will be taken, and then treatment will be delivered while your breast remains immobilized. This process will then be repeated for the other treatment angle.

Following the 1-2 week treatment course, we will see you for routine follow up at 2 weeks and at 6 weeks, 3, 6, 12, 18, 24 months. These follow up visits will consist of routine history and physical examination. A photograph of your treated and untreated (for comparison) breast will be taken at each follow up visit for cosmetic assessment. These images may be used in presentation or publication of study results, but will not include any personal identifiers. Standard imaging follow up will be followed with mammography on an annual basis and with any additional imaging as per standard evaluation.

**Costs for participating in this study**

The services you will receive during this research study are considered to be "routine clinical services" that you would have received even if you were not participating in the research study. These services will be billed to your health insurance company, but you will be responsible for paying any deductibles, co-payments, or co-insurance that are a normal part of your health insurance plan. If you do not have health insurance, you will be responsible for those costs.

**Contact Information:**
Any study related questions or concerns can be related to:

Jaroslaw T. Hepel, MD  
Dept of Radiation Oncology  
Rhode Island Hospital  
593 Eddy St.  
Providence, RI 02903  
(401) 444-8311

3. Discomforts and Risks  
NIBB carries standard risks associated with all forms of radiation therapy to the breast for breast cancer which may be more or less significant with this approach. Although NIBB based on dosimetric evaluation is expected to have the same likelihood of local breast cancer control as other partial breast irradiation techniques, the effectiveness of achieving local control using NIBB may be more, equivalent or less compared with other partial breast approaches. NIBB may also included risks that are currently unforeseeable.

Potential Acute Side Effects – Typically occurring during treatment or shortly after and are generally self limited resolving after several weeks.

- Mild breast discomfort during treatment due to breast compression
- Fatigue
- Acute radiation dermatitis – reddening, blistering, peeling, or ulceration of the skin.
- Breast swelling and/or discomfort
- Inflammation of the lung with cough and/or shortness of breath
- Inflammation of the heart sac with chest pain and palpitations

Potential Late Side Effects – typically occurring months after treatment and may or may not resolve with time or treatment.

- Skin thickening (in the treated area)
- Telangiectasia – small fine blood vessel forming on the skin in the treated area.
- Breast changes including thickening, firmness, tenderness, decrease in size of breast
- Breast discomfort or pain
- Fair or poor cosmetic outcome from skin or breast changes
- Rib damage causing pain or fracture
- Lung damage causing cough and/or shortness of breath
- Damage to heart muscle, arteries, or heart sac leading to heart failure
- Very rare risk of secondary cancers

I understand the potential risks of NIBB and breast radiation as outline above. _____ (Initials)

There is a potential risk to the fetus if you are to become pregnant during treatment.

I am not pregnant now and have no reason to suspect that I am pregnant. I understand there is a potential risk to the fetus if I become pregnant during treatment. My doctors have recommended that I try not to become pregnant during radiation therapy. _____ (Initials)
4. **Benefits**

Partial breast irradiation allows for focused radiation to the area around the lumpectomy cavity thus sparing breast tissue from the potential deleterious effects of radiation. Also by reducing the treatment volume, the treatment can be accelerated to 1-2 weeks instead of a standard 5-7 weeks. NIBB is a novel way to deliver partial breast irradiation. Unlike some partial breast radiation approaches, NIBB is not invasive.

There is no requirement for the surgical placement of catheters or devices, and thus there is no associated increased risk of infection with having these catheters or devices in place for up to a week. NIBB also utilizes breast immobilization and daily image guidance, allowing for more precise targeting of the lumpectomy cavity. This allows for less breast tissue to be treated compared to some partial breast radiation approaches which need to use large margins of normal breast tissue to account for uncertainty in the location of the lumpectomy cavity as well as to account for movement of the lumpectomy cavity during treatment from breast movement or movement with normal breathing. These benefits may result in a partial breast radiation approach that is more convenient to the patient and potential has a better outcome in terms of radiation affects on normal tissues including the breast and on the overall cosmetic outcome.

5. **Alternative Therapies**

Alternative treatment options include standard whole breast radiation therapy or partial breast irradiation using a standard technique. Standard whole breast radiation therapy consists of radiation treatment to the whole breast given daily over 5-7 weeks. Other partial breast irradiation techniques included multicatheter brachytherapy, balloon catheter brachytherapy, and 3D-CRT external beam technique.

6. **Refusal/Withdrawal**

You decide whether or not you want to be in the study. Participation is voluntary. If you decide now to participate, you can change your mind later and quit the study.

If you decide not to participate, or if you quit the study, it will not affect the health care services that you normally receive. If the researcher or your doctor feels it is in your best interest, they may choose to take you out of the study at any time before you complete the study.

As soon as it becomes available, the researcher will give you new information about the study that may or may not affect your decision to stay in the research study.

