A Radiation Therapy Study

A Phase II Study of Preoperative Boost Radiotherapy in Patients with Breast Cancer with Biomarker Analysis

DUKE CANCER INSTITUTE

A National Cancer Institute-designated Comprehensive Cancer Center

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2 LIST OF ABBREVIATIONS

3D	3 Dimensional
5-FU	5 fluoro-uracil
AE	Adverse events
ANC	Absolute Neutrophil Count
AP/PA	Anterior to Posterior, Posterior to Anterior
APC	Argon Plasma Coagulation
BED	Biologically Equivalent Dose
BID	Twice Daily
CBC	Complete Blood Count
CBCT	Cone Beam Computed Tomography
CDDP	Cisplatin
Chemo	Chemotherapy
CPC	Cancer Protocol Committee
CRT	Chemoradiotherapy
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTV	Clinical Tumor Volume
D10cc	Minimum dose to the 10 milliliters of any volume receiving the highest dose
D2cc	Minimum dose to the 2 milliliters of any volume receiving the highest dose
DCI	Duke Cancer Institute
DCIS	Ductal Carcinoma in situ
DLT	Dose Limiting Toxicity
Dmax	Maximum dose to any voxel within a volume
DUHS	Duke University Health System
DWI	Diffusion weighted imaging
ECOG	Eastern Cooperative Oncology Group
EFRT	Extended Field Radiotherapy
EQD2	Equivalent dose at 2 Gray per fraction
FIGO	International Federation of Gynecology and Obstetrics
G3 or G4	Grade 3 or Grade 4 toxicity
GCP	Good Clinical Practice
GOG	Gynecologic Oncology Group
GTV	Gross Tumor Volume
GU	Genitourinary
GY	Gray
HDR	High Dose Rate
ICRU	International Commission on Radiation Units and Measurement
ID	Identification
IMRT	Intensity Modulated Radiation Therapy (including Volumetric Modulated Arc Therapy)
IRB	Institutional Review Board
KPS	Karnofsky Performance Scale
LDR	Low Dose Rate
LINAC	Linear Accelerator
LRC	Loco-regional control
MRI	Magnetic Resonance Imaging.
MTD	Maximum Tolerated Dose
MV	Megavoltage
NCI	National Cancer Institute

NRG	National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group (GOG)
OBI	On board-imaging
OS	Overall Survival
PA	Para-aortic
PET	Positron Emission Tomography
PI	Primary Investigator
PTV	Planning Target Volume
SAE	Serious adverse event
SOC	Safety Oversight Committee
TD5/5	Toxic dose of 5% at 5 years
V18	Partial volume receiving greater than or equal to 18 Gray
WAI	Whole abdominal irradiation
WPRT	Whole Pelvic Radiotherapy

3 PROTOCOL SYNOPSIS

3.1 Purpose

This protocol seeks to utilize a novel method of tumor bed boost delivery and to better understand breast cancer radiation response through the analysis of pre-and post-radiation samples.

Primary Objective:

1. Determine physician and patient-reported rates of good/excellent cosmesis at baseline and 6 months, 1, 2, and 3 years post-treatment as measured by the NRG cosmesis scale.

Secondary Objective:

1. Evaluate changes in circulating free DNA pre and post-radiation in order to identify potential blood based radiation response biomarkers.
2. Assess patient-reported Quality of Life (FACT-B) and patient satisfaction at the same time points as above (primary objective).
3. Assess local control in the treated breast relative to historical controls.
4. To review treatment plans, evaluate delivery techniques, and assess positioning verification images.

Hypotheses

We hypothesize that the boost can be delivered preoperatively to the intact breast tumor with acceptable cosmetic outcomes. Furthermore, we anticipate that pre- and post-radiation blood samples will provide an avenue for understanding breast cancer radiation response.

3.2 Background and Significance

In 1990, the National Institutes of Health concluded that breast conservation, conservative surgery followed by radiotherapy, was the preferred treatment for women with early stage breast cancer as no survival advantage was seen in women receiving a more radical and disfiguring mastectomy. As a result, breast conservation consisting of lumpectomy followed by 6 weeks of daily external beam radiotherapy became the standard of care in the United States (US). Treatment typically consisted of 4.5-5 weeks of whole breast treatment followed by a 1-1.5 week boost to the surgical resection cavity. Unfortunately, some women electing to receive breast conserving surgery struggled to complete the recommended radiotherapy. Patterns of care studies demonstrated that older women, and those living in low-income regions or far from radiotherapy centers, often omitted radiotherapy altogether[1-3]. Numerous studies have demonstrated that the local recurrence rates in these women receiving conservative surgery alone are unacceptably high[4,5].

As a result, there has been much interest in development of a more convenient alternative to standard radiotherapy. Recently, robust data has documented that a 3 week course of whole breast radiotherapy is an efficacious and safe alternative[6,7] to standard therapy. Much additional work has been done on partial breast irradiation, rapid treatment of the tumor bed plus a small margin of normal tissue, delivered in 1 to 5 days. Randomized data for this approach is beginning to be reported. Preliminary data suggest comparable rates of local control. However, early results are mixed in regards to normal tissue toxicity[8,9] and may be technique dependent. Finally, numerous investigators have explored the concept of concurrent or intra-operative tumor bed boost, thus eliminating the final 1 to 1.5 weeks of treatment.

