**PROTOCOL TITLE:**

A Phase II Study of Preoperative Single Fraction Stereotactic Body Radiotherapy to the Intact Breast in Early Stage Low Risk Breast Cancer: Analysis of Radiation Response

***Principal Investigator:***

Jean Wright
Department of Radiation Oncology
401 North Broadway
Baltimore, MD 21287
Phone: 202 537 4787
Fax: 202 537 4964

***Co-Investigators:***

Fariba Asrari Radiation Oncology (East Baltimore)
Torie Croog Radiation Oncology (Sibley)
Andrea Richardson Pathology (overall)
David Euhus Surgery (East Baltimore)
Pouneh Razavi Radiology (Sibley)
Chen Hu Radiation Oncology (statistician)

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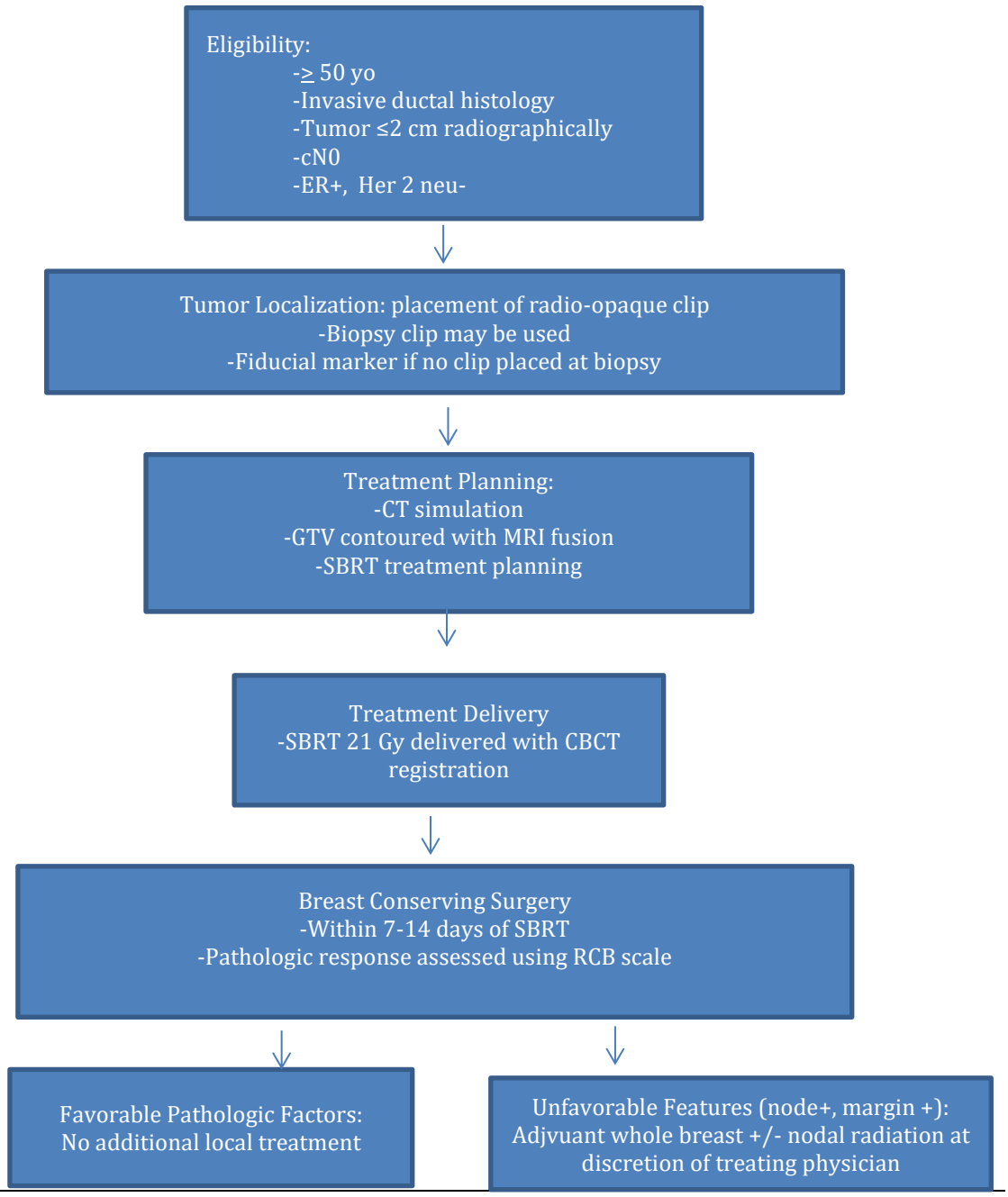
TABLE OF CONTENTS

## 1. STUDY DESIGN/SUMMARY

1.1 SUMMARY: This is a single arm phase II study design, evaluating the pathologic response (primary endpoint) as well as toxicity, cosmetic outcome, quality of life, and oncologic outcomes (secondary endpoints) to pre-operative stereotactic body radiotherapy (SBRT) to intact breast tumors in patients with hormone-receptor positive early stage breast cancer.

1.2 SCHEMA



## 2. OBJECTIVES

2.1 PRIMARY OBJECTIVE: To determine the rate of Residual Cancer Burden (RCB) designation 0 (also known as pathologic complete response (pCR)) and RCB I designation (combined endpoint of either of those designations) 7-14 days after pre-operative SBRT to intact breast tumors.

