Official Title:	A Phase II Prospective Clinical Trial to Assess the Feasibility of Preoperative Radiation Boost in Breast Cancer Patients
NCT number:	04871516
Document Type:	Protocol and SAP
Date of the Document:	01/03/2023

RUTGERS
THE STATE UNIVERSITY OF NEW JERSEY

INTERVENTIONAL
RESEARCH PROTOCOL TEMPLATE
(HRP-503a)

STUDY INFORMATION

- **Title of Project:** A PHASE II PROSPECTIVE CLINICAL TRIAL TO ASSESS THE FEASIBILITY OF PREOPERATIVE RADIATION BOOST IN BREAST CANCER PATIENTS
- **Principal Investigator Name**
  Bruce G. Haffty, MD
- **Principal Investigator Div. & Dept.** Department of Radiation Oncology
  CINJ, RWJMS, NJMS
- **Principal Investigator Contact Info:**
  hafftybg@cinj.rutgers.edu, 732-235-5203
  Rm 2012 CINJ
  195 Little Albany St.
  New Brunswick, NJ 08901
- **Protocol Version and Date:**
  16.0: 03JAN2023

RUTGERS | eIRB
APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

RUTGERS
THE STATE UNIVERSITY OF NEW JERSEY

Table of Contents

Skip To Section: Hold **CTRL** + **Click (Below)** To Follow Link in **Blue**

1.0	Research Design
1.1	Purpose/Specific Aims
1.2	Research Significance
1.3	Research Design and Methods
1.4	Preliminary Data
1.5	Sample Size Justification
1.6	Study Variables
1.7	Drugs/Devices/Biologics
1.8	Specimen Collection
1.9	Data Collection
1.10	Timetable/Schedule of Events
2.0	Project Management
2.1	Research Staff and Qualifications
2.2	Research Staff Training
2.3	Resources Available
2.4	Research Sites
3.0	Multi-Center Research
4.0	Subject Considerations
4.1	Subject Selection and Enrollment Considerations
4.2	Secondary Subjects
4.3	Number of Subjects
4.4	Consent Procedures
4.5	Special Consent Populations
4.6	Economic Burden and/or Compensation For Subjects
4.7	Risks of Harm/Potential for Benefits to Subjects to Subjects
5.0	Special Considerations
5.1	Health Insurance Portability and Accountability Act (HIPAA)
5.2	Family Educational Rights and Privacy Act (FERPA)
5.3	Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)
5.4	General Data Protection Regulation (GDPR)
5.5	NJ Access to Medical Research Act (Surrogate Consent)

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

6.0	Data Management Plan
6.1	Data Analysis
6.2	Data Security
6.3	Data Safety And Monitoring
6.4	Reporting Results
6.5	Secondary Use of the Data
7.0	Research Repositories – Specimens and/or Data
8.0	Approvals/Authorizations
9.0	Bibliography

1.0 Research Design

1.1 Purpose/Specific Aims

The purpose of our study is to assess feasibility of preoperative radiation boost in breast cancer patients. Primary outcome is acute wound complication rate. We also aim to evaluate cosmetic outcome and loco-regional control as secondary outcomes. Another goal is to look into the histopathology of tumors before and after radiation to assess response and other immunologic changes to the tumor and the tumor environment elicited by the radiation treatment. We hope that this will guide future trials that could change practice in certain patient subgroups

- **A. Objectives** Our primary Objective is to demonstrate that the incidence of grade 3 or more wound complications in patients with non-metastatic node negative breast cancer or DCIS who are eligible for BCS and treated with pre-operative radiation boost at 1 month after end of whole breast radiation is no worse than the rates in the current standard of care (6-20%). Our secondary objective is to demonstrate that the physician reported cosmetic outcome at 1 and 3 years after the end of treatment is better than what has been reported for the current standard of practice for patients undergoing BCS and hypofractionated WBI (around 35% reported poor/fair cosmesis at 3 years, Shaitelman et al.). Tertiary objectives are to measure the acute and late radiation related toxicities such as radiation dermatitis, telangiectasia and fibrosis in this cohort of patients.
- To measure the pre-operative boost CTV and compare to the post-op CTV volume that would have been contoured as CTV if the boost was to be delivered post-operatively.
- To measure the incidence of fair/poor patient reported cosmetic outcome using the BCTOS cosmetic scale
- To study the cancer biology before and after radiation treatment.

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

B. Hypotheses / Research Question(s)

Pre-operative radiation treatment approach allows for more accurate targeting of the tumor and thus of the high-risk areas of subclinical disease. It is possible that the treatment volumes would be smaller compared to when treating post-operative seroma for boost. This could result in a better cosmetic outcome and decreased toxicity. Our study aims to assess the feasibility of this approach and to assess the cosmetic and loco-regional outcomes with this novel approach.

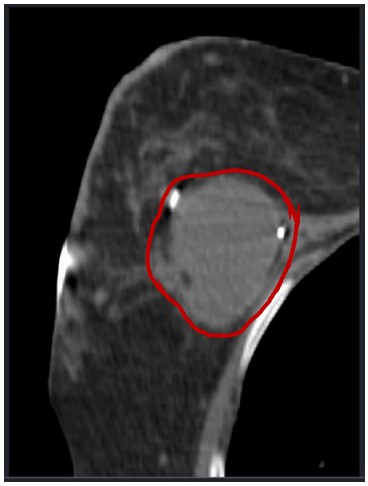
1.2 Research Significance

The current standard of care for patients with invasive non-metastatic breast cancer or DCIS who are candidates for Breast Conserving Surgery (BCS) is adjuvant whole breast radiation followed by an additional boost to the tumor bed. The benefit of tumor bed boost in reducing the local recurrence rates is established from historic clinical trials. However, the sequential delivery of the boost after surgery and radiation is done out of convention rather than any particular scientific rationale. Delivering the boost in the pre-operative setting provides the benefit of accurately directing the high radiation dose at the tumor and thus sparing normal breast tissue. It also takes advantage of a non-hypoxic microenvironment leading to an increase in the therapeutic ratio and superior outcome. We hypothesize that delivering the radiation boost pre-operatively will not result in a significantly higher risk of surgical wound complications. We also think that this approach will result in better cosmesis and less radiation toxicity to normal tissue.

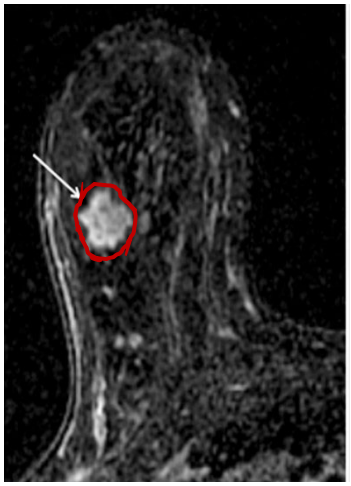
The picture below is an example to illustrate the difference between the pre-operative and postoperative targets for radiation boost. The pre-operative boost target would be the actual tumor; the post-operative tumor bed that we traditionally boost is usually defined by surgical clips; presence of seroma and other variables that are surrogates for where the tumor used to be. This volume delineation can vary between different radiation oncologists and is not as accurate as when we are treating the visualized tumor.