3.3 Rationale

A. Rationale for tumor bed boost

Radiotherapy significantly decreases the rate of local recurrence in women receiving conservative surgery[10-13]. A boost to the surgical resection cavity provides a small additional local control benefit at the cost of increased fibrosis and an extra 1 to 1.5 weeks of treatment. Two randomized trials have established the benefit of a tumor bed boost with a consistent relative risk reduction which extends across all subgroups[14,15]. However, higher risk women clearly derive a much larger absolute benefit from the boost. NCCN guidelines recommend boost treatment in women deemed to be at higher risk of locoregional recurrence. Many radiation

oncologists routinely deliver a boost to all subjects undergoing breast-conserving therapy. In this proposal, women judged as deriving a benefit from a tumor bed boost by the treating investigator based on clinical stage will be eligible for inclusion.

B. Rationale for alternative boost delivery

Radiation has historically involved 6 weeks of daily therapy at a radiation oncology facility. For many women, particularly those who are older, poor, or live in rural areas, this presents a significant hardship. Surveillance, Epidemiology, and End Results (SEER) registry data has noted in the past that many women were not receiving appropriate breast conservation therapy[1-3]. Inadequate breast conserving therapy (i.e., no radiotherapy, no axillary node evaluation or neither) increased from 10% of women in 1989 to 19% in 1995 attributable in approximately equal amounts to omission of axillary nodal evaluation and radiotherapy. As a result, numerous investigators spent the following decade proposing techniques to shorten the course of radiation.

Two such techniques were the delivery of a concurrent boost and the delivery of the boost at the time of surgical resection. These techniques were evolving simultaneously with partial breast irradiation, but captured a much larger population of women for whom partial breast treatment was not felt to be appropriate. There are now numerous early-phase trials[16,17] demonstrating favorable outcomes with the concurrent boost technique. In fact, this approach is currently the subject of a recently completed NRG phase III trial. Women felt to be at higher risk of locoregional recurrence were enrolled and randomized to receive a standard course of 4-6 weeks of radiation or a shortened 3 week course of treatment with a concurrent boost.

Intra-operative boost is another technique that has been investigated by a number of groups[18-21]. Doses of 9 to 12 Gy have been utilized in a single fraction. In general, this approach has been well-tolerated with no clear indications of increased toxicity. The key limitation for this technique is the costly intra-operative linear accelerator which is not widely available to many oncologists or subjects.

C. Rationale for single-fraction preoperative technique

We propose in this trial to build on the favorable results of the intraoperative boost trials but using a preoperative delivery approach. We have demonstrated the feasibility of the preoperative approach[22] and successfully completed a Phase I dose-finding partial breast trial. The preoperative approach has several advantages: 1) expensive intra-operative equipment is unnecessary, 2) a small intact breast tumor results in significantly less uninvolved breast tissue receiving high radiation doses which likely decreases toxicity; 3) more accurate targeting of the high-risk areas of subclinical disease surrounding the tumor is possible, 4) smaller treatment volumes are amenable to dose escalation which can further accelerate treatment and improve accessibility for subjects, and 5) the pre-operative approach provides a novel opportunity to study breast cancer radiation response.

While delivery of intra-operative treatment is likely to remain limited in its availability, nearly all radiation oncology facilities have the capability of delivering focused external beam radiotherapy. Significant technological advances have been made in recent years that support sophisticated treatment delivery and the ability to modulate the dose as needed to minimize toxicity.

D. Rationale for magnetic resonance imaging (MRI) treatment planning

Target delineation has always been highly subjective in the post-lumpectomy setting. The tumor bed is currently defined as the area of architectural distortion plus surgical clips. Defining this area is subject to inherent variability depending on the bias of the treating physician. Pre-operative assessment of the tumor should certainly improve delineation of the target and the surrounding area at risk. However, the typical tools used for defining breast tumors, mammography and ultrasound, cannot currently be used in conjunction with radiation planning software. MRI, on the other hand, has a growing role in breast imaging and can be used for radiation treatment planning.

E. Rationale for endpoints

Numerous investigators have documented limited toxicity in studies evaluating an intraoperative boost. In addition, we noted no acute dose-limiting toxicities in our Phase I trial delivering preoperative doses greater than the one planned in this study. Therefore, we feel that there is conceptual support from the existing literature for this approach.

Radiotherapy to the intact tumor is a relatively rare event in breast cancer irradiation, particularly in the setting of early stage breast cancer. Tumor and normal tissue radiation response remain relatively poorly understood. Markers capable of predicting radiation response are rare indeed.

3.4 Selection of Subjects and Sample Size

Women judged by clinical stage as someone to whom a tumor bed boost would be offered during conventional radiation therapy will be eligible. As a general guideline, this typically includes women with invasive cancer that are eligible for and electing breast-conserving therapy under the age of 60. Selected women greater than 60 may also be offered a boost at the discretion of the treating investigator. For example, known nodal involvement may prompt a boost in this scenario. Women with in situ cancers <50 are also typically offered a boost though again, certain women greater than 60 may also be included at the discretion of the treating physician.

The final sample size is 40 subjects. Given the broad eligibility criteria and the more than 400 new subjects with invasive breast cancer seen in Radiation Oncology at Duke each year, accrual is anticipated to be complete in 3 years once the first patient is enrolled.