2.2 SECONDARY OBJECTIVES

2.2.1 To determine the rate of severe acute toxicity, defined as any CTCAE v4 grade 3 or higher toxicity noted from RT delivery up to 90 days after completion of surgery.
2.2.2 To determine the rate of poor cosmetic outcomes from both provider and patient perspectives up to 3 years after pre-operative SBRT to intact breast tumors using the RTOG (Radiation therapy oncology group) cosmesis scale and digital images.
2.2.3 To measure local recurrence rate
2.2.4 To assess patient reported satisfaction and quality of life with treatment using the Breast Cancer Treatment Outcomes Scale (BCTOS)

## 3. BACKGROUND

3.1 INVESTIGATIONAL AGENTS: none

3.2 STUDY DISEASE: Early stage clinically node-negative hormone receptor positive breast cancer

3.3 RATIONALE:

Standard treatment for early stage breast cancers includes a 3-6.5 week course of whole breast radiation following breast conservative surgery. Studies have demonstrated that the requirement for multiple consecutive weeks of adjuvant radiation treatment puts older women, those who live in low-income areas, and those who live far from radiation centers at a disadvantage, leading to omission of this key part of definitive therapy.[1,2] At the same time, it has been observed that patients with certain low-risk features such as small (≤ 2cm) estrogen receptor (ER) positive tumors and negative lymph nodes have lower rates of local recurrence, and tend most commonly to recur in the lumpectomy bed as opposed to elsewhere in the breast.[3]

These observations have led to the development of abbreviated radiation treatment regimens focused solely on the tumor bed, rather than the whole breast, an approach known as accelerated partial breast irradiation (APBI). This approach was developed in the 1990's and over time various techniques for the delivery of APBI have been developed, including interstitial catheter-based brachytherapy, balloon-based brachytherapy, and

APBI delivered using standard external beam radiotherapy with multiple non co-planar beam angles. Despite variability in technique, all these approaches are most commonly delivered in 10 treatment sessions delivered twice daily over 5 days; each treatment session delivers a higher dose of radiation as compared to conventional techniques with the goal of achieving a biologically equivalent dose to the tumor bed in fewer sessions.

Single-institution and registry data compiled since the inception of the APBI approach have demonstrated low rates of locoregional recurrence in appropriately selected patients and the early favorable experience with APBI led to a randomized trial, NSABP B-39/RTOG 0413 , which compared outcomes with the various techniques for APBI with the standard approach of whole breast irradiation.[4,5] This study accrued over 4000 patients, and closed in 2013. Locoregional outcomes have not yet been published, and at this time there is no published phase III data demonstrating the equivalence of APBI and standard whole breast RT. However, in light of the weight of evidence accumulated from decades of retrospective data on the approach of APBI, consensus guidelines for the appropriate use of APBI outside the setting of a clinical trial were developed in 2009, and the ASTRO update was recently published in late 2016.[6] In summary of these guidelines, APBI has been found to be an acceptable technique for patients with early stage, node-negative breast cancer with low-risk features, and we await randomized data to determine if the approach can be expanded to patients with higher-risk features.

Thus, at this time, there is considerable data to support the use of APBI in well-selected low risk patients, but the optimal technique for delivery of APBI has not been determined. The ideal technique would combine accessibility (delivered using widely available technology, with low expense, and using the lowest number of treatment fractions) with excellent cosmetic results (recalling that the movement for breast conservation emerged from the desire to provide equivalent oncologic outcomes compared to mastectomy with superior cosmetic results).

The most accessible technique for APBI is external beam radiation, as this can be delivered via a standard linear accelerator and does not require extensive technical training. On the NSABP B-39 study, which allowed any of the three common techniques for APBI, 75% of patients were treated with EBRT. However, this technique has been associated with poorer cosmesis and higher rates of soft tissue fibrosis compared to whole breast radiation.[7,8] We await formal publication of the cosmetic outcomes using EBRT from NSABP B-39, but at this time there is ongoing concern that this approach results in inferior cosmesis compared to whole breast RT due to asymmetric fibrosis of the breast in the treated area. In addition, this approach still requires 10 treatment sessions delivered twice daily, 6 hours apart, a schedule that is cumbersome for many women.

Single-fraction approaches offer a more convenient schedule, and have been explored most commonly in the setting of intra-operative treatment. There are several techniques

for this approach.[9,10] The most widely marketed IORT approach in the US has been the Targit technique, using a KV source to deliver radiation intra-operatively in a setting that does not require special shielding. However, a phase III study comparing this approach to whole breast external beam radiation demonstrated higher local recurrence risk with the Targit technique compared to whole breast RT.[9] This finding may relate to the very low radiation dose that reaches a depth of 1 cm deep to the surface of the tumor bed, a depth generally considered to be within the clinical target volume for breast cancer. While 20 Gy is prescribed to the cavity surface, a sub-therapeutic dose of 7 Gy penetrates to a depth of 1 cm, a minimum depth presumed to be at risk for microscopic disease. Similar findings were reported using the ELIOT electron-based IORT technique, with a higher risk of local recurrence using IORT as compared to whole breast RT.[10] In addition, the technology needed to deliver IORT using Targit and ELIOT techniques is costly and this not widely available in the US.

Thus, none of the currently popular approaches to APBI is ideal, either due to inferior efficacy, poorer cosmesis, high cost/need for specialized equipment, and/or inconvenience.

