Weill Cornell Medicine NewYork-Presbyterian

COVER PAGE

Official Title: Prospective Randomized study of Accelerated Radiation Therapy (PRART)

IRB Protocol #: 19-07020533

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Prospective Randomized study of Accelerated Radiation Therapy (PRART)

IRB Protocol #: 19-07020533
Amendment 8
Version Date: 06DEC2024
Version 7.0

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Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCMC.

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DOCUMENT HISTORY

Document Name	Protocol version	Protocol Version Date
Amendment 8	**Version 7.0**	**06DEC2024**
Amendment 7	Version 6.0	07OCT2024
Amendment 6	Version 5.0	05JUL2023
Amendment 5	Version 4.0	21OCT2022
Amendment 4	Version 3.0	09JAN2021
Amendment 3	Version 2.2	13OCT2020
Amendment 2	Version 2.1	23MAR2020
Amendment 1	Version 2.0	18NOV2019
Initial	version 1.0	06NOV2019

Summary of changes for Protocol version 7.0 dated 06DEC2024

Section(s)	Changes	Rationale
Protocol Summary	Increasing the accrual ceiling from 420 to 430 subjects	Based on the number of patients that withdrew, the statistician recommends increasing the accrual ceiling from 420 to 430, to ensure to achieve the planned sample size of 400 patients

Summary of changes for Protocol version 6.0 dated 07OCT2024

Section(s)	Changes	Rationale
Protocol Summary, Objectives	Clarifying that, according with statistical consideration, the primary hypothesis and the primary endpoint of the study is the acute toxicity	Harmonization and consistency of the study protocol
Treatment plan, toxicities to be monitored and dosage modifications, study calendar	Clarifying that Breast cosmesis will be self-assessed by the patient using BCTOS questionnaires, before treatment (baseline), at the end of RT, at 1-month follow up visit and at 2-year follow up visit. The receipt of the survey will be recorded by the research nurses assigned to the study, but completion is not mandatory. Quality of life surveys will be sent to the patients' personal email address at the baseline, at the end of RT, at 1-month follow up visit and at 2-year follow up visit. Completed responses will be sent directly to our REDCAP database. The quality of life survey completion is optional.	Harmonization and consistency of the study protocol

Protocol Summary, Objectives, Study Calendar, Statistical and Data Management Considerations	Reporting the outcomes of late toxicity, breast cosmesis and local control at 2-3 years as well as at 5 years	To assess late toxicity, breast cosmesis and local control at 2-3 years, as well as at 5 years, because early results can provide valuable insights into the effectiveness and tolerability of treatments.
Patient Eligibility	Adding to inclusion criteria: women with previous contralateral breast cancer	A history of contralateral breast cancer does not compromise the radiotherapy treatment plan or the outcomes being assessed in this study.
Study Calendar	Removing KPS and Body weight	These data are redundant and not relevant for the study purpose
ECL	Adding to inclusion criteria: women with previous contralateral breast cancer	To reflect the change proposed in the section "Patient Eligibility"
No changes to the informed consent		

Summary of changes for Protocol version 5.0 dated 05JUL2023

Section(s)	Changes	Rationale
Cover page	Updating cover to reflect only the PI and the Co-PIs	To reduce multiple amendments that result due to change of personnel we will only have PI and the Co-PI information on the cover page.
No changes to the informed consent		

Summary of changes for Protocol version 4.0 dated 21OCT2022

Section(s)	Changes	Rationale

Adding personnel from Network sites	Adding personnel: NYP-Queens: Diamanise Sidberry, Sai Vishudhi Chandrasekhar, Hina Ali, Charlotte Fong, Renee Nichols, Sarah Stankiewicz. NYP-BMH: Mary Palmer, Izael Nino NYP-WCM – Logan Ritchie and Maria Fenton Kerimian (to IRB application. Note that Maria Fenton Kerimian was already approved before. Removing Jessica Richman, Charles Ekeh and Amanda Kluxen from the study.	Adding and removing Personnel.
13.1 Reporting Adverse events	1. Clarifying that CTCAE version 5.0 will be used for this study. 2. Clarifying the DSMB will be reviewing Grade 3 and above events including SAEs. 3. Adding AE and SAE definitions.	Based on the DSMB memo issued on 24MAY2022.
Informed Consent changes		
Adding Key information section	Adding Key information section.	IRB requested changes.