4 SUBJECT ELIGIBILITY

4.1 Inclusion Criteria

1. Women with a biopsy proven diagnosis of ductal carcinoma in situ or invasive carcinoma of the breast. Biopsy tissue (either slides or block) from outside institutions will be reviewed to confirm diagnosis.
2. Breast preservation candidates (no prior breast or nodal radiotherapy, no imaging evidence of multicentric disease preventing resection through a single incision, no pregnant women, and no comorbid conditions precluding surgery)
3. cTis-T3 cancer judged to benefit (by treating radiation oncologist) from a tumor bed boost
4. Women of child-bearing potential must consent to use adequate contraception during the course of the study: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use.
5. WBC > 3000, Hgb > 10, platelets >100000 within 30 days of consent
6. Eligible for contrasted MRI on initial evaluation with GFR≥ 60 ml/min. A diagnostic MRI ordered within 60 days of diagnosis will be considered an acceptable alternative and will not be repeated.
7. Outside breast imaging will be reviewed at Duke to confirm that findings are consistent with trial eligibility

4.2 Exclusion Criteria

1. Breast implant in the breast to be treated (contralateral breast implant is acceptable)
2. Medical conditions that may increase risk for poor cosmetic outcome (i.e. Lupus, rheumatoid arthritis, scleroderma)
3. Subjects unable to receive study treatment planning secondary to body habitus or inability to lie flat on the stomach for at least 1 hour
4. Positive serum pregnancy test
5. Insufficient breast imaging to judge clinical stage
6. Subjects without placement of a biopsy clip at the diagnostic procedure who are unwilling to undergo clip placement.
7. Subjects in whom treatment planning constraints cannot be met

4.3 Inclusion of Women and Minorities

Only women will be eligible for this study. Minority groups will also be eligible and accrual is expected to reflect the population of subjects seen in the Duke Multi-disciplinary Breast Cancer Clinic.

5 TREATMENT PLAN

5.1 Surgery

Surgical tumor resection will be completed 2-4 days after RT delivery (though up to 7 days will be allowed for logistical constraints without considering this a protocol deviation). Subjects will undergo intraoperative lymphatic mapping and sentinel lymphadenectomy as is standard at our institution. Standard axillary nodal dissection is acceptable if there is a contraindication to the sentinel node procedure or if felt to be clinically indicated based on nodal involvement. Negative margins, defined as no tumor on ink, are the institutional standard. Standard pathologic assessment will follow.

5.2 Radiotherapy

Target Volume:

Prior to treatment, a biopsy clip fiducial marker will be placed in the region of the tumor to provide localization for radiotherapy delivery. Kilovoltage on-board-imaging (OBI) and/or cone beam CT (CBCT) will be used for localization as described in the section on target localization.

The patient will then undergo a research magnetic resonance (MR) for radiation treatment planning. The patient will be placed on the MR table with the breast pendant in a dedicated breast surface coil with arms raised overhead. Alternatively, the patient will be placed supine and specialized thoracic coils will be utilized in order to keep the breast in the same shape for the MR, CT, and radiation treatment to the extent possible. MR/CT compatible surface markers will be used to assist in this effort. T1-weighted imaging, T2-weighted imaging, inversion-recovery imaging, diffusion weighted imaging (DWI), and Dynamic contrast enhanced (DCE) MRI of the breast will be performed on the 1.5 Tesla GE Signa scanner in the Department of Radiation Oncology, equipped with a research key.

More specifically, T1 weighted MRI will be acquired with a 3D gradient-echo with spoiler (SPGR) sequence to achieve spatial resolution of sub-millimeter; T2 weighted MRI will be acquired with a 2D fast spin-echo (FSE) sequence; inversion recovery MRI will be acquired by a 2D axial short-T1 inversion-recovery (STIR) sequence; DCE-MRI will be acquired with a 3D SPGR sequence. Before DCE-MRI acquisition, a MedRad Power Injector will be used to administer weight appropriate dose of gadolinium at 2cc/second after a 30 second inject delay.

Axial T1, axial short-T1 inversion-recovery (STIR), and dynamic VIBRANT images will be required for the delineation of the enhancing tumor, the gross tumor volume (GTV). A planning CT scan will also be acquired in order to generate dose calculations.

Treatment Planning and Dose:

The MR images will be used to define the GTV. A 1.5 cm uniform expansion will be applied around the GTV to create the clinical target volume (CTV). MRI images will be fused to the CT images for further identification of normal structures and target volumes. The first 5mm of subcutaneous tissue and any chest wall (pectoralis muscle and deeper) if >1 cm from the GTV will be excluded from this volume. The first 5mm of tissue is in the photon “build-up” region and to include this area would skew the dose calculations. The chest wall is considered an anatomic boundary to tumor that is separate from the chest wall. An additional 0.5 cm margin to beam edge, will be used to generate the planning target volume (PTV) in order to account for set-up uncertainty. A PTV eval will be utilized for analysis of dose coverage. The PTV eval will include the same volume as the PTV with the exception of the first 5mm of skin. The CTV will be utilized for target dose-volume analysis.