An alternative to the above strategies that mitigates many of these limitations is pre-operative single fraction SBRT. There are several potential advantages to this approach over a post- or intraoperative approach. First, it can be delivered with standard radiation equipment using linear accelerator technology that is available in the majority of radiation oncology departments in the US. Second, by treating an intact tumor and using MRI fusion for target delineation, the radiation target is well-defined compared to a postoperative bed that can be difficult to identify. Third, because the tumor is intact, the treatment area is smaller than a typical postoperative bed, decreasing radiation exposure to normal tissue, and the majority of the targeted volume is subsequently resected. Fourth, by treating pre-operatively, we overcome the theoretical concern of postoperative hypoxia in the tumor bed. Finally, a preoperative approach allows for real-time study of radiation response.

Investigators at Duke University have piloted this approach with excellent results: in a cohort of 32 patients, a maximum tolerated dose of 21 Gy has been determined, no grade 3 or 4 toxicities were seen, fibrosis at 18 months followup was minimal (58% grade 1, 10% grade 2, 3% grade 3) and cosmesis was rated as excellent or good in all patients.[11] While these phase I results are promising, the study cohort is very small. These findings warrant replication in a Phase II study such as the one we propose here.

Authors in the Netherlands recently published their preliminary results of preoperative accelerated partial breast irradiation using a hypofractionated approach of 40 Gy in 10 fractions delivered once daily over 2 weeks. Eligible patients include those aged > 60 years, cT1-2, pN0 and invasive ductal histology. Median follow-up for 70 patients was 23

months, and two ipsilateral breast tumor recurrences were diagnosed. In terms of patient reported outcomes, at 3 years 79% of patients were satisfied to very satisfied with their cosmetic result. After 36 months, only 11 (19%) patients were noted to have any fibrosis, and all cases were mild. In summary, the authors concluded that given the good to excellent cosmetic results and low complication and fibrosis rates, pre-operative APBI is a feasible technique for low-risk breast cancer patients.[12] This approach to ABPI has the disadvantage of a longer course of therapy as compared to SBRT. Pathologic response was not reported in this series.

Pathologic response to chemotherapy has been shown to be prognostic for both locoregional and survival outcomes in breast cancer, and has become an increasingly utilized endpoint in preoperative chemotherapy studies. Studies have demonstrated that lower-risk tumors such as those with ER positive/HER2 negative phenotype are less chemosensitive and thus less likely to show a pathologic complete response to chemotherapy.[13] At the same time, response to chemotherapy is less prognostic in this setting.[14] A more nuanced system of evaluating response in those tumors that do not show a pCR is the residual cancer burden (RCB) scoring system (REF), which evaluates tumor size, nodal involvement and cellularity has been demonstrated to be predictive of outcome and is used to define categories of less than complete response.[15]

While response to pre-operative chemotherapy is less prognostic in ER-positive disease, the opposite may be true in terms of radiation response. There is little data evaluating response to radiation to intact breast tumors, but data looking at the benefit of adjuvant radiation in breast cancer shows a greater impact of RT in reduction of locoregional recurrence, and a greater survival impact in ER positive tumors as compared to ER negative or triple negative.[13,15] Thus, a better understanding of tumor response to radiation is critical. Unlike chemotherapy response, response to radiation may in fact be prognostic based on adjuvant RT data, and can be used as a baseline for future study.

Additionally, we also plan to study pathologic specimens for change in hormone receptor status, conversion of Ki 67, and presence of residual DCIS and evaluate the utility of these as biomarkers to predict response.

## 4. PATIENT SELECTION

### 4.1 INCLUSION CRITERIA

4.1.1 Female sex
4.1.2 Age $\geq$ 50
4.1.3 Invasive ductal carcinoma
4.1.4 Clinically and radiographically T1 tumor
4.1.5 Clinically node negative

4.1.6 Clearly demarcated tumor on magnetic resonance imaging (MRI), as determined by treating physician (MRI may be done after enrollment if not done prior)
4.1.7 Planning breast conserving surgery
4.1.8 ≥10% expression of ER and/or PR
4.1.9 HER2- using the current College of American Pathologists guidelines
4.1.10 Post-menopausal
4.1.11 Willing and able to provide informed consent
4.1.12 Patient's case has been reviewed and approved for trial by medical oncologist

4.2 EXCLUSION CRITERIA

4.2.1 Medical conditions that may increase risk for poor cosmetic outcome (i.e. Lupus, rheumatoid arthritis, scleroderma
4.2.2 Pure DCIS without invasive cancer
4.2.3 Patients who have received or will be receiving neoadjuvant systemic therapy, endocrine therapy, or targeted agents
4.2.4 Breast implant in the involved breast unless the implant will be removed prior to initiation of study treatment
4.2.5 Subjects without placement of a biopsy clip at the diagnostic procedure who are unwilling to undergo clip placement.
4.2.6 Unable to meet dosimetric constraints due to tumor location and/or patient anatomy
4.2.7 Planning mastectomy
4.2.8 Unable to tolerate prone positioning

4.3 INCLUSION OF WOMEN AND MINORITIES

Individuals of all races and ethnic groups are eligible for this trial. This trial is open to the accrual of post-menopausal women only.

## 5. REGISTRATION PROCEDURES

5.1 RECRUITMENT

Patients will be identified by screening in the surgical clinics. Patients will be referred to radiation oncology pre-operatively after screen identification. Once a subject has successfully completed all of the screening procedures and is considered eligible by the principal investigator, the subject can be enrolled in the study.