RUTGERS | eIRB
APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

Post-operative boost target



Pre-operative boost target

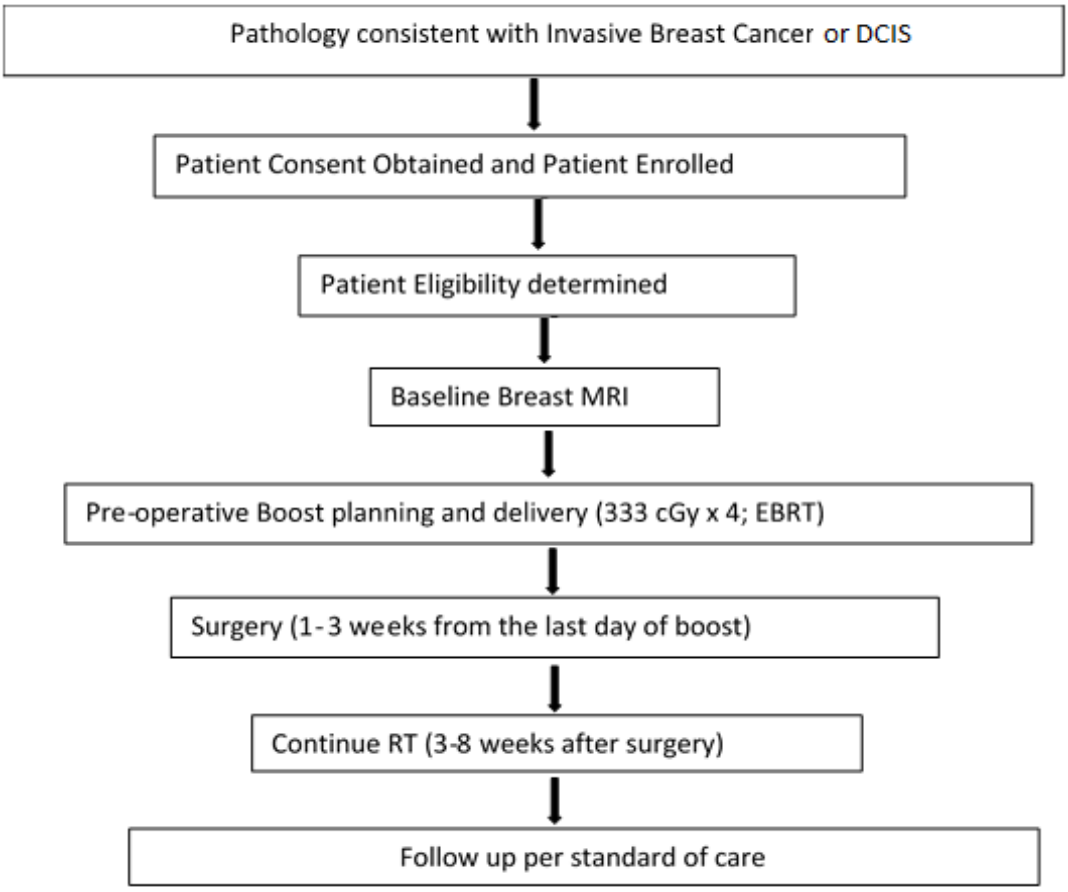


1.3 Research Design and Methods

This study is a Phase II prospective, non-randomized, single arm clinical trial evaluating the feasibility of delivering the radiation boost *pre-operatively* in non-metastatic, node negative breast cancer patients who are eligible for breast conserving surgery.

Schema:

RUTGERS | eIRB
APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024



A. Research Procedures

Patients will be recruited from the Cancer Institute of New Jersey Comprehensive Breast Care Center, or the Radiation Oncology Facility. Patients will be enrolled via the Rutgers Cancer Institute of New Jersey's Office of Human Research Services (OHRS). A unique study number will be issued for each patient after enrollment. We will be evaluating the feasibility of preoperative radiation boost in these patients. Eligible patients will be consented to enroll on the trial when seen by the surgical oncology team for a consult. Consents will be done by the PI, resident or other study personnel. Patients who consent to be enrolled will undergo a baseline breast MRI. They will then undergo pre-operative radiation boost which is the main clinical intervention in this trial. After the pre-operative boost, patients will go on for their scheduled surgery. Surgery will not be different from what the patient would have been assigned for if not on trial. After surgery, patients will proceed with the rest of radiation treatment. If the patients is a candidate for adjuvant chemotherapy, they will proceed with chemotherapy after completion of the radiation course.

Modification (03JAN2023):

RUTGERS | eIRB
APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

In collaboration with Ankit Saxena, PhD, Managing Director of the Immune Monitoring Flow Cytometry shared resource (IMFC-SR), we propose to assess the frequencies, and co-inhibitory molecule expression of immune cell populations in tumor, before and after radiation therapy. We will measure the following immunologic parameters that may be indicative of responsiveness to treatment using advanced multi-parameter flow cytometry. The frequencies of T, B, NK, myeloid, Myeloid derived suppressor cells (MDSC's) subsets will be analyzed by flow cytometry using antibodies for CD45, CD3, CD4, CD8, CD11b, CD11c, CD14, CD15, CD66, CD19, NKG2D, HLA-DR, CD206, CD80, PD-1, TIM3, LAG-3, FOX-P3, Ki-67. Special attention will be paid to CD8 T cell: CD4 Treg and NK: CD4 Treg cell ratios as well as MDSC's. We hypothesize that increased effector (CD8 and NK cell subsets versus Treg subsets and MDSC's) following radiation therapy will be a biomarker positively associated with responsiveness to treatment and other major prognostic indicators for survival.

B. Data Points

Demographic data, known breast cancer risk factors, family history, age and stage at diagnosis, tumor characteristics, previous and current treatments and medication history will be collected at first visit. After surgery, and in the consecutive follow up visit after completion of RT, acute toxicities, cosmesis and disease outcomes and relapse will be collected. We will then collect toxicities and clinical outcomes every three months for at least 3 years. Patient and physician reported cosmetic outcomes will be collected at 1 month follow up, 6 months follow up, 1 year, 2 years, and 3 years after completion of RT.

Study Duration

We expect to complete enrollment within 3 years of study opening date. We will follow the patients up for at least 3 years after completion of radiation.

C. Endpoints

Primary endpoint: Grade 3 wound complication after breast conserving surgery as defined by the CTCAE V5.0 to require operative intervention. The incidence of wound complications after breast surgery have been variably reported to be between 6% and 30% [13, 14, and 15]. In soft-tissue extremity sarcoma and rectal cancer, we know that pre-operative radiation results in higher acute wound complications after surgery.

Historic data from clinical trials using pre-operative radiation to the breast have reported higher wound complication rates and surgical delays with radiation [16]. However, these trials utilized old radiation techniques, irradiated the whole breast, the majority of them utilized neoadjuvant chemotherapy combination. There is a small risk with this trial that the wound complication rate would be higher than the baseline expected wound complicated rate after breast conserving surgery; hence, this is a phase I trial to assess safety of this approach.

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

Secondary endpoint: Physician reported cosmetic assessment at 1 month, 6 months,1 year, 2 years, and 3 years after WBI using the Harvard Cosmesis assessment Scale for Breast Cancer Patients which is a 4point scale describing the breast cosmetic outcome (excellent, good, fair or poor).

Modification (04OCT2022):

In this modification, we are proposing an expansion cohort so we are able to demonstrate that the good-excellent cosmetic outcome exceeds 90%. Our preliminary data indicate good-excellent cosmesis in a majority of patients, exceeding 90%. The original trial, which was powered to evaluate Grade 3 surgical complications, is not powered for cosmetic outcome. In this modification, we propose to expand the cohort to definitively demonstrate a cosmetic outcome of good-excellent exceeding 90%, as compared to historical control rate of 80% in hypofractionated whole breast radiation including a boost. The specific rationale for the expansion cohort given in the statistical section.

Breast Conserving Surgery (BCS) was primarily developed to reduce the morbidity and improve the cosmetic outcome in comparison to mastectomy; these factors are crucial to patients' quality of life. The RAPID trial which is a phase III non-inferiority trial comparing APBI to whole breast; 88% of the patients who had whole breast irradiation and had excellent or good cosmesis at baseline, maintained excellent or good cosmesis after 3 years of RT [17].

Shaitelman et. Al, reported a rate of poor or fair physician reported cosmetic outcome after hypofractionated WBI with boost to be 35.4% at 3 years after completion of radiation [18]. Table 1.0 shows the Harvard scale. Administering the radiation boost pre-operatively, we expect better targeting of the tumor bed because the tumor can be visualized and targeted and smaller treated volume which hypothetically associated with a better cosmetic outcome.

Table 1: Harvard scale (4-point Likert scale).