The skin, ipsilateral and contralateral lung, ipsilateral and contralateral breast tissue, spinal cord and heart will be segmented as per institutional standard and analyzed for dose. The skin will be defined as a 3 mm layer from the external body surface. The ipsilateral and contralateral breast tissue will be segmented utilizing the guidelines from ongoing phase III NRG trials. In short, the breast tissue typically included in standard breast tangents minus the lungs and chest wall will be designated the breast volume with hand modification as needed by the principal investigator or designee.

The skin, spinal cord, and lungs will be auto-contoured in standard fashion. The heart should be contoured from the apex to the root of the great vessels. The thyroid and brachial plexus will also be contoured as appropriate depending on tumor location. The thyroid should be easily visible and contoured at the base of the neck. The brachial plexus should be visible on MRI and will be contoured with the assistance of radiology as indicated. Alternatively, the axillary vessels will be used as a surrogate for the brachial plexus[23].

A treatment plan utilizing arc therapy, or multiple conformal beams, or intensity-modulated therapy, or a combination of these techniques will then be designed. The beam arrangement can be organized in any fashion provided that the dose constraints listed below are met. The dose will be normalized to provide a desired coverage (95% to 98%) to the CTV. Subjects will receive a single fraction of 7 Gy.

Dose coverage (taken with some modifications to account for the single-dose preoperative delivery technique from the ongoing NRG phase III trial evaluating concurrent boost) will be considered appropriate as follows:

Target volume (CTV): prescribed dose covers >90% of the CTV without exceeding maximum dose of 110% of prescribed dose
Normal breast: <30% of the whole breast reference volume should receive 50% or more of the prescribed dose and <15% of the whole breast reference volume should receive the prescribed dose
Contralateral breast: the contralateral whole breast reference volume should receive <10% of the prescribed dose to any point
Lungs: Mean lung dose <3.6Gy, V5<10%
Heart: Mean should not exceed 50cGy, no point should receive greater than 4Gy, Dose to 1cc <2Gy
Thyroid: maximum point dose < 10% of the prescribed dose
Brachial plexus: no point in the brachial plexus should receive more than 10% (1Gy maximum) of the prescribed dose.
Skin dose: 1) Maximum dose will not exceed prescription dose. 2) Dose to 1cc: <6Gy (85% prescription)
Cord: maximum dose to 1 cc should be 1 Gy.

In addition, a low dose survey will be performed to ensure no unanticipated regions are receiving inappropriate dose.

Target Localization and Treatment Delivery:
Subjects will be taken to the treatment machine and positioned comfortably as they were at the time of CT simulation. Image-guidance will be used to localize the treatment volume, including on-board radiographic imaging and cone-beam CT. Cone-beam CT will always be completed except in cases where this is not technically feasible due to machine technical constraints. Positioning correction will be performed as necessary, verified and documented. Implanted marker may be considered as surrogates for effective target localization. The target localization procedure will be documented and adjustments will be made as appropriate. Treatment will be delivered to the target volume in one fraction. Each treatment plan will be checked for quality assurance in both calculation and dosimetry. All treatment will be recorded and verified through ARIA information system.

Post-operative Radiation:
Following pre-operative boost subjects will proceed to surgical resection. Systemic therapy will then be delivered as indicated and radiation will resume following systemic therapy in standard fashion. Alternatively, women will return following surgical resection and initiate conventional whole breast radiation +/- regional

nodal treatment as per standard procedures. Hypofractionated breast treatment will be considered an acceptable alternative to standard therapy (46-50Gy) when clinically appropriate.

Cosmesis, recurrence and late RT toxicities outcomes will be gathered and recorded separately for subjects deemed to require mastectomy based on unexpected findings at the time of surgical resection. It would not be accurate to compare the secondary endpoints of these subjects to those receiving breast conservation.

5.3 Supportive Care

Standard supportive therapies at the discretion of the treating radiation oncologist.

5.4 Early Study Termination

This study can be terminated at any time for any reason by the PI-sponsor. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 10.7, which describes procedures and process for prematurely withdrawn subjects.

6 PATIENT ASSESSMENTS

Assessment	Pre-Tx.	Follow-up
Consent	X	
History/Physical	X	X[a]
Complete Blood Count (no differential)/CMP	X	
Breast imaging (mammogram minimum)	X[g]	X[a]
Core Biopsy/Fiducial Markers	X[b]	
Planning MRI	X	
Surgical Excision		X[c]
Acute Toxicity Evaluation		X[d]
Cosmetic Evaluation Form/Digital Photographs/QOL	X[e]	X[e]
Clinical Outcomes		X[a]
Serum Collection	X[f]	X[f]

a. Physical exam by member of oncology team recommended every 4-6 months for 2 years, every 6 months through year 5 and annually years 5-10. Bilateral mammogram recommended at least annually.
b. Verify placement of a biopsy clip at diagnostic procedure.
c. Within 2-4 days following radiation (up to 7 allowed if needed – see below).
d. Appointment by a radiation oncology physician/mid-level provider 1-2 months post-radiation.
e. At baseline (prior to treatment), six months and one year after treatment and then annually for 2 additional years. To be filled out by both patient and physician/mid-level provider. Digital photographs at the same time points and at investigator's discretion.
f. 2 lavender tubes drawn prior to radiation therapy and post radiation therapy (before surgery)
g. Mammogram will not be repeated if one has been obtained within 6 months of signed study consent. Mammography does not need to be repeated unless clinically indicated.