Summary of changes for Protocol version 3.0 dated 09JAN2021.

Section(s)	**Changes**	**Rationale**
Adding Network sites	Adding NYP-BMH, NYP-Q as addition sites for patient enrollments	Adding sites.
Adding network sites	Adding NYP-BMH, NYP-Q as addition sites for patient enrollments	Adding sites

Summary of changes for Protocol version 2.2 dated 13OCT2020.

Section(s)	**Changes**	**Rationale**
Study Team	Adding Jessica Richman to the study team as key personnel. Removing Sally Sa and Viji Nagaraj from the Personnel section	Personnel changes

Summary of changes: Version 2.1 Dated 23MAR2020

Sections 6.1.6, section 8.1 and section 9 have been modified to include the following statement:

"Quality of life surveys will be sent to the patients' personal email address. Completed responses will be sent directly to our REDCAP database."

Summary of Changes: Version 2.0 Dated 18NOV2019

1. Page 8 Hypothesis: ARM 2 boost dose was incorrect and has been changed to 4200cGY.
2. Page 6 schema had N0-1 and this has been changed to N0. This has been made consistent across the protocol.
3. Section 7.3 Treatment duration section has been revised to state that, the whole breast will be treated for five consecutive fractions for either three (Arm 1) or two (Arm 2) consecutive weeks.

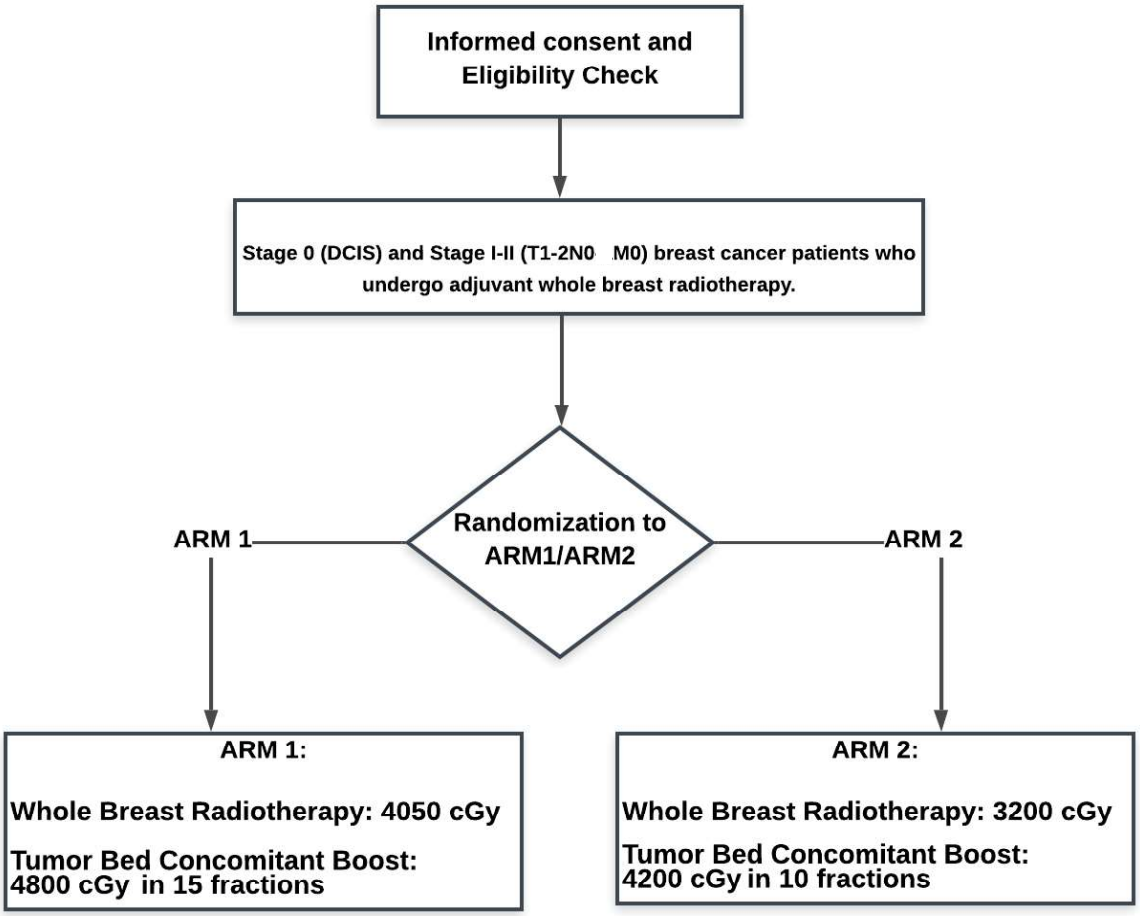
Informed Consent changes:

1.The footer of the informed consent has been changed to indicate the correct version of the protocol.

No other changes have been made in the informed consent.

SCHEMA

These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study.



Protocol Summary

Full Title: Prospective Randomized study of Accelerated Radiation Therapy (PRART): a Non-Inferiority Trial to Compare Breast Cosmesis and Local Control after Concomitant Boost Breast Radiotherapy with Fifteen Fractions in Three Weeks (arm 1, standard) versus Ten Fractions in Two Weeks (arm 2, experimental)

Short Title:	Randomized
Clinical Phase:	Phase III
Principal Investigators:	**Drs. Silvia C. Formenti and John Ng**
Sample Size:	N= 400 (200 per Arm)
Accrual Ceiling:	430
Rate of subject accrual:	Approx. 8 subjects per month or 100 patients per year
Study Population:	S/p segmental mastectomy patients with Tis (DCIS), T1-T2, N0 breast cancers.
Accrual Period:	4 years
Study Design:	Patients with Tis (DCIS), T1-T2, N0 breast cancers will be randomized to receive whole breast radiotherapy with a concomitant boost to the tumor bed over 15 fractions (Arm 1, standard) versus 10 fractions (Arm 2, experimental).
Study Duration:	**10 years to report: 2-3 years and 5 years late toxicity, local control rate, and breast cosmesis.**
Intervention Description:	Radiotherapy: 4050cGy whole breast radiotherapy with a concomitant tumor bed boost to 4800 cGy to the tumor bed in 15 fractions (Arm 1) versus 3200cGy whole breast radiotherapy with a concomitant tumor bed boost to 4200 cGy in 10 fraction (Arm 2). **Hypothesis:** A regimen of whole breast radiotherapy to 3200cGy with a concomitant tumor bed boost to 4200 cGy in 10 fractions (Arm 2) is not inferior to the current standard of whole breast radiotherapy of 4050 cGy with a concomitant tumor bed boost to 4800 cGy in 15 fractions (Arm 1), in terms of acute toxicity and long-term fibrosis, breast cosmesis and local control, at 2-3 years and at 5 years.
Primary Objectives:	**1.** To prospectively randomize patients to one of two hypo-fractionation regimens of concomitant boost breast radiotherapy as part of breast conservation therapy in patients with T1-2N0 breast cancers or Stage 0 (Tis) DCIS: 4050cGy whole breast radiotherapy with a concomitant tumor bed boost to 4800 cGy to the tumor bed in 15 fractions (Arm 1) versus 3200 cGy whole breast radiotherapy with a concomitant tumor bed boost to 4200 cGy in 10 fractions (Arm 2).