Excellent	Treated breast nearly identical to untreated breast
Good	Treated breast slightly different from untreated breast
Fair	Treated breast clearly different from untreated breast but not seriously distorted
Poor	Treated breast seriously distorted

Tertiary endpoints:

1. Overall end point of acute and late radiation toxicity which includes:
    - Rate of fibrosis (different grades per the CTCAE V 5.0)

RUTGERS | eIRB
APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

- Rate of telangiectasia formation (different grades per the CTCAE V 5.0)
- Rate of radiation dermatitis (different grades per the CTCAE V 5.0)
- Changes in pathology between the biopsy and the surgical specimen

1. Patient reported cosmetic outcomes at 1 month, 6 months, 1 year, 2 years, and 3 years after WBI using the Breast Cancer Treatment Outcomes Scale (BCTOS). The BCTOS cosmetic scale describes patient-reported changes in the treated breast and surrounding area relative to the contralateral breast, which serves as an internal control. Items were scored on a 1 to 4 scale, with 1 indicating no difference between the treated breast and untreated contralateral breast, 2 indicating a slight difference, 3 indicating a modest difference, and 4 indicating a large difference. The BCTOS patient reported cosmetic outcome score is the arithmetic mean of the nine items that assess the cosmetic outcome [19].

2. The difference between the pre-operative boost CTV volume and the post-op CTV volume that would have been contoured as CTV if the boost was to be delivered post-operatively.

1.4 Preliminary Data

Breast cancer is the most commonly diagnosed cancer among women worldwide [1]. In the United States, the estimated number of new cases and deaths from breast cancer in 2019 is approximately 295,290 and 65,540 respectively [2]. Due to the effectiveness of screening tests, for most patients in the developed world, <10% of patients are first diagnosed with advanced stages [3]. Locoregional therapies for breast cancer patients consist of either mastectomy or lumpectomy followed by whole breast radiation therapy (WBRT). Both have been shown to be equivalent to mastectomy in terms of local control and overall survival [4].

A radiation boost targeted at the tumor bed is routinely administered to breast cancer patients as part of breast-conserving therapy. The rationale for a boost is based on the patterns of recurrence data that has demonstrated that the vicinity of the original index tumor is the most common site of local recurrence and therefore requires a higher tumoricidal dose from RT compared to the rest of the breast [5]. Several randomized controlled trials have shown that the addition of a boost to standardly fractionated whole breast RT (WBRT) in women with localized breast cancer led to an improvement in local control [5, 6]. The largest of these trials, the EORTC 22881, included 5318 patients with stage I-II breast cancer who underwent lumpectomy + axillary lymph node dissection [6]. Following WBRT (50 Gy/25 fractions), patients were randomized to +/- 16 Gy boost. With a median of 17.2 years of follow-up, the cumulative incidence of local failure was 13% in boosted patients compared with 9% in the non-boost group HR 0.65 (99% CI 0.52-0.81, p<0.0001). The benefit of a boost was observed in all age groups.

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

Today, oncoplastic surgery and rearrangement of breast tissue has been increasingly used in order to optimize the cosmetic outcome. While the rearrangement of the tumor bed may optimize long-term cosmetic results, is also has the unintended consequence of relocating the tumor bed tissue thought to be at highest risk of local recurrence, the area to which a radiation tumor bed boost is typically delivered. As a result, it is sometimes not feasible to localize the tumor bed and a tumor bed boost is either omitted or a much larger volume of the breast is irradiated in order to target what is believed to be at risk tissue. This is concerning particularly because those patients undergoing oncoplasty appear to relatively younger in age, for whom a tumor bed boost has been shown to have the greatest benefit [7, 8]. Delivering the boost pre-operatively would enable a more accurate delineation of the tumor and high-risk vicinity.

In breast cancer, the data on pre-operative radiation treatment delivery is limited. Retrospective breast cancer series from France have looked at patients treated definitively with pre-operative radiation therapy between the 1970s and 1980s. Pathologic CR rate was achieved in 10% of all patients and in 26% in patients with TNBC; the post-operative complication rate (grade>2) was 19% with 4.3% of localized skin necrosis [9].

Another study from Russia compared neoadjuvant chemoRT to RT alone prior to mastectomy in patients with Stage II and III breast cancer and reported pCR in 19.4% of patients undergoing pre-operative RT alone and 29.1% in patients who had pre-operative chemoRT; statistical significance was not assessed for pCR. Among the post-surgical complications was a high incidence of prolonged (3-4 weeks) lymphorrhea, observed in 18.2% of patients receiving neoadjuvant chemotherapy, and in 16.4% of those treated with preoperative radiotherapy alone. Suppuration of the postoperative wound occurred in 4.3% of patients treated with neoadjuvant chemotherapy, and in 6.7% of those treated with preoperative radiotherapy alone [10].

The current standard of care in breast cancer treatment is adjuvant radiation after completion of surgery and chemotherapy (when needed).
Few more recent trials were conducted assessing pre-operative radiation in the breast; these trials used different dose fractionation than the standard adjuvant RT fractionation. In a phase I dose escalation trial of single-dose preoperative partial breast irradiation in early stage breast cancer patients, 32 patients were enrolled and no acute dose-limiting grade 3 or 4 radiation related toxicities were reported. They did not see wound dehiscence in any of the patients. Patients who only received the pre-operative partial breast treatment all had good or excellent cosmesis as rated by the physicians. They reported 3 patients who received post-operative external beam radiotherapy because of upgrade of pathology at the time of surgery. Among these three, two grade 3 chronic toxicities were seen in a patient from this group who was diagnosed post treatment with a connective tissue disorder. Another patient with diabetes developed a postoperative wound infection and all three had fair/poor cosmetic outcomes [11].

Another dose escalation study of stereotactic body radiation therapy (SBRT) combined with neoadjuvant chemotherapy in breast cancer patients was published from France in 2013. Five dose levels of SBRT were tested concomitantly with neoadjuvant chemotherapy. Of the 25

RUTGERS | eIRB
APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

women that were treated, Maximum tolerable dose was not reached. Only 1 case of dose-limiting toxicity was reported (grade 3 dermatologic toxicity), and SBRT was overall well tolerated. The pCR rate was 36%, with none being observed at the first 2 dose levels, and the highest rate being obtained at dose level 3 (25.5 Gy delivered in 3 fractions) [12].

In this study, we aim to deliver the radiation boost portion pre-operatively using the same dose fractionation as we would in the post-operative setting. We will benefit from the more accurate targeting of the high radiation dose at the tumor and we anticipate sparing more normal breast tissue. As mentioned above, this approach will also take advantage of a non-hypoxic microenvironment leading to an increase in the therapeutic ratio. These factors combined may lead to a superior outcome.

1.5 Sample Size Justification:

Our sample size calculation is based on data reporting incidence of wound complications after breast surgery to be between 6% and 30% [13, 14, and 15]. Data from soft-tissue extremity sarcoma and rectal cancer, as well as historic data on breast pre-operative RT, describes higher acute wound complications rates after surgery in the pre-operative RT settings [16].

In this study; we aim to deliver the boost dose in the pre-operative setting. Because of the boost low dose and because this irradiated tissue will be resected; we expect the wound complication rate to be comparable to the standard treatment.

We have calculated a sample size of 50 subjects to provide 80% power using a two-sided exact test for binomial proportion to conclude that the combined Grade 3 or greater wound complication rate is less than 20%, assuming an expected rate of Grade 3 wound complications in our cohort of 6% or less as detailed below. We will account for a 10% loss to follow up rate; so, we will aim for a sample of 55 subjects.