6.1 Pretreatment Evaluations/Management

Prior to treatment each patient will be required to have a complete history and physical including signed informed consent, basic clinical laboratory studies, staging and a biopsy demonstrating ductal carcinoma in situ or invasive breast carcinoma.

Assessment of the tumor by physical exam and mammogram (further imaging at radiologist/physician discretion) should include tumor measurements. Each patient will complete a baseline cosmetic evaluation as will her physician/mid-level provider. QOL measures will also be assessed. Prior to study treatment, placement of a biopsy clip at the time of diagnostic biopsy will be verified as this will serve as a fiducial marker (described in section 8.2) to assist in radiotherapy localization. MRI and CT of the affected breast will then be completed in Radiation Oncology for radiation treatment planning.

6.2 Screening Examination

The screening examination will take place up to 45 days before study treatment. An informed consent must be signed by the patient before any screening procedure takes place. If however, standard of care evaluation procedures have been obtained and are within the screening evaluation time points, the SOC procedures do not need to be repeated and may be included in the screening examination.

6.3 End of Treatment/Follow-up Period

Lumpectomy will be completed 2-4 days (though up to 7 days will be allowed for logistical constraints without considering this a protocol deviation) following RT delivery. Tissue will be processed as described below in section 8.1. A surgical margin will be considered negative if there is no ink on tumor. The patient will be assessed by a Radiation Oncology physician/mid-level provider within 2 months after preoperative treatment, to evaluate for treatment toxicity. Subjects will then go on to complete systemic therapy as indicated or proceed to conventional radiation.

Subjects will be seen weekly during conventional treatment as is standard procedure in our department. Follow-up after conventional radiation will follow national guidelines and includes a history and physical every 4-6 months for the 1st 2 years, every 6 months to a year through year 5 and annually through year 10. Mammograms will be obtained at least annually. Other laboratory or radiographic studies will be obtained as directed by patient symptoms or physical exam. Quality of life and cosmetic assessments, physician/mid-level provider and patient, will be performed at 6 month, 1 year, and then annually through 3 years of follow-up as will digital photographs. Locoregional recurrence will be monitored on protocol at each follow-up visit.

6.4 Early Withdrawal of Subject(s)

6.4.1 Criteria for Early Withdrawal

Subjects may voluntarily withdraw from the study at any time. The PI may also withdraw a subject from the study at any time based on his/her discretion. Reasons for PI-initiated withdrawal may include, but is not limited to the following:

- Adverse events
- Abnormal laboratory values
- Abnormal test procedure results
- Protocol deviation
- Administrative issues
- Disease progression
- Pregnancy

6.4.2 Follow-up Requirements for Early Withdrawal

Standard of care follow up will adhered to.

7 Statistical Considerations

7.1 Statistical Analysis of Cosmetic Outcome

This trial will accrue a total of 40 patients over 3 years. The rate of *physician-reported* good/excellent cosmetic outcome will be estimated at baseline and at the following four follow-up time points: 6, 12, 24, and 36 months. A true rate of good/excellent cosmetic outcome rate of ≥ 0.80 would be considered acceptable, while a true rate of ≤0.60 would be unacceptable. The cosmetic outcome rate at 6-months will be monitored with the following rules.

Sample size	Review patient data if and when the number of patients with fair/poor cosmetic outcome at 6 months is:
20	≥ 8
40	≥ 12

Specifically, if and when 8 or more of the first 20 patients (40%) have a fair/poor outcome, or if and when 12 or more of the 40 patients (30%) have a fair/poor outcome, the data will be reviewed and a decision will be made whether to close the trial. In other words, least 29 of the 40 patients (0.725) must have a good/excellent cosmetic outcome in order to consider the cosmetic outcome rate acceptable. If the true cosmetic rate is 0.60 and 0.80, then the probability that the rules above will call for a review is 0.93 and 0.10, respectively. Assuming an observed good/excellent cosmesis rate of 0.75, a sample size of 40 will provide a 95% CI's of 0.62 − 0.88.

7.2 Statistical Analyses of the Secondary Objectives

(a) To identify potential blood-based radiation response biomarkers, we will estimate mean (with 95% CI) and median change in circulating free DNA from pre- to post-RT, by level of biomarker.
(b) Quality of life (FACT-B) and patient satisfaction will be measured at baseline and at 6, 12, 24, and 36 months. For each scale, the mean and its 95% CI's will be estimated at each time point; boxplots will be used to estimate the distribution of these scales at each time point.
(c) Time to local or regional failure will be defined as the time from start of treatment to date of local or regional failure, whichever comes first; distant failures will be ignored; deaths will be censored. Time to distant failure will be defined as the time from start of treatment to date of distant failure; local and regional failures will be ignored; deaths will be censored. The Kaplan Meier method will be used to estimate both of these distributions.

8 SAFETY MONITORING AND REPORTING

The PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred.

8.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject receiving study therapy and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of radiation therapy, whether or not related to use of the radiation therapy. Abnormal laboratory findings without clinical significance (based on the PI's judgment) should not be recorded as AEs. But laboratory value changes that require therapy or adjustment in prior therapy are considered adverse events. All acute toxicities will be captured from time of preoperative boost therapy to 1 month post conventional radiation therapy. Chronic toxicities to be captured include breast pain, fibrosis, skin induration, hyperpigmentation, lymphedema, breast atrophy and swelling, infection, seroma, and wound healing.