**Follow-up after Withdrawal of Consent**

*If you decide to stop your participation in the study, it would still be useful to us to know how you do over the next 24 months. We'd appreciate it if you'd give your permission for us to continue to obtain follow-up information about your health status from your doctor or from your medical record.*

- [ ] If I withdraw from the study, you have my permission to collect information about my health from my doctor or medical record.

- [ ] I do not give my permission for you to continue to collect information about me if I stop participating in the study.
7. Medical Treatment/Payment in Case of Injury
   A research injury is any physical injury or illness caused by your participation in the study. If you are injured by a medical treatment or procedure that you would have received even if you were not in the study, that is not a research injury. To help avoid research injury and potential added medical expenses, it is very important to follow all study directions carefully. If you experience a research injury, Lifespan, or the study doctor, are available to arrange for medical treatment for you. The cost of your treatment will be paid for as described below.

   If you suffer a research injury and you are covered by insurance, it is possible that some or all of the costs of treating your condition could appropriately be billed to your insurance company. If such costs are not covered by your health insurance, Lifespan will pay for what it considers fair and proper treatment. Lifespan has no policy to cover payment for such things as lost wages, expenses other than medical care, or pain and suffering.

   Signing this form does not lessen or take away any of your lawful rights. For more facts, please contact Patricia E. Houser in the Office of Research Administration at 401-444-6246.

8. Rights and Complaints
   If you have any complaints about your taking part in this study, or would like more facts about the rules for research studies, or the rights of people who take part in research studies, you may contact Patricia E. Houser, in the Lifespan Office of Research Administration, at (401) 444-6246.

9. Confidentiality
   The section at the end of this document called “Research Authorization for Use and Disclosure of Information” provides detailed information about how the information learned about you during this study will be used and shared. More generally, all of your records from this study will be treated as private health care records. The records will be protected according to the rules of Lifespan. The Lifespan privacy practices and policies are based on the rules about protection of private health care information contained in Rhode Island law and in the Federal Health Insurance Portability and Accountability Act of 1996 and its regulations (“HIPAA”). The privacy practices of Lifespan and of the people who provide services at or with Lifespan are explained in more detail in the Lifespan Joint Privacy Notice (the “Privacy Notice”) which will be given to you.

   You should also know that there are times when the law might require or permit Lifespan to release your health information without your permission. The Privacy Notice explains when this might happen. To give you some examples, State law requires health care workers to report abuse or neglect of children to the Department of Children, Youth and Families (DCYF). State law also requires health care workers to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.
10. **Research authorization for use and disclosure of information**

The purpose of this section of the document is to provide you with some more information about how the information learned about you during the study will be used and shared.

We understand that your medical information is very personal and we will work hard to keep it private. **If you sign this form you consent to participate in this research study and are giving us permission to use and share your personal health information in the ways described in this form.**

**Understandings and notifications**

The main purpose of permitting the use and release of your information is to allow the research project to be conducted and to ensure that the information relating to that research is available to all parties who may need it for research purposes. Your information may also be used as necessary for your research-related treatment, to collect payment for your research-related treatment (when applicable), and to run the business operations of the hospital.

All health care providers are required to protect the privacy of your information. However, most persons or entities (i.e., businesses, organizations) that are not health care providers are not bound by law to protect the privacy of your information. You understand that if the person or entity that receives your information is not a health care provider bound to protect your privacy, such person or entity might re-release your health information.

You have the right to refuse to sign this form. If you do not sign this form, none of your health care outside the study, or the payment for your health care, or your health care benefits will be affected. However, if you do not sign this form, you will not be able to enroll in the research study described in this form, and you will not receive treatment as a study participant.

If you sign this consent form, you may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission. This information or action may be needed to complete analysis and reports of this research. This permission will never expire unless you cancel it. To cancel this permission, please write to

Jaroslaw T. Hepel, MD  
Dept of Radiation Oncology  
Rhode Island Hospital  
593 Eddy St.  
Providence, RI 02903  
(401) 444-8311

If after you have signed this form you have any questions relating to your rights, please contact Patricia E. Houser, RN, MSJ in the Office of Research Administration, (401) 444-6246.
Uses and releases covered by this authorization (permission):

Who will release, receive, and/or use your information? This form will allow the following person(s), class(es) of persons, and/or organization(s)* to release, use, and receive the information listed below in connection with this Study, or as required by law:

- Every research site for this study, including this hospital, and including each site's research staff and medical staff
- Health care providers who provide services to you in connection with this study
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, in accordance with the study’s protocol
- The following research sponsors and the people and companies that they use to oversee, administer, or conduct the research: Advanced Radiation Therapy Inc., Brown University Oncology Research Group
- The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights.
- The members and staff of the Institutional Review Board(s) or Ethics Committee(s) that approves this study
- Principal Investigator and other Investigators
- Study Coordinator
- Additional members of the Research Team
- The Patient Advocate or Research Volunteer Protector: _____
- Members of the hospital's administrative staff responsible for administering clinical trials and other research activities
- Contract Research Organization (A contract research organization is an independent organization that agrees to oversee and make possible, various aspects of the clinical research process for the research sponsor.)
- Data and Safety Monitoring Boards and others that monitor the conduct of the Study, for example a Clinical Events Committee
- The members and staff of the hospitals affiliated Privacy Board (if such a board is used)
- Others (as described below): _____

* If, during the course of the research, one of the companies or institutions listed above merges with or is purchased by another company or institution, this permission to use or release protected health information in the research will extend to the new company or institution.