5.2 INFORMED CONSENT

All subjects considered for enrollment in the study must complete an IRB approved

informed consent prior to any study-specific procedures being performed.
The investigator (or his/her designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that she may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the study or have study-specific procedures performed before her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

### 5.3 SCREENING/BASELINE ASSESSMENT AND PROCEDURES

Patients must undergo complete history and physical exam including complete clinical breast and regional nodal exam, weight, and Karnofsky performance status assessment within 30 days prior to enrollment. Patients must also have a biopsy confirmed invasive ductal breast cancer on which ER, PR, and Her2 receptor status must be assessed per CAP guidelines, as well as Ki67 documented. If possible, percent tumor cellularity should be reported on the biopsy specimen. Bilateral mammograms must have been performed within 120 days of study entry for all patients with an intact contralateral breast. A medical oncologist will also review the case prior to enrollment and determine need for formal consultation pre-operatively, specifically to ensure that adequate information is available based on the available tissue to inform treatment decisions in the event of pCR. MRI is not required to be done before enrollment but if an MRI was already done, this can be used for study purposes. The MRI must have been completed within 60 days of enrollment.

## 6. **TREATMENT PLAN**

### 6.1. FIDUCIAL PLACEMENT

Prior to treatment patients must have at least one radio-opaque fiducial marker placed in the tumor, which will be used for image guidance for precise radiation delivery. If a clip or clips have been placed at biopsy, they may serve as fiducial markers. The markers must be located within the tumor on the treatment planning MRI.

6.2 SIMULATION

All patients will undergo standard CT simulation with 2 mm cuts in the prone position with arms overhead and treated breast pendant, per our institutional procedure for prone breast simulation; if the treating physician deems appropriate, supine positioning is allowed. If MRI simulation is available in the clinical location, MRI simulation may be performed. Any palpable tumor will be marked with a BB. A Vac-fix bag will be required to standardize immobilization. Verification of fiducial marker placement and visibility will be confirmed at the time of simulation.

6.3 MRI FUSION

All patients will undergo MRI for target delineation. If patients have had diagnostic MRI within 60 days of study enrollment, this will be fused in our planning system to the CT simulation scan. This diagnostic MRI must have been performed in a dedicated breast surface coil with arms overhead. If the patient has not had such an MRI prior to enrollment, they will undergo MRI simulation in a breast surface coil. The following sequences will be fused to the CT scan for gross tumor delineation: axial T1, axial T2 with fat saturation, diffusion weighted imaging, and any additional sequences on which the tumor is clearly delineated as determined by the physician contouring.

6.4 RADIATION TREATMENT PLANNING

6.4.1 Target Volumes: The gross tumor volume (GTV) will be contoured using the fused MR images as well as the fiducial clip and any abnormality noted on CT. A uniform 1.5 cm expansion will be applied around the GTV to create the clinical target volume (CTV). The first 5mm of tissue deep to the patient's body surface and any chest wall (pectoralis muscle and deeper) if >1cm from the GTV will be excluded from this CTV volume. The exclusion of tissue under body surface relates to concerns for inaccurate dosimetry in the build-up region; this is standard in cooperative group breast protocols. The exclusion of chest wall from the target volume relates to the anatomic boundary created by this structure. To account for set-up uncertainty at the machine, we will generate two planning target volumes for generation of beam apertures: a GTV_21_PTV which is a 0.5 cm expansion of the GTV, and a CTV_15_PTV which is a 0.5 cm expansion of the CTV. Beam apertures may be smaller than 5 mm if dose constraints below can be met with smaller margins.

6.4.2 Organs at risk to be contoured will include: skin, each lung, each breast, spinal cord, heart, esophagus, thyroid and brachial plexus.

6.4.3 Treatment planning will be completed by a dosimetrist and may utilize arc therapy, multiple conformal beams, or intensity-modulated therapy, or a combination of these techniques. Dose will be normalized to provide a desired coverage to the GTV and CTV, detailed below. There is no restriction on photon energy, but electrons are prohibited. Patients will receive a single fraction of 21 Gy delivered to the GTV and 15 Gy to the CTV using a dose-painting method.

6.4.4 Target Localization and Treatment Delivery: All institutional protocols for stereotactic body radiotherapy pre-treatment quality assurance will be followed. At the time of treatment, patients will be positioned and immobilized as they were at the time of CT simulation, per institutional procedures. After set-up, cone beam CT (CBCT) will be used for localization as described in the section on target localization, unless CBCT is not technically feasible in a given patient. In addition to CBCT, kilovoltage on-board imaging (OBI) may also be used at the treating physician's discretion. Both biopsy clips and soft tissue will be used for registration. These images will be approved by the treating radiation oncologist before treatment proceeds.

6.4.5 Dose Constraints: Dose constraints are derived from the phase I experience with pre-operative SBRT at Duke University, establishing the safety of 21 Gy in a single fraction observing the following constraints:

6.4.5.1 Target volumes. All beam apertures will be demarcated by the PTVs to account for setup uncertainty. Beam apertures may be smaller than 5 mm if dose constraints below can be met with smaller margins. The GTV and CTV will be utilized for target dose-volume analysis. Subjects will receive a single fraction of 21Gy to the GTV, and 15 Gy to the CTV. The prescribed doses will cover >95% of the GTV and CTV respectively without exceeding maximum dose of 110% of the maximum prescribed dose.

6.4.5.2 Normal breast: <30% of the whole breast volume should receive 50% or more of the prescribed dose and <15% of the whole breast volume should receive the prescribed dose. This constraint is in line with the majority of partial breast irradiation protocols and will select for a group of patients with larger breasts. Irradiation to a larger relative volume of the breast may be associated with poorer cosmetic outcomes.