From the time the subject signs the informed consent form through the End of Study visit (as defined in Section 10.4), all AEs must be recorded in the subject medical record and adverse events case report form.

AEs will be assessed according to the CTCAE version 4.0. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study therapy
- Probably: The AE is likely related to the study therapy
- Possible: The AE may be related to the study therapy
- Unlikely: The AE is doubtfully related to the study therapy
- Unrelated: The AE is clearly NOT related to the study therapy

8.1.1 AEs of Special Interest

All possible treatment related adverse events/toxicities reported or observed, the information should be recorded in the patient's medical record and on the study's Toxicity Evaluation Form or in the study's toxicity database. This should include a description of the event, its severity grade, the relationship to the study treatment and the onset date.

8.1.2 Reporting of AEs

All grade 4 or higher unexpected and possibly related toxicity will be reviewed by the PI and study team and reported to the Duke University Health System IRB via the eIRB system.

8.2 Serious Adverse Events

An AE is considered "serious" if in the opinion of the investigator it is one of the following outcomes:

- Fatal
- Life-threatening
- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions

8.3 Safety Oversight Committee (SOC)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews includes but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team (see Section 12.1 for Monitoring Team description) oversees the conduct of DUHS cancer-related, sponsor-investigator greater-than-minimal-risk intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements. The DCI Safety Oversight Committee (SOC) will perform annual reviews on findings from the DCI Monitoring Team visit and additional safety and toxicity data submitted by the Principal Investigator.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Monitoring

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard

operating procedures, good clinical practice, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1 – 3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Cancer Protocol Committee, the Safety Oversight Committee (SOC), the sponsor, the Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

9.2 Audits

The Duke School of Medicine Clinical Trials Quality Assurance (CTQA) office may conduct confidential audits to evaluate compliance with the protocol and the principles of GCP. The PI agrees to allow the CTQA auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the CTQA auditor(s) in order to discuss findings and any relevant issues.

CTQA audits are designed to protect the rights and well-being of human research subjects. CTQA audits may be routine or directed (for cause). Routine audits are selected based upon risk metrics generally geared towards high subject enrollment, studies with limited oversight or monitoring, Investigator initiated Investigational Drugs or Devices, federally-funded studies, high degree of risk (based upon adverse events, type of study, or vulnerable populations), Phase I studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.

CTQA audits examine research studies/clinical trials methodology, processes and systems to assess whether the research is conducted according to the protocol approved by the DUHS IRB. The primary purpose of the audit/review is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit/review will serve as a quality assurance measure, internal to the institution. Additional goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize “best practices” in the research/clinical trials environment.

10 ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

10.1 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

10.2 DUHS Institutional Review Board and DCI Cancer Protocol Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

10.3 Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator or authorized key personnel, must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject.

10.4 Study Documentation

Study documentation includes but is not limited to source documents, case report forms (CRFs), monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

Electronic case report forms (eCRF) in REDCap will be the primary data collection document for the study. The CRFs will be updated within two weeks of acquisition of new source data. Only approved study staff will be permitted to make entries, changes, or corrections in the CRF. For paper CRFs, errors will crossed out with a single line, and this line will not obscure the original entry. Changes or corrections will be dated, initialed, and explained (if necessary). The Principal Investigator or authorized key personnel will maintain a record of the changes and corrections. For electronic CRFs, an audit trail will be maintained by REDCap.

10.5 Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained. Research Data Security Plans (RDSPs) will be approved by the appropriate institutional Site Based Research group.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff,

the patient and his family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Subjects will be identified only by a unique study number and subject initials. Electronic records of subject data will be maintained using a secure online REDCap database. Access to the REDCap database will be limited to essential study personnel. Subject data may be stored temporarily on encrypted and password-protected portable memory devices such as flash drives and external hard drives, but only when absolutely necessary. Data stored on portable memory devices will be de-identified. Subject data will be deleted from the portable memory device at the earliest opportunity. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per DUHS HRPP policy.

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

10.6 Data and Safety Monitoring

This clinical research study will be monitored both internally by the PI and institutionally by the Duke Cancer Institute (DCI). In terms of internal review the PI will continuously monitor and tabulate adverse events. Appropriate reporting to the Duke University Medical Center IRB will be made. If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

Stopping rules for toxicity and/or response are met;
Risk/benefit ratio is not altered to the detriment of the subjects;
Appropriate internal monitoring of AEs and outcomes is done;
Over-accrual does not occur;
Under-accrual is addressed with appropriate amendments or actions;
Data are being appropriately collected in a reasonably timely manner.

DCI review and monitoring of this protocol occurs in accordance with the NCI-approved Data and Safety Monitoring Plan. Briefly, protocol review begins with an initial review by the Cancer Protocol Committee (CPC), which assesses the ethics and safety of the protocol. Documentation of these assessments will be maintained. Formal, independent monitoring will be conducted by the DCI Monitoring Team after the first 3 subjects are enrolled, followed by annual monitoring of 1-3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk. DCI Monitoring Team reports and additional data/safety/toxicity reports submitted by the PI will be reviewed by the Safety Oversight Committee (SOC) on an annual basis. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns. Monitoring visits may also be initiated upon request by DUHS and DCI Leadership, CPC, SOC, a sponsor, an investigator, or the IRB.