2. To test the primary hypothesis that the proportion of patients with grade ≥ 2 acute toxicity with 2 weeks regimen (10 fraction arm) would not be > 5% greater than the rate of 10% with a standard 3weeks regimen (15 fraction arm).

Endpoints:

Primary endpoint is the rate of acute toxicity. Expected acute toxicities include fatigue and skin reactions within the radiation field. Erythema, dry and wet desquamation of the skin will be recorded weekly, during RT treatment. The toxicities will be graded by the research nurses assigned to the study according to Common Terminology Criteria for Adverse Events, version 5.0.

Secondary endpoints are the evaluation at 2-3 years and 5 years of fibrosis, breast cosmesis and local control. The LENT/SOMA scoring system will be used in the reporting of late radiation morbidity, including fibrosis, at baseline (prior to treatment) and at each subsequent follow-up after completing radiotherapy, scored by the research nurses assigned to the study. Breast cosmesis will be assessed using the BCTOS patient self-reports before treatment (baseline), at the end of RT, at 1-month follow up visit and at 2-year follow up visit. Local control at 2-3 years and at 5 years will be extracted from the medical record, and can be derived from clinical reports from medical, surgical or radiation oncologists as well as from the primary care doctor who is following the patient.

1 OBJECTIVES

1. To prospectively randomize patients to one of two fractionation regimens of whole breast radiotherapy with a concomitant boost as part of breast conservation therapy in post-menopausal women with T1-2 N0 breast cancers or Stage 0 (Tis) DCIS:
   4050 cGy whole breast radiotherapy with a concomitant tumor bed boost to 4800 cGy to the tumor bed in 15 fractions (Arm 1) versus 3200cGy whole breast.
   radiotherapy with a concomitant tumor bed boost to 4200 cGy in 10 fractions (Arm 2).

2. To assess the rate of acute toxicity (grade 3 or higher).

3. To assess the rate of long-term fibrosis (grade 3 or higher) and changes in breast cosmesis in the 2 arms at 2-3 years and at 5 years.

4. To assess and compare local control at 2-3 years and at 5 years between the two arms.

1.1 Study Hypothesis

A hypo-fractionation breast radiotherapy regimen delivered over two weeks is not inferior to standard treatment over three weeks (whole breast radiotherapy with a concomitant boost), in terms of acute toxicity and long term fibrosis, breast cosmesis and local control, at 2-3 years and at 5 years follow up.

1.2 Inclusion Criteria by Staging

Stage 0 (DCIS), Stage I-II patients (T1-2N0 M0) with breast cancer patients who undergo adjuvant whole breast radiotherapy.

2 Background and Hypotheses

Breast conserving surgery and adjuvant whole breast radiotherapy is a standard treatment option for most patients with early-stage invasive breast cancer [1]. Hypofractionated whole breast irradiation (HF-WBI) has become a standard radiotherapy fractionation regimen and is usually delivered over 15 to 16 fractions [2]. With greater than 10 years of follow up, several large randomized clinical trials have shown similar local control and overall survival [3-7]. Recent randomized evidence indicates that patient convenience, quality of life, and breast cosmetic outcome may be better with the shorter treatment course [5,8]. Given the advantages and increasing nationwide utilization of the shorter radiation treatment course, we are conducting a randomized, phase III non-inferiority clinical trial to test the hypothesis that hypofractionation over two weeks is not inferior to treatment over three weeks when delivering whole breast radiotherapy with a concomitant boost.

2.1 Advantages of hypo-fractionation

The advantages of shorter treatment courses in whole breast radiotherapy have led to better understanding of the properties of tumor control and normal tissue tolerances. Several large

randomized clinical trials have now led to wide acceptance that whole breast radiotherapy over 15 to 16 fractions leads to similar tumor control outcomes. The START trials and a randomized trial from MDACC would suggest that patients may also have better quality of life and cosmetic outcomes with shorter fractionation courses.