6.4.5.3 Contralateral breast: the contralateral whole breast volume should receive <10% of the prescribed dose to any point

6.4.5.4 Lungs:
1 Mean lung dose <3.6Gy

2 <37% of lung volume should receive 8Gy
3 <1500cc to 7Gy
4 <1000cc 7.6Gy

6.4.5.5 Heart: 1) Mean should not exceed 1.5Gy; 2) Point dose <5Gy.

6.4.5.6 Chest wall: D20cc <16.3Gy.

6.4.5.7 Thyroid: maximum point dose <10% of the prescribed dose

6.4.5.8 Brachial plexus: no point in the brachial plexus should receive more than 10% (2.1Gy maximum) of the maximum prescribed dose. The brachial plexus will be contoured as per RTOG consensus.

6.4.5.9 Skin dose: 1) Maximum dose will not exceed prescription dose. 2) Dose to 1cc: <15Gy dose to 10cc <8Gy. Of note the skin contour will consist of a 2 mm rind around the patient's body surface. The skin contour should extend to a level at least 10 cm above and 10 cm below the CTV-PTV structure.

6.4.5.10 Cord: maximum dose to 1 cc should be 1 Gy.

6.5 SURGERY

Resection of the tumor will be completed 7-14 days after delivery of radiation. Surgery will include sentinel node assessment per our institutional standards, but omission of sentinel biopsy is permitted in patients age 70 and over with no clinical evidence of nodal involvement. Resection of the tumor must include a 2mm margin of normal tissue. A re-excision vs post-operative whole breast RT should be considered if the margin is less. Positive margins must be re-excised unless deemed technically not feasible by the surgeon (eg anterior margin dissected to skin).

6.6 PATHOLOGIC ASSESSMENT:
Standard pathologic assessment per our institutional guidelines will be followed and additionally will include RCB analysis and repeat evaluation of Ki67 and receptor status (ER, PR and HER2) if there is any residual invasive cancer.

6.7 ADJUVANT THERAPIES

6.7.1 RADIATION:

Following standard pathologic assessment, patients will be assessed for any adverse features that would warrant adjuvant whole breast radiation with or without regional

nodal radiation. This would include margins <2mm, positive lymph nodes, or as recommended by treating radiation oncologist due to any other adverse feature identified. Hypofractionated and conventionally fractionated regimens (40.50-50 Gy) can be considered by the treating radiation oncologist. In these patients requiring adjuvant radiation, a boost will not be delivered.

6.7.2 ADJUVANT SYSTEMIC THERAPY

Adjuvant systemic therapies including chemotherapy and endocrine therapy will be at the discretion of the medical oncologist. If Oncotype DX or other genetic scoring is desired for evaluation, this will be sent on the pre-treatment biopsy specimen obtained before enrollment on study and which was used for initial diagnosis. Medical oncology approval via case discussion or formal consultation is required prior to pre-operative SBRT to ensure the medical oncologist will be able to obtain all needed information to determine adjuvant systemic recommendations.

6.8 CRITERIA FOR DISCONTINUATION FROM PROTOCOL TREATMENT.

Because SBRT is delivered in one day, discontinuation is unlikely. However if at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue on the study long-term, the patient shall be removed from the protocol follow-up. In this event the reason(s) for discontinuation of study participation will be noted by the PI in the Radiation Oncology record. Subjects who prematurely withdraw will not be replaced unless radiation has not been initiated. 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

6.9 DURATION OF THERAPY:

The duration of protocol-specified therapy will be approximately 2 months. It is expected that treatment planning may take 2 weeks from simulation to treatment delivery, and that 4-6 weeks will elapse from treatment delivery to surgery.

6.10 DURATION OF FOLLOW-UP

Follow-up for this study includes physical exam by member of oncology team every 6 months for the first 2 years, every 6-12 months through year 5, and annually through year 10. Bilateral mammogram will be obtained annually. Other laboratory or radiographic studies will be obtained as directed by patient symptoms or physical exam. Quality of life and cosmetic assessments by both physician and patient will be performed at 6 months, 1 year, and then annually through 3 years of follow-up. Loco regional recurrence will be monitored on protocol at each follow-up visit. Please see study calendar, section 8.0, for detail. Standard follow-up should continue per NCCN guidelines, off protocol, after 3 years.

## 7. EXPECTED TOXICITIES

### 7.1 POSSIBLE TOXICITIES FROM RADIATION

#### 7.1.1 Potential Short Term Reactions

Common:

- Skin redness and irritation in area treated
- Darkened skin and dryness in area treated
- Fatigue
- Temporary hair loss in the area treated
- Occasional aches and pains in the breast
- Temporary edema in treated breast

Uncommon:

- Post-operative bleeding at the time of surgery
- Increased risk of post-operative wound infection
- Seroma formation
- Skin blistering or ulceration

#### 7.1.2 Potential Long Term Reactions

Common:

- Minor pigment change in the treated breast
- Occasional discomfort and sensitivity in the treated area
- Mild to moderate increased firmness of the treated breast
- Mild swelling of the treated breast which can last a number of years
- Minor shrinkage of the treated breast

Uncommon:

- Significant increase in firmness or fibrosis of the treated breast

- Significant shrinkage of the treated breast
- Breast Pain

Rare:

- Lung inflammation and scarring
- Rib fractures in the treated area

Extremely Rare:

- Damage to the heart causing heart failure or heart attack
- Tumors caused by radiation
- Damage to the nerves of the arm