10.7 Protocol Amendments

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

10.8 Records Retention

The Principal Investigator will maintain study-related records for the longer of a period of at least six years after study completion, per Duke policy.

11 REFERENCES

1. Morrow M, White J, Moughan J, et al: Factors predicting the use of breast-conserving therapy in stage I and II breast carcinoma. J Clin Oncol 19:2254-62, 2001
2. Nattinger AB, Hoffmann RG, Kneusel RT, et al: Relation between appropriateness of primary therapy for early-stage breast carcinoma and increased use of breast-conserving surgery. Lancet 356:1148-53, 2000
3. Nattinger AB, Kneusel RT, Hoffmann RG, et al: Relationship of distance from a radiotherapy facility and initial breast cancer treatment. J Natl Cancer Inst 93:1344-6, 2001
4. Foley KL, Kimmick G, Camacho F, et al: Survival disadvantage among Medicaid-insured breast cancer subjects treated with breast conserving surgery without radiation therapy. Breast Cancer Res Treat 101:207-14, 2007
5. Darby S, McGale P, Correa C, et al: Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 378:1707-16, 2011
6. Whelan TJ, Pignol JP, Levine MN, et al: Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 362:513-20, 2010
7. Haviland J, Agrawal R, Aird E, et al: The UK START (Standardisation of Breast Radiotherapy) Trials: 10-year follow-up results. Cancer Research 72, Supplement 3 (abs), 2012
8. Olivotto IA, Whelan TJ, Parpia S, et al: Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. J Clin Oncol 31:4038-45, 2013
9. Vaidya JS, Wenz F, Bulsara M, et al: Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 383:603-13, 2014
10. Fisher B, Anderson S, Bryant J, et al: Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 347:1233-41, 2002
11. Veronesi U, Marubini E, Mariani L, et al: Radiotherapy after breast-conserving surgery in small breast carcinoma: long-term results of a randomized trial. Ann Oncol 12:997-1003, 2001
12. Clark RM, Whelan T, Levine M, et al: Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario Clinical Oncology Group. J Natl Cancer Inst 88:1659-64, 1996
13. Liljegren G, Holmberg L, Bergh J, et al: 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. J Clin Oncol 17:2326-33, 1999
14. Bartelink H, Horiot JC, Poortmans PM, et al: Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. J Clin Oncol 25:3259-65, 2007
15. Romestaing P, Lehingue Y, Carrie C, et al: Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. J Clin Oncol 15:963-8, 1997
16. Freedman GM, White JR, Arthur DW, et al: Accelerated fractionation with a concurrent boost for early stage breast cancer. Radiother Oncol 106:15-20, 2013
17. Osa EO, DeWyngaert K, Roses D, et al: Prone Breast Intensity Modulated Radiation Therapy: 5-Year Results. Int J Radiat Oncol Biol Phys, 2014
18. Forouzannia A, Harness JK, Carpenter MM, et al: Intraoperative electron radiotherapy boost as a component of adjuvant radiation for breast cancer in the community setting. Am Surg 78:1071-4, 2012
19. Ivaldi GB, Leonardi MC, Orecchia R, et al: Preliminary results of electron intraoperative therapy boost and hypofractionated external beam radiotherapy after breast-conserving surgery in premenopausal women. Int J Radiat Oncol Biol Phys 72:485-93, 2008
20. Lemanski C, Azria D, Thezenas S, et al: Intraoperative radiotherapy given as a boost for early breast cancer: long-term clinical and cosmetic results. Int J Radiat Oncol Biol Phys 64:1410-5, 2006

21. Reitsamer R, Peintinger F, Kopp M, et al: Local recurrence rates in breast cancer subjects treated with intraoperative electron-boost radiotherapy versus postoperative external-beam electron-boost irradiation. A sequential intervention study. Strahlenther Onkol 180:38-44, 2004

22. Palta M, Yoo S, Adamson JD, et al: Preoperative single fraction partial breast radiotherapy for early-stage breast cancer. Int J Radiat Oncol Biol Phys 82:37-42, 2012

23. Hall WH, Guiou M, Lee NY, et al: Development and validation of a standardized method for contouring the brachial plexus: preliminary dosimetric analysis among subjects treated with IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys 72:1362-7, 2008

24. DeRose YS, Gligorich KM, Wang G, et al: Patient-derived models of human breast cancer: protocols for in vitro and in vivo applications in tumor biology and translational medicine. Curr Protoc Pharmacol Chapter 14:Unit14 23, 2013

12 APPENDICES

APPENDIX I: Blood Processing

Blood collected pre and post treatment will be used to explore the biologic response to radiotherapy by comparing changes in circulating cell-free DNA expression pre and post-radiotherapy:

cfDNA

2 EDTA tubes will be collected prior to radiation and following radiation. Following collection, plasma will be isolated with the following protocol.

1. Spin blood at 3200xg for 12 minutes at room temperature.
2. Pipette off plasma using a plastic pasteur pipette. Transfer into tube.
3. Spin NEW plasma tube at 2000xg for 10 minutes at 4°C.
4. Aliquot into 1ml aliquots in labelled cryovials.
5. Store at -80°C.