Delivering a tumor bed boost concurrently can further shorten a patient's radiation treatment course to three weeks. A series of PHASE II prospective clinical trials have established the safety and efficacy of delivering the boost concomitantly [9-11]. A large RTOG study, RTOG 1005, has completed accrual and should report randomized results shortly [12]. The IMPORT High trial in the United Kingdom has reported similar cosmetic outcomes for the effect on breast appearance between a concurrent boost regimen with a sequential boost regimen. With the trend towards shorter treatment courses in the adjuvant breast radiotherapy setting, we are proposing a study to investigate the equivalence of delivering whole breast irradiation in two weeks with a equivalent radiobiologic effective dose.

2.2 The NYU experience of three weeks whole breast radiotherapy with a concomitant boost

Our group has developed extensive experience with hypofractionated whole breast irradiation over three weeks, most notably over a series of four prospective clinical trials. From 2003 to 2015, we conducted five investigator-initiated trials that resulted in local control and cosmetic outcomes comparable to those achieved by the original six-week regimen of whole breast radiotherapy and sequential boost to the tumor cavity. The series of prospective trials showed that the shorter regimen was associated with decreased acute toxicity [13], that prone technique and IMRT allowed for decreased radiation doses to the heart and lung tissues [14,15] while assuring efficacy [16], and that regional nodal treatment in prone position was also safe and well tolerated over three weeks [17]. More recent analysis demonstrated avoidance of radiation to the left anterior descending artery when our prone breast technique is adopted [18], and that excellent outcomes and cosmesis are also achieved in women younger than 50 years old [19]. Based on the safety, efficacy and greater convenience demonstrated with the shorter hypofractionation schedules, we now propose to investigate a two-week whole breast irradiation course, in the attempt to establish a new standard of care.

2.3 Optimal accelerated fractionated regimen of 10 fractions delivered over 2 - weeks.

The optimal accelerated dose fractionation for external beam whole breast irradiation remains to be established. One of the main objectives of this study will be to determine the acute and late effects using a regimen of 10 fractions. Our current standard of care treatment is the fifteen fractions regimen. Only minimal acute effects resulted from this regimen [16].

The biologically equivalent doses of different fractionation schedules are the total doses for which the probabilities of a certain outcome/complication are the same. They can be different for specific outcomes/complications. The biologically equivalent doses in regard of several outcomes/complication to a treatment delivered in the standard 2 Gy fractions five times a week was estimated by the widely used formula [20-23]:

$$Dnew = Dref * (\alpha / \beta + dref) / (\alpha / \beta + dnew)$$

or - in this case - using 5 fractions of dref dose:

Dnew=5*dref* (α / β+ dref) / (α / β+ 2)

where α / β is a tissue dependent parameter, arising from the radiobiological linear - quadratic cell survival model.

From the randomized prospective trials, there is an estimate that breast cancer may have an alpha/beta for tumor control of 4.6 and normal breast tissue an alpha beta ratio of 3.4 [6]. The relative closeness in alpha/beta ratios of tumor and normal tissue would support a rationale for hypo-fractionation [20-23]. Based on the formula above, Table 1 includes the calculation of BEDs (biologically equivalent doses) between the 2 arms. The breast cavity is predicted to have an alfa/beta value between 3-4.

Based on Table 1 a regimen of 42 Gy in 10 fraction to the boost is comparable to 48 Gy in 15 fractions. The latter regimen has been proven to both be effective (local recurrence rate <5% at 5 years) and to be associated with excellent cosmetic results (16), justifying our choice for a biologically equivalent regimen) in the experimental arm comparable to standard arm (see α/β values in Table 1, in bold).