RUTGERS | eIRB
APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

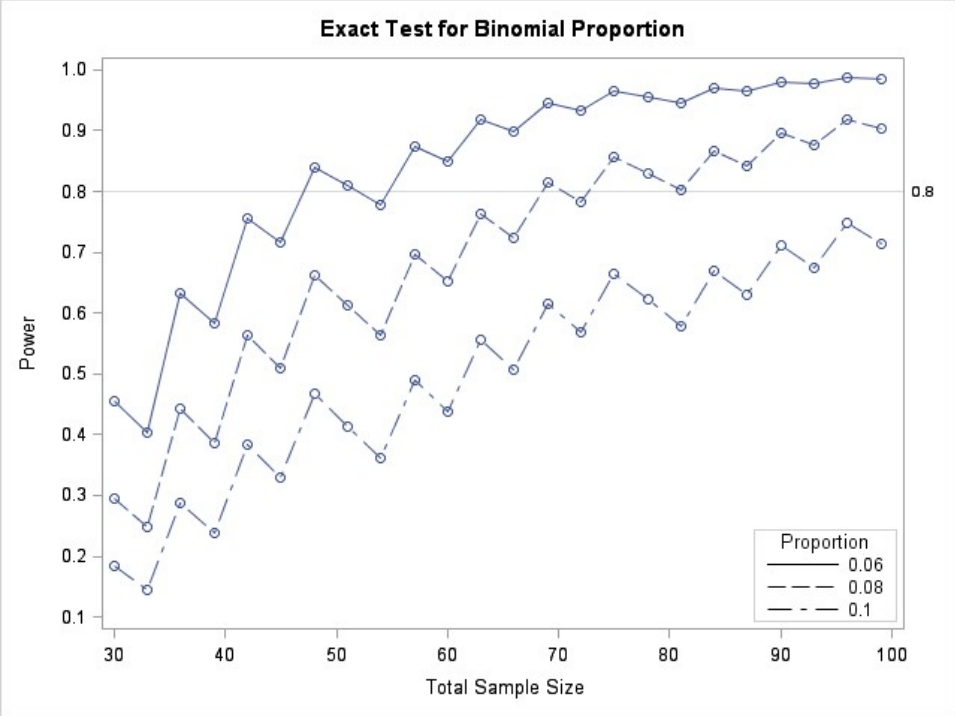


Figure 1. The estimated statistical power of the two-sided 0.05 level exact binomial test for testing the null hypothesis that grade 3 wound complication rate is less than 20%.

A key concern is to ensure that that rate is no higher than 20%. Thus, we plan to stop the trial if, at any point, we are 80% sure that that rate is higher than 20%, using a Bayesian calculation of the posterior probability using a non-informative prior. The stopping rules are outlined in the following table:

Number of patients enrolled	Allowed complications
10	2
14	3
19	4
24	5
29	6
34	7
39	8
44	9

For example, if there were 3 complications among the first 14 patients, the trial would be allowed to continue. But if there were 4 complications among these 14 patients, the trial would stop for

RUTGERS | eIRB
APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

an excessive rate of wound healing complications. Grade 3 and above wound complications will be reported as Events of special interest.

1.6 Study Variables

A. Independent Variables, Interventions, or Predictor Variables
All patients enrolled on this trial will receive a pre-operative radiation boost the breast cancer tumor which is the study intervention. The standard of care would be postoperative radiation followed by boost; but this is a single arm trial and patients will not be randomized.

B. Dependent Variables or Outcome Measures
Wound complications post operatively will be measured. Cosmesis and locoregional control will be assessed every 3- 6 months interval for at least 3 years after completion of radiation treatment.

1.7 Drugs/Devices/Biologics

Pre-operative radiation boost will be delivered the same way as we would for post-operative radiation boost which is standard of care. External beam radiation using photon or electron plans will be utilized. CTV will be contoured based on baseline MRI to help delineate the tumor. The boost dose fractionation will be 333 cGy x 4 fractions. The boost is delivered in one fraction per day for four consecutive days, not including weekends or holidays. If the boost were to start on a Wednesday for example, the last fraction will be on the Monday after.

Specifics of Radiation Treatment:

Dose Prescription:

- Dose to the PTV_ Boost: 333 cGy x 4 fractions to a total of 1332 cGy using EBRT.
- WBRT dose Post-lumpectomy: 333 cGy x11 fractions to a total of 3663 cGy.
- RLN dose (if at surgery it was determined there is need to treat regional LN): 333 cGy x 11 fractions to a total of 3663 cGy.

Patient simulation: A CT simulation is required for the boost treatment. The patient will need another CT simulation for WBRT after surgery. Diagnostic MRI will be used to assist delineate the Boost volume. Patient positioning will be performed based on the discretion of the treating radiation oncologist, who will determine this based on the patient's unique anatomy and the ability to delineate the tumor volume on CT (boost CT sim may be done prone to facilitate fusion with the MRI if needed). Four surface BB's will be placed on the breast at the time of simulation to assist with alignment for treatment delivery; this can vary per the attending discretion.

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

Treatment Planning:

- Gross tumor volume (GTV) is contoured on the CT sim using the CT image as well as the MRI images. If fusion cannot be obtained accurately, the physician can use the MRI to localize the tumor on CT; this should be done per the attending discretion.
- Clinical target volume (CTV) will be delineated with a uniform expansion of 0.5 cm subtracted off the chest wall musculature and within the first 0.5cm of the external skin surface.
- Planning Treatment Volume (PTV) an additional uniform margin of 0.5 cm from the CTV. For the purposes of dosimetric coverage evaluation, an evaluative PTV (PTV_Eval) will be created, which is the PTV subtracted 5mm from the skin surface and from the chest wall musculature.
- Treatment planning with electrons/ photons (6, 10 or 15 MV) will depend on the patient anatomy and the depth of the tumor.
- 95 % of the PTV_EVAL is to be covered by >= 90% of the prescribed dose and 100% of the GTV to be covered by 100% of the prescription dose. (Minor deviation if < 95% of PTV_eval covered by >=90% of prescribed dose; unacceptable if less than 88% of the PTV_eval is covered by prescribed dose).
- Max dose % preferred < 110% but acceptable if <115%; consider using wedges or field in field to decrease hotspots

WBRT post-op

- Whole breast to be covered by >= 95% of the prescribed dose (unacceptable if =< 88%).

Acceptable constraints:

- Max dose < 110%
- V105% =< 200 cc; minor deviation if < 400 cc
- V107% =< 2cc; minor deviation if < 30 cc
- Mean heart dose =< 2 Gy
- Heart V5 < 40% (less than 50% for L sided breast)
- Total Lung V20 < 15%

If Node positive at surgery:

- Whole breast to be covered by >= 95% of the prescribed dose
- Nodal CTV covered by > 90% of prescribed dose; IMN coverage is at the discretion of the treating physician.

Acceptable constraints:

- Max dose < 115%
- V105% =< 200 cc; minor deviation if < 400 cc
- V107% =< 2cc; minor deviation if < 30 cc
- Mean heart dose =< 5 Gy
- Heart V5 < 40% (less than 50% for L sided breast)
- Total Lung V20 < 35%
- Total lung V40 < 20%

A. Drug/Device Accountability and Storage Methods NA

1.8 Specimen Collection

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

A. <u>Primary</u> Specimen Collection

- **<u>Types of Specimens</u>**: The patients will be given the option to provide blood & tissue samples that will could be used in the future. The patient can still participate in the study if they refuse to provide samples. If the patient consents for blood and tissue collection, a frozen section tumor samples from the lumpectomy specimens will be sent to CINJ tissue repository. A peripheral whole blood sample will be collected from every patient. This can be done at any point during the study. Blood collection will be done at the office by the nurse using venipuncture. The samples will be places in cryovials and will be labeled with the patient's assigned study number. These will be transported from the clinic to the biospecimen repository services (BRS) at the Rutgers Cancer institute of New Jersey on the day that it is obtained. Transport will be the responsibility of the study personnel. Whole blood samples will be collected using a peripheral venous line into 1 EDTA (purple top) tube (10 ml), a maximum of 30 ml can be drawn for the purpose of the study (total of 3 tubes). Each site will use their own tubes. Once collected in EDTA tube, they will be gently inverted 5-10 times to mix. Specimens will be maintained at ambient temperature (room temperature) during collection and transport.

- **<u>Annotation</u>**: Bloods samples are to be labeled with:
  - A generated specimen ID (which includes the treatment protocol number and the study Patient ID)
  - Specimen type (blood)
  - Collection period (specifying "Simulation" versus Surgery").
  - Collection date.

- **<u>Transport</u>**: BRS will collect and transport the tubes to CINJ biorepository from all the sites (shipping address: CINJ biorepository, 195 little Albany St. New Brunswick, NJ 08901). Specimen can be shipped the day of collection or the day after collection.
- **<u>Processing</u>**: This is to be determined.
- **<u>Storage</u>**: The tubes will be stored in a -80◦c freezer in CINJ biorepository.
- **<u>Disposition</u>**: The specimen will be kept indefinitely.

B. <u>Secondary</u> Specimen Collection-Frozen section tumor samples from the lumpectomy specimens will be sent to CINJ tissue repository for potential immunologic markers (Only CINJ subjects that consent to tissue collection).