Plasma isolation will be performed in the Clinical Cancer Research Lab and stored as above for future biomarker analysis.

APPENDIX II: NRG Cosmesis Scale

1. ____-____-_____DATE EVALUATION DONE

2. PLEASE ASSESS THE COSMETIC RESULTS OF BREAST CONSERVATION THERAPY AT THIS TIME.
(Circle the number next to the word that best describes the cosmetic results.)

1 EXCELLENT: when compared to the untreated breast or the original appearance of the treated 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 seroma within the breast but not enough to change the appearance.

2 GOOD: there is mild asymmetry between the breasts, which means that there is some acceptable difference in the size or shape of the treated breast as compared to the opposite breast or the appearance of the breast before treatment. There may be some mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes a mild change in its shape or size.

3 FAIR: moderate deformity of the breast, with an obvious difference in the shape and size of the treated breast. This change involves 1/4 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.

4 POOR: marked change in the appearance of the treated breast involving more than 1/4 of the breast tissue. The skin change may be obvious and detract from the appearance. Severe scarring and thickening of the breast which clearly alters its appearance may be present. In retrospect, the breast may have been better treated by a mastectomy.

Please circle one (1) number for each of the following treatment effects.

	None	Yes, present but does not affect cosmesis	Yes, present and affects cosmesis
Skin telangiectasia	0	1	2
Skin atrophy	0	1	2
Pigment change	0	1	2
Erythema	0	1	2
Fat necrosis	0	1	2
Fibrosis	0	1	2
Retraction or contour defect	0	1	2
Volume loss	0	1	2
Other significant tx effects Specify: _____	0	1	2

APPENDIX III: Patient Self-Assessment

1. Please assess the cosmetic outcome of your treatment. (Circle the number next to the word that best describes the appearance of the breast.)

1 Excellent - when compared to the untreated breast, there is minimal or no difference in the size, shape or texture of the treated breast. There may be mild thickening or scar tissue within the breast or skin, but not enough to change the appearance.

2 Good - there is mild asymmetry in the size or shape of the treated breast as compared to the normal breast. The thickening or scar tissue within the breast causes only a mild change in the shape.

3 Fair - there is obvious difference in the size and shape of the treated breast. This change involves 1/4 or less of the breast.

4 Poor - marked change in the appearance of the treated breast involving more than ¼ of the breast tissue.

2. How satisfied with your treatment are you?

Extremely satisfied Very Satisfied Satisfied Unsatisfied

3. Would you choose this treatment again?

Yes No

APPENDIX IV: Quality of Life

Below is a list of statements that other people with breast cancer have said are important to their quality of life. Please indicate the extent to which you have experienced each of the following statements during the past 7 days by circling the appropriate number using the following scale.

During the past week:

PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
1. I have a lack of energy	0	1	2	3	4
2. I have nausea	0	1	2	3	4
3. Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
4. I have pain	0	1	2	3	4
5. I am bothered by **side effects of treatment**	0	1	2	3	4
6. I feel sick	0	1	2	3	4
7. I am forced to spend time in bed	0	1	2	3	4
SOCIAL/FAMILY WELL-BEING					
8. I feel close to my friends	0	1	2	3	4
9. I get emotional support from my family	0	1	2	3	4
10. I get support from my friends	0	1	2	3	4
11. My family has accepted my illness	0	1	2	3	4
12. I am satisfied with family communication about my illness	0	1	2	3	4
13. I feel close to my partner (or the person who is my main support)	0	1	2	3	4
14. I am satisfied with my sex life	0	1	2	3	4

During the past week:

EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
15. I feel sad	0	1	2	3	4
16. I am proud of how I am coping with my illness	0	1	2	3	4
17. I am losing hope in the fight against my illness	0	1	2	3	4
18. I feel nervous	0	1	2	3	4
19. I worry about dying	0	1	2	3	4
20. I worry that my condition will get worse	0	1	2	3	4
FUNCTIONAL WELL-BEING					
21. I am able to work (include work at home)	0	1	2	3	4
22. My work is fulfilling (include work at home)	0	1	2	3	4
23. I am able to enjoy life	0	1	2	3	4
24. I have accepted my illness	0	1	2	3	4
25. I am sleeping well	0	1	2	3	4
26. I am enjoying the things I usually do for fun	0	1	2	3	4
27. I am content with the quality of my life right now	0	1	2	3	4
ADDITIONAL CONCERNS					
28. I have been short of breath	0	1	2	3	4
29. I am self-conscious about the way I dress	0	1	2	3	4
30. My arms are swollen or tender	0	1	2	3	4
31. I feel sexually attractive	0	1	2	3	4
32. I have been bothered by hair loss	0	1	2	3	4
33. I worry about the effect of stress on my illness	0	1	2	3	4
34. I am bothered by a change in weight	0	1	2	3	4
35. I am able to feel like a woman	0	1	2	3	4

APPENDIX V: Digital Photographs

The first photograph should be a close-up encompassing only the treated breast at a 45 degree oblique with arms elevated over the head. The second photograph should be a straight frontal view of both breasts taken in either a standing or seated position with the patient's hands symmetrically placed on her hips, taking care to exclude her face and framing or focusing on both the treated and untreated breast to allow optimal comparison of the breasts for symmetry.