## 8. STUDY CALENDAR

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

| | Pre-SBRT (baseline) | SBRT | Post-SBRT ≤ 1 week prior to surgery | Surgical Procedure | 4-6 weeks Post-Surgery | From time of surgery. All visits have a window of +/- 1 Month except where indicated | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Month 6 | Month 12 | Month 18 | Month 24 | Month 30 | Month 36 |
| History/Physical | X[a] | | | | X | X | X | X | X | X | X |
| Vitals signs, height weight | X | | | | X | X | X | X | X | X | X |
| Demographics | X | | | | | | | | | | |
| Breast imaging (mammogram minimum) | X[a] | | | | | | X (+/- 3 months) | | X (+/- 3 months) | | X (+/- 3 months) |
| Core Biopsy/fiducial markers | X[b] | | | | | | | | | | |
| Medical Oncology Approval | X | | | | | | | | | | |
| Planning MRI | X | | | | | | | | | | |
| Patient Questionnaire (BCTOS) | X[d] | | | | X | X | X | | X | | X |
| Patient Cosmesis evaluation (RTOG) | X[e] | | | | X | X | X | | X | | X |
| Physician Cosmesis evaluation (RTOG) | X[e] | | | | X | X | X | | X | | X |
| Digital image of breasts | X | | | | | | X | | | | X |
| Performance Status (KPS) | X | | | | X | X | X | X | X | X | X |
| Toxicity Assessment | X[c] | | X[c] | | X | X | X | X | X | X | X |

a. Physical exam by member of oncology team every 6 months for the first 3 years. Bilateral mammogram annually for the first 3 years. Follow-up will continue per NCCN guidelines, off protocol, after 3 years.

b. Verify placement of a biopsy clip at diagnostic procedure and availability of pre-treatment tissue for correlative science.

c. Post-SBRT toxicity evaluation in Radiation Oncology within 1 week prior to surgery and again 4-6 weeks after surgery.

d. BCTOS to be completed by patient at baseline (prior to treatment), at first FU 4-6 weeks after surgery, six months and one year after surgery, and then annually for 2 additional years.

e. RTOG cosmesis scoring to be completed by physician and patient at baseline (prior to treatment), at first FU 4-6 weeks after surgery, six months and one year after surgery and then annually for 2 additional years.

## 9. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

9.1 PATHOLOGIC RESPONSE – Standard pathologic assessment per our institutional guidelines will be followed. Additionally, we will include calculation of percent cellularity on the biopsy specimen, residual cancer burden (RCB) analysis and repeat evaluation of Ki67 and receptor status (ER, PR and Her2) if there is any residual invasive cancer at surgery. Residual cancer burden will be assessed by staff pathologists and is calculated using a published continuous index that combines pathologic measurements of the primary tumor (size and cellularity) and nodal metastases (number and size) (reference Symanns). This RCB index has been validated as a predictor of distant relapse.

9.2 ACUTE TOXICITY- Acute toxicity will be graded with the Common Terminology Criteria for Adverse Events (CTCAE) version 4. Grade ≥3 acute toxicity will be considered severe (Appendix 15.2).

9.3 COSMESIS- As noted in the introduction, early cosmetic results from other published pre-operative radiation series for early stage breast cancer have been favorable.[11] We expect similar favorable outcomes, and for the pre-operative single fraction cosmetic results to be equivalent to that of partial breast radiation results. We expect cosmesis to stabilize at 3 years following treatment and thus our endpoint will be to measure results at this timepoint. We will also assess cosmesis at specified time points per the study calendar to quantify changes in breast cosmesis over time.

Cosmetic results will be evaluated by both the patient and the physician. Patients will rate cosmesis using the Breast Cancer Treatment Outcome Scale (BCTOS), which will also be used to evaluate patient reported quality of life (Appendix 15.1). This self-report instrument has been used in a number of studies for this purpose and has both reliability and validity (reference Stanton AL, Krishnan L, Collins CA. Form or function? Part 1. Subjective cosmetic and functional correlates of quality of life in women treated with breast-conserving surgical procedures and radiotherapy. Cancer 91:2273-2281, 2001)

Patients will first complete this after informed consent, and then at multiple intervening assessment points up to 3-years of follow-up (see Study Calendar). At the same time points, patients will also score cosmesis using the RTOG 4-point scale.

The cosmetic evaluation will also be completed by the radiation oncologist or surgeon after consent and prior to treatment. This will be done using the RTOG scale, using criteria established in previous RTOG trials (Appendix 15.3).

Lastly, digital images of patients' breasts will be taken after consent and prior to initiation of treatment, as well as at later time points (see Study Calendar). Two pictures will be taken at each time point, taking care to exclude the patient's face. As done in NSABP B39, the first image will be of the breast to be treated and at a 45 degree oblique angle with arms elevated overhead. The second image should be at a straight angle and frontal view of both breasts taken in either a standing or seated position with the patient's hands on her hips, taking care to exclude her face. These pictures will be taken at baseline (prior to any treatment), at 1-year and 3-year assessment points.

## 10. ADVERSE EVENT REPORTING

### 10.1 GENERAL

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v 4.0) that is available at http://ctep.cancer.gov/reporting//ctc.html.
Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.
Adverse events experienced by participants will be collected and recorded from initiation of study medication, throughout the study, and within 90 days of the definitive surgery. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 90 days post-op will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.
Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued

### 10.2 DEFINITION OF ADVERSE EVENT (AE) Serious adverse event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:
• is fatal or life-threatening;
• requires or prolongs inpatient hospitalization;
• results in persistent or significant disability/incapacity;
• constitutes a congenital anomaly or birth defect; or
• jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:
• routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
• elective or pre-planned treatment for a pre-existing condition that did not worsen
• emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
• respite care

10.3 Expectedness
• Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure (8.0), the package insert or is included in the informed consent document as a potential risk.
• Unexpected: An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure (8.0), the package insert or when it is not included in the informed consent document as a potential risk

10.4 Attribution
Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:
• Definite – The AE is clearly related to the study treatment.
• Probable – The AE is likely related to the study treatment.
• Possible – The AE may be related to the study treatment.
• Unlikely - The AE is doubtfully related to the study treatment.
• Unrelated - The AE is clearly NOT related to the study treatment.