- **<u>Types of Specimens</u>**: Tissue samples from lumpectomy.
- **<u>Annotation</u>**:
  - A generated specimen ID (which includes the treatment protocol number and the study Patient ID)

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

- Specimen type (breast tumor)
- Collection period (specifying "Simulation" versus Surgery").
- Collection date

- **Transport**: BRS will collect and transport tissue sample to immunology core
- **Storage**: Per immunology core
- **Disposition**: Kept indefinitely

1.9 Data Collection

A. Primary Data Collection

- **Location**: Patients will be seen for follow up per protocol in a similar schedule to what would be the case if they were not on trial. The collected data will be similar to what we would collect on a patient if not on trial.
- **Process of Data Collection**: Data will be collected by the resident, APN or attending physician who is taking care of the patient.
  Timing and Frequency: Patients will be seen at 1 month follow up after completion of RT and then every 3 months for 1 year; then every 6 months for 2 additional years. Data on clinical outcome, side effects and cosmesis will be collected at each follow up.
- **Procedures for Audio/Visual Recording**: NA
  Study Instruments: We will use the BCTOS and Harvard scale to assess cosmesis at 1 month, 6 months after RT and at 1, 2, and 3 years. BCTOS is a self-report instrument that has high reliability and validity. The Harvard Cosmesis scale is a physician rated form that will be used by the physician to assess cosmesis at each time point as above (see appendix).
- **Ethnographic Studies, Interviews, Or Observation**: NA
- **Subject Identifiers**: Each patient will be assigned a study ID which will be linked to the patient MRN. The link will be available on Oncore and access will be limited to PI and study personnel. The link will be available indefinitely.

B. Secondary Data Collection NA

- **Type of Records**: NA
- **Location**: NA
- **Inclusion/Exclusion**: NA
- **Data Abstraction Form(s):** NA

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

1.10 Timetable/Schedule of Events

Procedures	First Visit (Pre-Boost)	Boost-RT (any day of Boost)	Post-Operative Visit (WBI simulation)	Last day WBRT (EOT summary)	FU 1 month (+/- 2 weeks)	FU 3 months (+/-6 weeks) #	FU 6 months (+/-6 weeks)	FU 9 months (+/-6 weeks) #	FU 12 months (+/-6 weeks)	FU 18 months (+/-6 weeks)	FU 24 months (+/-6 weeks)	FU 30 months (+/-6 weeks)	FU 36 months (+/-6 weeks)
Informed Consent	X												
Demographics	X												
Medical History	X												
Performance Status (ECOG)	X	X	X	X	X	X	X	X	X	X	X	X	X
Mammogram	X												
MRI	X												
Blood Sample*	X				X		X		X		X		X
Tissue Sample^			X										
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease status Evaluation	X		X	X	X	X	X	X	X	X	X	X	X
BCTOS					X		X		X		X		X
Photographs*	X				X		X		X		X		X
Harvard Cosmesis					X		X		X		X		X
Wound Evaluation†			X	X	X	X	X	X	X	X	X	X	X
Radiation Toxicity Evaluation†				X	X	X	X	X	X	X	X	X	X

Optional visits
^ Optional (CINJ Subjects)
* Optional and can be obtained at any time point
† per CTCAE V5.0 criteria

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

2.0 Project Management

2.1 Research Staff and Qualifications: All Co-investigators are CITI trained Rutgers faculty or staff.

2.2 Research Staff Training: All Co-investigators are CITI trained Rutgers faculty or staff.

2.3 Resources Available: Research intervention will be done within RWJ radiation oncology department which is staffed with the capabilities of performing the pre-operative boost and the rest of the study parameters.

2.4 Research Sites: Robert Wood Johnson University Hospital – Hamilton, Robert Wood Johnson University Hospital-Somerset, Rutgers Cancer Institute of New Jersey at University Hospital, Cooperman Barnabas Medical Center, Community Medical Center, Monmouth Medical Center, Monmouth Medical Center Vantage Point Infusion Center, Trinitas Regional Medical Center, Jersey City Medical Center, Newark Beth Israel Medical Center, and Clara Maass Medical Center.

3.0 Multi-Center Research

NA

4.0 Subject Considerations

4.1 Subject Selection and Enrollment Considerations

A. Method to Identify Potential Subjects

Patients will be primarily recruited from the Cancer Institute of New Jersey Comprehensive Breast Cancer Center, or the Radiation Oncology Facility.

B. Recruitment Details

We normally see around 8-15 clinically, node negative breast cancer patients per month with biopsies revealing invasive disease. Considering patients with multi-centric disease, those who cannot undergo a pre-operative MRI, and/or will not want to be on trial, we expect to enroll around 3-5 patients a month. The recruitment will happen at CINJ or at RWJ hospital in the Rad Onc department.

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

Subject Screening

The treating physician – surgeon, medical oncologist or radiation oncologist will determine if the subject maybe eligible to the study. If so, a research nurse will meet with the patient to go over eligibility criteria.

- **Inclusion Criteria**

- Breast cancer patients with biopsy proven invasive cancer or DCIS
- Clinically and radiographically node negative disease
- No indication of metastatic disease
- Age >= 18
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1.
- Synchronous bilateral invasive cancer allowed
- Negative serum pregnancy test
- Willingness to participate in the clinical trial and adhere to the study protocol
- Individuals of all races, genders and ethnic groups are eligible for this trial.
- Ability to understand and consent to the study

- **Exclusion Criteria**

- Need for Neoadjuvant Chemotherapy
- Inflammatory Breast Cancer (cT4)
- Multicentric tumor
- Prior ipsilateral breast or thoracic RT
- Contraindication for baseline MRI
- Contraindication for surgery
- Distant metastatic disease
- Other synchronous cancer (besides bilateral breast)
- Contraindication to Radiation therapy (presence of scleroderma or other collagen vascular disease)
- Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

RUTGERS | eIRB
APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

4.2 Secondary Subjects NA

Registration/Enrollment

Patients with breast cancer or DCIS who are eligible for the study will be enrolled in the clinical trial after they provide informed consent for study participation. A copy of the institution's IRB approved informed consent document and written justification for any changes made to the informed consent for this protocol will be on file at Rutgers Cancer Institute of New Jersey's Office of Human Research Services (OHRS) before any participating institutions may enter patients.

All patients will be registered and enrolled through OnCore®, the Clinical Trials Management System for this study.

- **Registration**: The date the patient signs consent form and is registered in OnCore®. Signed consent form must be uploaded into OnCore®. Screening should be completed within 28 days prior to enrollment**.**
- **Enrollment:** Once eligibility has been confirmed the patient will be enrolled (indicated as "On Study") through OnCore®. The completed, signed and dated eligibility checklist must be uploaded into OnCore®.

  Patients will not start protocol treatment prior to enrollment. Trial treatment should begin within 30 days of enrollment.
- **On-Treatment date**: The date the patient starts pre-operative boost.
- **Off-Treatment date:** The last day of adjuvant radiation treatment after surgery will be listed as the off-treatment date.
- **Off-Study**: Patient will be considered off-study if the patient does not complete the pre-operative boost treatment or if discontinued by the PI, or the patient dies. Patients are considered to be lost to follow up if they do not show up for follow up after finishing the course of treatment for 3 appointments and with no response to phone calls. Those patients can be included until the last day they are seen on study.

4.3 Number of Subjects

A. Total Number of Subjects

We have calculated a sample size of 50 subjects to provide 80% power using a two-sided exact test for binomial proportion to conclude that the combined Grade 3 or greater wound complication rate is less than 20%, assuming an expected rate of Grade 3 wound complications in our cohort of 6% or less as detailed below. We will account for a 10% loss to follow up rate; so, we will aim for a sample of 55 subjects.

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

A1. Modification: In order to demonstrate good to excellent cosmesis in over 90% of patients we will conduct an expansion protocol. Historically with hypofractionated whole breast radiation and a boost the good-excellent cosmesis outcome is 80%. With our smaller boost volume pre-operatively, we hypothesize that our good-excellent cosmesis is greater than 90%. In order to demonstrate this the following analysis indicates we would need a sample size of 98 which would give us a 90% power to demonstrate an increase in good-excellent cosmesis in over 90% of patients with a 5% two-sided test of proportions.