- The entire research record and any medical records held by the hospital may be used and released.

- The following information:

________________________________________________________________________

________________________________________________________________________
SIGNATURE

I have read this informed consent and authorization form. ALL OF MY QUESTIONS HAVE BEEN SATISFACTORILY ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.

By signing below, I give my permission to participate in this research study and for the described uses and releases of information. I also confirm that I have been now or previously given a copy of the Lifespan Privacy notice.

This informed consent document expires on ______. DO NOT sign this document after this expiration date.

Signature of study volunteer/authorized representative* ___________________________ Date ___________ and Time when Signed ___________

I was present during the consent PROCESS AND signing of this agreement above by the study volunteer or authorized representative

Signature of Witness (Required if consent is presented orally or at the request of the IRB) ___________________________ Date ___________

I ASSURE THAT I HAVE FULLY EXPLAINED TO THE ABOVE STUDY VOLUNTEER/AUTHORIZED REPRESENTATIVE, THE NATURE AND PURPOSE, PROCEDURES AND THE POSSIBLE RISK AND POTENTIAL BENEFITS OF THIS RESEARCH STUDY.

Signature of Researcher or Designate ___________________________ Date ___________ and Time when Signed ___________

* If signed by agent other than study volunteer, please explain below.
Documentation that a copy of this Informed Consent was given to the research participant is a Federal requirement. Prior to making a copy of the signed and dated Informed Consent please check appropriate box(es) as applicable to indicate copy provided to:

☐ Study Volunteer  ☐ Medical Record  ☐ Researcher  ☐ Other (Specify)
Appendix 2 - Performance status (ECOG)

Grade:

0 - Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100).

1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work) (Karnofsky 70-80).

2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).

3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40).

4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
Appendix 3 – TNM classification (AJCC 7th Edition)

Primary tumor
- T0 No evidence of primary tumor
- Tis Carcinoma in situ
- T1 ≤ 2 cm
  - T1mic ≤ 0.1 cm
  - T1a > 0.1 cm but not > 0.5 cm
  - T1b > 0.5 cm but not > 1.0 cm
  - T1c > 1.0 cm but not > 2.0 cm
- T2 > 2 cm but not > 5 cm
- T3 > 5 cm
- T4 Any size, with direct extension to chest wall or skin
  - T4a Extension to chest wall (excluding pectoral muscle)
  - T4b Edema (including peau d'orange)/ulceration/presence of satellite skin nodules
  - T4c Both T4a and T4b
  - T4d Inflammatory carcinoma

Regional lymph nodes
- N0 No regional lymph node metastasis identified histologically.
- N1 Micrometastases; or metastases in 1 to 3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node dissection but not clinically detected.
- N2 Metastasis in 4 to 9 axillary lymph nodes, or in clinically detected internal mammary nodes in the absence of axillary lymph node metastases
- N3 Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph node(s), or in clinically detected ipsilateral internal mammary lymph node(s) and in the presence of 1 or more axillary lymph node metastasis; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected, or ipsilateral supraclavicular lymph node(s).

Distant Metastasis
- M0 No distant metastasis
- M1 Spread to distant organs is present
Appendix 4 - NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0

NCI CTC Version 3.0
Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov). Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: Grade the event using the NCI CTCAE.

Step 3: Determine whether the adverse event is related to the protocol therapy (investigational or commercial). Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is NOT listed in:
Appendix 5 – Cosmesis criteria (As it relates to radiation effects)

**EXCELLENT:** when compared to the untreated breast or the original appearance of the breast, there is minimal or no difference in the size or shape of the treated breast. The way the breast feels (its texture) is the same or slightly different. There may be thickening, scar tissue or fluid accumulation within the breast, but not enough to change the appearance.

**GOOD:** there is a slight difference in the size or shape of the treated breast as compared to the opposite breast or the original appearance of the treated breast. There may be some mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes only a mild change in the shape or size.

**FAIR:** Obvious differences in the size and shape of the treated breast. This change occurs in a quarter or less of the breast. There can be moderate thickening or scar tissue of the skin and the breast, and there may be obvious color changes.

**POOR:** marked change in the appearance of the treated breast involving more than a quarter of the breast tissue. The skin changes may be obvious and detract from the appearance of the breast. Severe scarring and thickening of the breast, which clearly alters the appearance of the breast, may be found.