10.5 REPORTING PROCEDURES
All adverse events will be captured on the appropriate study-specific case report forms (CRFs).

10.6 INSTITUTIONAL REVIEW BOARD
Institutional Review Board

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification to the study protocol, these modifications will be provided to the IRB as soon as is possible

## 11. DATA AND SAFETY MONITORING PLAN

This is a DSMP Level I study under the SKCCC Monitoring Plan. A Level I study requires both internal and external data monitoring. The Principal Investigator is responsible for internal monitoring for both safety and data quality. External data monitoring will be performed by the SKCCC at Johns Hopkins Clinical Research Office Quality Assurance Program (CRO QA).

Data and safety monitoring oversight will be conducted by the SKCCC at Johns Hopkins Safety Monitoring Committee. Per the SKCCC at Johns Hopkins Safety Monitoring plan, the CRO AQ will forward summaries of all monitoring reports to the Safety Monitoring Committee for review. All reportable anticipated and unanticipated protocol events/problems and amendments that are submitted to the IRB will also be reviewed by the Safety Monitoring Committee Chair (or designee) and QA manager.

## 12. REGULATORY CONSIDERATIONS

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards.

### 12.2 **Informed Consent**

The investigator (or his/her designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that she may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the study or have study-specific procedures done before his/her informed consent has been obtained.
In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a

regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

12.3 **Ethics and GCP**

This study will be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

12.4 PROTOCOL REVIEW AND AMENDMENTS

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB prior to implementation.

## 13. STATISTICAL CONSIDERATIONS

This is a prospective, single-arm study to determine the pathologic outcomes, acute toxicities, cosmetic outcomes, and local recurrence rates of preoperative singe fraction partial breast radiation in early stage breast cancer. All analyses will be undertaken in the enrolled population who initiate treatment.

13.1 Primary analysis, sample size, accrual and monitoring

The pCR and RCB status as assessed at surgery (defined in Section 2) will be tabulated, and the number and percentage of patients who achieve RCB 0/pCR or RCB 1 will be reported with two-sided 90% CIs. The primary endpoint will be rate of RCB 0 or 1.

Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true response rate is 0.1 will be tested against a one-sided alternative. In the first stage, 16 patients will be accrued. If there are 1 or fewer responses in these 16 patients, a study team will be convened to determine if the study should proceed. Otherwise, 24 additional patients will be accrued for a total of 40. The null hypothesis will be rejected if 7 or more responses are observed in 40 patients. This design yields a type I error rate of 0.089 and power of 86.9% when the true response rate is 0.25.

13.2 Analysis of secondary objectives

Acute toxicities (up to 90 days after completion of surgery) will be collected using CTCAE v4.0 and will be tabulated by body system, type and grade. The number and percentage of patients who experience at least one grade 3 or higher AE will also be reported. The presence or absence of all CTCAE toxicities included in Appendix 15.2 will be assessed in addition to those listed here: breast pain, dermatitis, atrophy, fatigue, fibrosis, lymphedema, pruritis, seroma, surgical would dehiscence, fat necrosis, surgical site infection, hyperpigmentation, skin ulceration. We will use continuous toxicity monitoring throughout the trail as described below. Stopping rules are described below in 13.3.

Local recurrence rates will be calculated using cumulative incidence function, where death without local recurrence is considered as competing event. The associated 95% confidence intervals at landmark timepoints including 6 months, 1 year, 2 years and 3 years will also be provided.

Physician assessment of cosmesis (see Section 9.3) will occur at baseline, 4-6 weeks after surgery, 6 months, 1, 2 and 3 years. The secondary endpoint of poor cosmetic outcome is a physician-assessment of unacceptable (fair or poor) cosmesis at any time point through 3 years and/or occurrence of grade 3 or higher toxicity through 3 years. The number and percentage of patients, with 2-sided x% CIs, will be reported. The timepoint of unacceptable cosmesis assessment and of the grade 3 or higher AEs will be summarized descriptively. Additionally, when all enrolled subjects have had 1 year of follow-up, a working group of investigators will be assembled to evaluate cosmesis on all patients.

Patient-reported satisfaction with cosmetic outcome will be assessed at baseline, 6 months, 1, 2 and 3 years. Satisfaction over time will be summarized descriptively and graphically.