We therefore would like to proceed with an expansion cohort to bring the total sample size to 98 from the current sample size of 55 in order to demonstrate good-excellent cosmesis in over 90% of patients. To account for a 10% loss follow-up we propose a total sample size of 108 patients. This includes the original 55 patients resulting in an expansion cohort of 53 patients.

B. Total Number of Subjects If Multicenter Study: NA

C. Feasibility: Since we see at least around 5-10 eligible subjects per month, we should be able to accrue the requested number within 3 years from initiation of trial.

4.4 Consent Procedures

A. Consent Process

- **Location of Consent Process**
  Written informed consent will be obtained from all potential study participants in the clinic. The study will be explained to the prospective patient by the principal investigator or his designee. The timeline, potential risks and benefits will be explained in detail. The patient and the investigator will both sign and date the consent form. One copy will be provided to the patient and the other copy will be retained in the medical records and on OnCore®.

- **Ongoing Consent**
  Patients will continue to be seen for follow up throughout the study duration (3 years) and they will be reminded at the time of follow up that they have the right to be taken off the study anytime they want to.

- **Individual Roles for Researchers Involved in Consent**
  The PI, and other certified study personnel (residents, co-investigators that are listed on the IRB protocol) will be authorized to consent patients. They will be in charge of explaining to the patients in detail, the purpose of the study as well as outlining the possible side effects or benefits associated with the study.

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

- **Consent Discussion Duration:** The consent process will usually take 30 minutes to an hour. The patient will be able to ask more follow up questions on subsequent visits and to withdraw from the study at any time.

- **Coercion or Undue Influence**
  The PI will ensure that all necessary steps are taken to minimize the possibility of any chance of coercion or undue influence. The PI will make sure that consent will be seek only under circumstances where the patient will have sufficient opportunity and understanding of whether to be on the study or not. The patients will be informed that whether they decide to enroll or not, it will not affect their care in any way (except for the change in treatment that is endorsed by the trial if they decide to be on it).

- **Subject Understanding**
  The consent form will include the details of the study. A detailed description of potential risks and benefits will be included. The study personnel will go over all these will the patient and ensure understanding. The patients will be made aware that they can withdraw consent at any time and that this will not affect their care in any way.

B. Waiver or Alteration of Consent Process NA

- **Waiver or Alteration Details**
  NA
- **Destruction of Identifiers**
  NA
- **Use of Deception/Concealment**
  NA
  - **a. Minimal Risk Justification**
    NA
  - **b. Alternatives**
    NA
  - **c. Subject Debriefing**
    NA

C. Documentation of Consent

- **Documenting Consent**
  We will make sure that the patient understands the consent form language and all the details listed on the consent form. The patient (or a patient representative) will print their name, date the consent and sign. The same steps will also be taken by the PI or other authorized personnel obtaining the consent. The patient will be provided a copy of the signed consent form and another copy will be retained in the patient chart and on OnCore®.

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

- **Waiver of <u>Documentation</u> Of Consent (i.e., will not obtain subject's signature)**

NA

4.5 Special Consent/Populations: NA

A. Minors-Subjects Who Are Not Yet Adults

- **Parental Permission**

  NA
- **Non-Parental Permission**

  NA
- **Assent Process**

  NA
- **Documentation of Assent**

  NA
- **Reaching Age of Majority During Study**

  NA

B. Wards of the State

NA

- **Research Outside of NJ Involving Minors**

  NA

C. Non-English-Speaking Subjects

- **Process for Non-English-Speaking Subjects**

  If subjects who do not speak English will be enrolled, a certified translation service will be used to facilitate the consent discussion. An IRB-approved short form in the subject's native language will be obtained. The translator's ID number will be documented on the consent form.
- **Short Form Consent for Non-English Speakers** An IRB-approved short form consent will be obtained for any non-English speaking subjects. A short form consent will be used to consent no more than five subjects before a fully translated consent form in the given language is obtained.

D. Adults Unable to Consent / Decisionally Impaired Adults; NA

- **NJ Law-Assessment of Regaining the Capacity to Consent NA**
- **Capacity to Consent NA**
- **NJ Law-Selecting A Witness NA**
- **Removing a Subject**

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

Participants may withdraw voluntarily from the study at any time. The PI may discontinue a participant from the study. Based on patient follow up data from similar phase II trials that were carried out at our institution, we anticipate a drop-out rate of less than 10% [21, 22].

If a subject enrolls on the study and then discontinue for any reason prior to the delivery of the pre-operative boost; she will be taken off the study and will not contribute to the study endpoint analysis. Subjects who have received the pre-operative boost will all contribute to the study end point analysis (could be censored if lost to follow up at some point). The calculated sample size is for patients who received the pre-operative boost.

4.6 Economic Burden and/or Compensation for Subjects

A. Expenses

There should be no additional expenses incurred on the subjects by taking part in this study.

B. Compensation/Incentives

There will be no compensation provided to enrolled subjects

C. Compensation Documentation NA

4.7 Risks of Harm/Potential for Benefits to Subjects

A. Description of Risks of Harm to Subjects

- **Reasonably Foreseeable Risks of Harm**

Patients participating in this trial could be at a higher risk of wound complications after surgery. This risk is estimated to be lower than 10% and will be explained to the patients in detail. The rest of the study parameters should incur minimal risks on the subjects. Data from other cancer sites such as extremity soft-tissue sarcoma and rectal as well as the limited historic reports of pre-operative radiation in Breast [9, 10, 11, 12] suggest that the use of pre-operative radiation in breast cancer patients can be administered safely. Our suggested dose is lower than the doses used in sarcoma or other pre-operative RT regimen which would incur a very low risk on the patients.

Administering the radiation boost pre-operatively theoretically will have several advantages including better targeting of the tumor bed because the tumor can be visualized and targeted, resulting in a smaller treated volume and a smaller volume of irradiated normal tissue. This study aims to assess the feasibility of administering pore-operative boost in breast cancer patients.

- **Risk of Harm from an Intervention on a Subject with an Existing Condition**

Subjects with any serious or uncontrolled medical disorder that, in the opinion of the

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results will be excluded from the study.

- **Other Foreseeable Risks of Harm**

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.
All research activities will be conducted in as private a setting as possible.

- **Observation and Sensitive Information** NA

B. Procedures which Risk Harm to Embryo, Fetus, and/or Pregnant Subjects NA
C. Risks of Harm to Non-Subjects NA
D. Assessment of Social Behavior Considerations NA
E. Minimizing Risks of Harm

The study participant's contact information will be securely stored at the radiation oncology department for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be also stored at the Radiation Oncology Department. The data will be deidentified; it will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. There will be a link to the patient's MRN on Oncore which only the PI will have access to.

- **Certificate of Confidentiality** NA

- **Provisions to Protect the Privacy Interests of Subjects**

Patients will be mainly interacting with the physician, APN or resident who are the same personnel that they would interact with have they not elected to be on the study.

F. Potential Benefits to Subjects

Administering the radiation boost pre-operatively theoretically will have several advantages including better targeting of the tumor bed because the tumor can be visualized and targeted,

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

resulting in a smaller treated volume and a smaller volume of irradiated normal tissue. By participating in this study, the patients may have better outcomes, with the understanding that this is investigational and could also not result in better outcomes.

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA) NA

5.2 Family Educational Rights and Privacy Act (FERPA) NA

5.3 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations) NA

A. Special Populations

- NA

5.4 General Data Protection Regulation (GDPR) NA

5.5 NJ Access to Medical Research Act (Surrogate Consent) NA

6.0 Data Management Plan

6.1 Data Analysis

Sample size calculation was explained above. The outcome data analysis will be mainly descriptive data looking at the percentage of wound complications and the percentage of fair/poor cosmetic outcome using this new protocol. Descriptive analysis will be performed at baseline and will be presented as percentages, mean and standard deviation, median and range, depending on the respective variables.

6.2 Data Security

All participating staff are trained to protect data safety and security and are CITI certified. The study participant's contact information will be securely stored at the radiation oncology department for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be also stored at the Radiation Oncology Department. The data will be deidentified; it will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. There will be a link to the patient's MRN on Oncore which only the PI will have access to.

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

6.3 Data and Safety Monitoring

A. Data/Safety Monitoring Plan

Baseline assessment:

At first consult (or at the time of consent): Each potential subject will undergo multi-disciplinary evaluation and will be evaluated by the treating physician in Radiation Oncology, in coordination with the clinical research team, to determine eligibility for participating in the clinical trial. The written informed consent will be signed before starting any protocol-related procedures or interventions. All patients will be informed during the Screening period that all available radiographic and laboratory values obtained during the Screening, Treatment, and Follow-up periods may be provided to the patient at the patient's request.

History and Physical examination:

- History including histologically-confirmed primary cancer diagnosis and prior cancer treatment and significant prior and concurrent illness
- Baseline existing signs and symptoms evaluation graded according to NCI-CTCAE version 5.0.
- Prior and concomitant medications
- Physical examination: including weight, height, Breast exam, ECOG, and vital signs (heart rate/blood pressure/temperature/oxygen saturation/respiratory rate).

Radiographic or lab assessments:

- Mammogram to determine if multicentric disease in which case patient would not be eligible.
- Breast MRI if available and if not this will be requested.
- Blood sample collection if patient consents (optional).
- Pregnancy test (serum or urine)

Treatment Period Assessment:

The following assessments and interventions will be performed on the specified days during the Treatment Period as described below. Adverse event data will be collected by the radiation oncologist or surgeon and provided to the institutional Data Safety and Monitoring Board (DSMB) for independent review and validation of adverse events and other relevant clinical outcomes.

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

First Visit (Pre-operative Radiation Treatment):

History and Physical examination:

- Any side effect of radiation including fatigue, radiation dermatitis, pain or other (signs and symptoms evaluation graded according to NCI-CTCAE version 5.0).
- Any new medications
- Physical examination: including weight, height, Breast exam, ECOG, and vital signs (heart rate/blood pressure/temperature/oxygen saturation/respiratory rate).

Post-operative visit:

History and Physical examination:

- Any wound complications including dehiscence, infection, pain or other (signs and symptoms evaluation graded according to NCI-CTCAE version 5.0).
- Any new medications
- Physical examination: including weight, height, Breast exam, ECOG, and vital signs (heart rate/blood pressure/temperature/oxygen saturation/respiratory rate).

END of Adjuvant Radiation:

History and Physical examination:

- Any side effect of radiation including fatigue, radiation dermatitis, pain or other (signs and symptoms evaluation graded according to NCI-CTCAE version 5.0).
- Any new medications
- Physical examination: including weight, height, Breast exam, ECOG, and vital signs (heart rate/blood pressure/temperature/oxygen saturation/respiratory rate).

Follow-up Period Assessment:

During the Follow-up Period, assessments will be collected as detailed below. After completing the adjuvant phase of the radiation, subjects will be seen on the last day of treatment, one month after treatment then every 3 months until 1 year, and then approximately every 6 months until 3 years. The visits maybe alternating between the radiation oncologist and the surgeon. All assessments below will be conducted at each Follow-up visit and as otherwise clinically indicated:

RUTGERS | eIRB
APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

History and Physical examination:

- Any adverse events of radiation/surgery including wound complications, fatigue, radiation dermatitis, pain or other (signs and symptoms evaluation graded according to NCI-CTCAE version 5.0).
- Any new medications
- Physical examination: including weight, height, Breast exam, ECOG, and vital signs (heart rate/blood pressure/temperature/oxygen saturation/respiratory rate).
- Physician cosmesis assessment of breast

Administration of questionnaires or other instruments:

- Breast Cancer Treatment Outcomes Scale (BCTOS). The BCTOS cosmetic scale describes patient-reported changes in the treated breast and surrounding area relative to the contralateral breast which serves as an internal control. Patients will be trained to fill this scale (See appendix).

Radiographic assessment of disease:

- Breast mammogram or other imaging will be done per the NCCN guidelines [23].

B. Data/Safety Monitoring Board Details

The following assessments and interventions will be performed on the specified days during the Treatment Period as described below. Adverse event data will be collected by the radiation oncologist or surgeon and provided to the institutional Data Safety and Monitoring Board (DSMB) for independent review and validation of adverse events and other relevant clinical outcomes.

Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs following the administration of the trial medication regardless of the dose or causal relationship. We are not delivering any medication in our study; an adverse event will be any medical occurrence in a patient subject during or after receiving the pre-operative breast boost.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE. Disease progression

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

Adverse events related to treatment experienced by participants will be collected from initiation of study, throughout the study, and within 30 days of the last dose of adjuvant radiation treatment. Participants who experience an ongoing adverse events related to a study procedure and/or study medication beyond 30 days 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.

Adverse events related to Radiation Treatment include (see appendix):

1. Fatigue
2. Dermatitis in the radiation field
3. Pain in the radiation field
4. Fat necrosis in the radiation field
5. Fibrosis in the radiation field
6. Breast or ipsilateral arm Lymphedema
7. Breast scar wound healing
8. Breast hyperpigmentation
9. Radiation pneumonitis

Adverse events related to surgery include:

1. Wound dehiscence
2. Infection
3. Bleeding
4. Hematoma/seroma formation
5. Lymphedema

All adverse events, whether observed by the physician or reported by the patient, occurring during the active portion of therapy, through 30 days after the last day of radiation of treatment will be graded by a numerical score according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (http://ctep.cancer.gov/reporting/ctc.html) and recorded in the patient's medical record. Grade 2 and above adverse events related to treatment and all wound complication grades will be recorded on the adverse event CRF pages. Information entered on the adverse event CRF pages will include:

- Specific type and duration of reaction (i.e., start and stop dates, resolution).

RUTGERS | eIRB
APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

- Severity/grade.
- Relationship to study drug (causality, attribution).
- Management of the event, if treated with medication and other actions taken to alleviate the clinical event.
- Whether or not it was considered a SAE.

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

Serious Adverse Events (SAE)

Adverse events and adverse drug reactions which are considered as serious are those which result in:

- Death
- A life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- Hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above)

Unexpected adverse events are any adverse experience and/or specificity that is not listed in. the radiation side effect list.
All "unexpected" (defined above), Events of Special Interest (section 1.5), and/or "serious" (defined above) adverse events occurring during the active portion of therapy, through 30 days after the last dose of treatment, will be reported to the Office of Human Research Services via OnCore within 24 hours of site notification. The completed SAE report (signed by the Investigator) must be sent to the Rutgers CINJ OHRS QA department.

Events will be promptly reported, in writing, in accordance with the local and Rutgers Health IRB policy. If a death occurs the IRB will be notified **within 24-hours** of initial receipt of information. All other SAEs must be reported to the IRB **within 3 to 10 days** of initial receipt of

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

information. Written follow-up reports are required when additional information is needed to fully characterize the event. Copies of each report sent to the IRB will be kept in the study regulatory file.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

Relationship to Study Intervention: For each AE or SAE the investigator will determine whether there is a reasonable possibility demonstrated by evidence that suggests a causal relationship between radiation treatment and the AE

Action Taken:

In response to an AE, the investigator will take the appropriate actions regarding the study intervention. If the patient encounters a SAE during the pre-operative radiation period and before completion of the pre-operative radiation; the radiation oncologist may decide to stop treatment and take the patient off trial. The event will still be reported and counted in the outcome assessment (with an explanation of relation to study intervention).

If a SAE or a grade 3 and above Event of clinical interest happens after surgery, such as wound infection or dehiscence requiring hospitalizations, the patients will receive the appropriate care and the adjuvant RT will be delayed until complete healing of the wound. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days 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.

6.4 Reporting Results

A. Individual Subjects' Results Not applicable

B. Aggregate Result Not applicable

C. Professional Reporting

Any significant results will be published in medical literature and/or at national meetings.

D. Clinical Trials Registration, Results Reporting and Consent Posting

This research qualifies as a clinical trial that must comply with the federal requirement for public registration, results reporting and consent posting at its conclusion.

RUTGERS | eIRB
APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

6.5 Secondary Use of the Data

There is no plan to share data or specimens with other researchers.