13.3 Monitoring

To minimize the risks of preoperative SBRT, safety will be monitored by A Bayesian stopping rule for the rate of acute toxicity grade $\geq$ 3 convincingly greater than 10%. Specifically, the Bayesian toxicity monitoring rule that suspends the accrual any time if the posterior probability of acute toxicity grade $\geq$ 3 risk being larger than 10% is 75% or higher. We assume a priori that this experimental regimen has an average risk around 5% and there is about 10% chance that the risk will be 10% or higher. This corresponds to a Beta (1,20) prior distribution. The following table gives the corresponding stopping rule for the 40 patients. For example, if 3 patients out of the first 5 treated patients experience acute toxicity grade $\geq$ 3, we will suspend accrual temporarily and the principle investigators and study team will review the toxicity data and recommend either modification or termination of the trial.

| # patients with toxicity | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|
| Out of total # patients treated | 5 | 6-14 | 15-22 | 23-31 | 32-40 |

14. **REFERENCE**

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15. APPENDICES:
15.1 BCTOS
15.2 CTCAE V 4.0
15.3 RTOG COSMESIS SCALES

Appendix 15.1 BCTOS

| | Difference between treated and untreated breast and area | | | |
|---|---|---|---|---|
| | None | Slight | Moderate | Large |
| 1. Breast size..... | 1 | 2 | 3 | 4 |
| 2. Breast texture (hardening) ..... | 1 | 2 | 3 | 4 |
| 3. Arm heaviness..... | 1 | 2 | 3 | 4 |
| 4. Nipple appearance..... | 1 | 2 | 3 | 4 |
| 5. Shoulder movement ..... | 1 | 2 | 3 | 4 |
| 6. Arm movement ..... | 1 | 2 | 3 | 4 |
| 7. Breast pain..... | 1 | 2 | 3 | 4 |
| 8. Ability to lift objects..... | 1 | 2 | 3 | 4 |
| 9. Fit of shirt sleeve..... | 1 | 2 | 3 | 4 |
| 10. Breast tenderness..... | 1 | 2 | 3 | 4 |
| 11. Shoulder stiffness..... | 1 | 2 | 3 | 4 |
| 12. Breast shape..... | 1 | 2 | 3 | 4 |
| 13. Breast elevation (how high the breast is)..... | 1 | 2 | 3 | 4 |
| 14. Scar tissue..... | 1 | 2 | 3 | 4 |
| 15. Shoulder pain..... | 1 | 2 | 3 | 4 |
| 16. Arm pain..... | 1 | 2 | 3 | 4 |
| 17. Arm swelling..... | 1 | 2 | 3 | 4 |
| 18. Breast swelling..... | 1 | 2 | 3 | 4 |
| 19. Arm stiffness..... | 1 | 2 | 3 | 4 |
| 20. Fit of bra..... | 1 | 2 | 3 | 4 |
| 21. Breast sensitivity..... | 1 | 2 | 3 | 4 |
| 22. Fit of clothing..... | 1 | 2 | 3 | 4 |

Appendix 15.2 CTCAE v. 4

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

| Skin and subcutaneous tissue disorders | | | | | |
|---|---|---|---|---|---|
| | Grade | | | | |
| Adverse Event | 1 | 2 | 3 | 4 | 5 |
| Rash maculo-papular | Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness) | Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL | Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL | - | - |
| Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus. | | | | | |
| Scalp pain | Mild pain | Moderate pain; limiting instrumental ADL | Severe pain; limiting self care ADL | - | - |
| Definition: A disorder characterized by marked discomfort sensation in the skin covering the top and the back of the head. | | | | | |
| Skin atrophy | Covering <10% BSA; associated with telangiectasias or changes in skin color | Covering 10 - 30% BSA; associated with striae or adnexal structure loss | Covering >30% BSA; associated with ulceration | - | - |
| Definition: A disorder characterized by the degeneration and thinning of the epidermis and dermis. | | | | | |
| Skin hyperpigmentation | Hyperpigmentation covering <10% BSA; no psychosocial impact | Hyperpigmentation covering >10% BSA; associated psychosocial impact | - | - | - |
| Definition: A disorder characterized by darkening of the skin due to excessive melanin deposition. | | | | | |
| Skin hypopigmentation | Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact | Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact | - | - | - |

| Skin and subcutaneous tissue disorders | | | | | |
|---|---|---|---|---|---|
| | Grade | | | | |
| Adverse Event | 1 | 2 | 3 | 4 | 5 |
| Definition: A disorder characterized by loss of skin pigment. | | | | | |
| Skin induration | Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up) | Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL | Severe induration, unable to slide or pinch skin; limiting joint movement or orifice (e.g., mouth, anus); limiting self care ADL | Generalized; associated with signs or symptoms of impaired breathing or feeding | Death |
| Definition: A disorder characterized by an area of hardness in the skin. | | | | | |
| Skin ulceration | Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema | Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat | Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia | Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss | Death |
| Definition: A disorder characterized by circumscribed, inflammatory and necrotic erosive lesion on the skin. | | | | | |
| Stevens-Johnson syndrome | - | - | Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment) | Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment) | Death |
| Definition: A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes. | | | | | |

Appendix 15.3.1 RTOG cosmesis scale- PHYSICIAN FORM

| | |
|---|---|
| 1 | **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. |
| 2 | **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. |
| 3 | **FAIR**: obvious differences in the size and shape of the treated breast. This change involves 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. |
| 4 | **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. |

(Circle the number next to the word that best describes the cosmetic results.)

| | 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 |
| Breast shrinkage | 0 | 1 | 2 |
| Other significant tx effects<br>Specify: _____ | 0 | 1 | 2 |

Appendix 15.3.2 RTOG cosmesis scale- PATIENT FORM

1. How satisfied with your treatment are you?

Extremely satisfied Very satisfied Satisfied Unsatisfied

2. Would you choose this treatment again?

Yes No

3. Please circle the number that correlates with your assessment of the cosmetic result of your treatment:

| | |
|---|---|
| 1 | **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. |
| 2 | **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. |
| 3 | **FAIR**: obvious differences in the size and shape of the treated breast. This change involves 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. |
| 4 | **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. |