7.0 Research Repositories – Specimens and/or Data

Research specimens will be stored in CINJ Biorepository and may be used in future research for subjects who have provided consent.

8.0 Approvals/Authorizations

SRB approval was already obtained.

9.0 Bibliography

1. Torre, L.A., et al., *Global Cancer in Women: Burden and Trends.* Cancer Epidemiol Biomarkers Prev, 2017. **26**(4): p. 444-457.
2. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2019.* CA Cancer J Clin, 2019. **69**(1): p. 7-34.
3. Society, A.C. *Breast Cancer Facts & Figures 2017-2018*. 2017.
4. Holland, R., et al., *Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery.* Cancer, 1985. **56**(5): p. 979-90.
5. Bartelink, H., et al., *Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial.* Lancet Oncol, 2015. **16**(1): p. 47-56.
6. Polgar, C., et al., *Electron and high-dose-rate brachytherapy boost in the conservative treatment of stage I-II breast cancer first results of the randomized Budapest boost trial.* Strahlenther Onkol, 2002. **178**(11): p. 615-23.
7. Vrieling, C., et al., *Prognostic Factors For Local Control in Breast Cancer After Longterm Follow-up in the EORTC Boost vs No Boost Trial: A Randomized Clinical Trial.* JAMA Oncol, 2016.
8. Carter, S.A., et al., *Operative and Oncologic Outcomes in 9861 Patients with Operable Breast Cancer: Single-Institution Analysis of Breast Conservation with Oncoplastic Reconstruction.* Ann Surg Oncol, 2016. **23**(10): p. 3190-8.
9. Riet, F.G., et al., *Preoperative radiotherapy in breast cancer patients: 32 years of followup.* Eur J Cancer, 2017. **76**: p. 45-51.

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

10. Semiglazov, V.F., et al., *Primary (neoadjuvant) chemotherapy and radiotherapy compared with primary radiotherapy alone in stage IIb-IIIa breast cancer.* Ann Oncol, 1994. **5**(7): p. 591-5.
11. Horton, J.K., et al., *Preoperative Single-Fraction Partial Breast Radiation Therapy: A Novel Phase 1, Dose-Escalation Protocol With Radiation Response Biomarkers.* Int J Radiat Oncol Biol Phys, 2015. **92**(4): p. 846-55.
12. Bondiau, P.Y., et al., *Phase 1 clinical trial of stereotactic body radiation therapy concomitant with neoadjuvant chemotherapy for breast cancer.* Int J Radiat Oncol Biol Phys, 2013. **85**(5): p. 1193-9.
13. Sorenson LT et al. Smoking as a risk factor for wound healing and infection in breast cancer surgery. Eur J Surg Oncol. 2002; 28:815–820.
14. Tran CL et al. Does reoperation predispose to postoperative wound infection in women undergoing operation for breast cancer. Am J Surg. 2003; 69:852–856.
15. Hall JC et al. The measurement of wound infection after breast surgery. Breast J. 2004; 10:412–415.
16. S.V. Lightowlers et al. Preoperative breast radiation therapy: indications and perspectives. European Journal of Cancer 2017; 82: 184-192
17. T Whelan et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. Lancet 2019. 2019 Dec 14; 394(10215):2165-2172.
18. Shaitelman et al. Three-Year Outcomes with Hypofractionated versus Conventionally Fractionated Whole-Breast Irradiation: Results of a Randomized, Noninferiority Clinical Trial. J Clin Oncol. 2018 Oct 31:JCO1800317
19. 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
20. Gupta et al. 5-Year Results of a Prospective Phase 2 Trial Evaluating 3-Week Hypofractionated Whole Breast Radiation Therapy Inclusive of a Sequential Boost. Int J Radiat Oncol Biol Phys. 2019 Oct 1:105(2):267-274
21. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol 1989; 62:679-694.
22. White J, T.A., Douglas A, Buchholtz T, MacDonald S, Marks L, Pierce L, Recht A, Rabinovitch R, Taghian A, Vicini F, Woodward W, Li X.A. *Breast Cancer Contouring Atlas*. 2019 [cited 2019; Available from: https://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx.
23. Network, N.C.C. *NCCN Guidelines for Patients: Invasive Breast Cancer* 2018; Available from: https://www.nccn.org/patients/guidelines/breast-invasive/44/index.html.

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

APPENDIX

BREAST CANCER TREATMENT OUTCOME SCALE (BCTOS)

BCTOS SELF-ASSESSMENT

Patient ID Number: ___ ___ – ___ ___ ___ ___ (Site) Visit Date: ___ ___ / ___ ___ / ___ ___ (M M / D D / Y Y) or ☐ not done

INSTRUCTIONS:

You are participating in a research study that compares cosmetic and functional outcomes after breast cancer therapy. The self-reported questionnaire below will assist your doctors in comparing the outcomes from this study to those for other breast cancer patients.

We are interested in your evaluation of your physical appearance and functioning since breast surgery. Please rate the following items on this four-point scale:

☐ 1 No difference between treated and untreated breast and area

☐ 2 Slight difference between treated and untreated breast and area

☐ 3 Moderate difference between treated and untreated breast and area

☐ 4 Large difference between treated and untreated breast and area

ITEMS:

A	Breast size	☐ 1	☐ 2	☐ 3	☐ 4
B	Breast texture	☐ 1	☐ 2	☐ 3	☐ 4
C	Nipple appearance	☐ 1	☐ 2	☐ 3	☐ 4
D	Shoulder movement	☐ 1	☐ 2	☐ 3	☐ 4
E	Arm movement	☐ 1	☐ 2	☐ 3	☐ 4
F	Breast pain	☐ 1	☐ 2	☐ 3	☐ 4
G	Ability to lift objects	☐ 1	☐ 2	☐ 3	☐ 4
H	Breast tenderness	☐ 1	☐ 2	☐ 3	☐ 4
I	Shoulder stiffness	☐ 1	☐ 2	☐ 3	☐ 4
J	Breast elevation (how high the breast is)	☐ 1	☐ 2	☐ 3	☐ 4
K	Scar tissue	☐ 1	☐ 2	☐ 3	☐ 4
L	Shoulder pain	☐ 1	☐ 2	☐ 3	☐ 4
M	Arm pain	☐ 1	☐ 2	☐ 3	☐ 4
N	Arm stiffness	☐ 1	☐ 2	☐ 3	☐ 4
O	Fit of bra	☐ 1	☐ 2	☐ 3	☐ 4
P	Breast sensitivity	☐ 1	☐ 2	☐ 3	☐ 4
Q	Fit of clothing	☐ 1	☐ 2	☐ 3	☐ 4

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

HARVARD COSMESIS SCALE

TABLE 1: Harvard scale (4-point Likert scale).

Excellent	Treated breast nearly identical to untreated breast
Good	Treated breast slightly different from untreated breast
Fair	Treated breast clearly different from untreated breast but not seriously distorted
Poor	Treated breast seriously distorted

RUTGERS | eIRB
APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

CTCAE VERSION 5.0 FOR RELATED TOXICITIES

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Wound complication	Observation only Topical Intervention indicated	Bedside local care indicated	Operative intervention indicated	Life-threatening consequences	Death
Fibrosis	Mild induration (able to move skin parallel to plan and perpendicular to plane)	Moderate induration (able to slide skin, unable to pinch skin)- limiting instrumental ADLs	Severe Induration; unable to slide or pinch skin, limiting self-care ADL	Generalized associated with signs or symptoms or impaired breathing or feeding	Death
Telangiectasia	Covering < 10% of surface area	Covering >10% of surface area	-	-	-
Fatigue	Relieved by rest	Not relieved by rest, limiting instrumental ADLs	Not relieved by rest; limiting self-care ADLs	-	-
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Breast Pain	Mild pain	Moderate pain limiting instrumental ADLs	Severe pain limiting self-care ADLs		

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024

Lymphedema	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation; limiting instrumental ADL	Severe symptoms; limiting self - care ADL		
Radiation Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Wound Infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Hematoma/seroma	Mild symptoms; intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

RUTGERS | eIRB APPROVED
IRB ID: Pro2020001306
Approval Date: 7/5/2023
Expiration Date: 7/4/2024