In view of the fact that most recurrences tend to occur at the original tumor bed and that other studies have shown efficacy of lower doses of adjuvant radiation to the rest of the breast (4-8), we elect to test a dose of 32 Gy in 10 fractions. Maintaining a relative low dose to the rest of the breast tissue, which is a much lower risk of local recurrence than the area of the tumor cavity, will reflect on very low risk of fibrosis and will enhance the likelihood of optimal breast symmetry and cosmesis.

TABLE 1

Alfa/Beta (Gy)	2 Gy x 23	2.7 Gy x 15	3.2 Gy x 15*	3.2 Gy x 10	4.2 Gy x 10*
2	46	47	62.4	41.6	65.1
3	46	46.1	**59.5**	39.68	**60.48**
4	46	45.2	**57.6**	38.4	**57.34**
10	46	42.8	52.8	35.2	49.7

- Boost Dose delivered at tumor bed

3 Staging Criteria

TNM Stage 0 (Tis N0 M0), Stage I-II, T1-2 N0 M0, newly diagnosed breast cancer patients.

4 Patient Eligibility

Inclusion criteria:

1. Women status post segmental mastectomy
2. If unilateral, pT1-2 breast cancer excised with negative margins
3. If bilateral, pT1-2 breast cancer excised with negative margins AND/OR pTis excised with negative margins.
4. Clinically N0 or pN0 or sentinel node negative
5. Ductal carcinoma in situ DCIS with negative margins (no DCIS on inked margins).
6. Women with previous contralateral breast cancer.

Exclusion criteria:

1. Previous radiation therapy to the ipsilateral breast.
2. 90 days from last surgery, unless s/p adjuvant chemotherapy
3. 60 days from last chemotherapy
4. Male breast cancer

5 Descriptive Factors/Stratification/Randomization Scheme

This is a prospective, randomized study. No stratification is planned. The study schema describes the study design.

5.1 Study Schema /Table 2

Eligibility	**Stage 0 or Stage I-II breast cancer s/p segmental mastectomy.**	
Day 0	**Informed consent and randomization CT planning for determination of tumor bed on the prone position**	
Days 1-15 (start within 90 days from last breast surgery)	**Weekly IGRT, IMRT or Conformal breast irradiation, randomly assigned to:** **15 fractions whole breast radiotherapy with concomitant boost (arm 1)** **or** **10 fractions whole breast radiotherapy with concomitant boost (arm 2)**	
Note: Patients with bilateral breast cancer will be randomized to receive the same dose and fractionation to both breasts		

6 Treatment plan

6.1.1 The women in this study will be randomly assigned to receive either 10 or 15 radiation fractions. The study design permits to test non inferiority of the 2 weeks versus 3 weeks regimen in terms of acute toxicity, fibrosis, breast cosmetic results and local control at 2-3 years and at 5 years follow up.

6.1.2 The informed consent process is as follows. The principal investigator explains all elements of the protocol to the patients and answers any and all questions. Clinical procedures are performed by the principal investigator. The research nurse will obtain blood sample by venipuncture. The consent process takes place in the Department of Radiation Oncology at Weill Cornell Medical Center. The consent form process is concluded when the patient, principal investigator and the witness all have signed the consent form. The witness is a present adult able to verify that the patient was given the proper information needed to make an informed decision to participate in the clinical study. year 1

6.1.3 Once the process of randomization is concluded, patients will be informed of the schedule based on the assigned one of the 2 arms.

6.1.4 Simulation and treatment will be started within 90 days from surgery, in order to maximize the chances of optimal lumpectomy cavity visualization on the planning and cone beam CT scans.

6.1.5 Our routine follow up is once a year after completion of radiation therapy. For the purpose of protocol significance (for assessment of fibrosis), we will require at least one follow up visit to our department, after years 2. (See 11.1 Study calendar).
Breast cosmesis will be self-assessed by the patient using BCTOS questionnaires, before treatment (baseline), at the end of RT, at 1-month follow up visit and at 2-year follow up visit. The receipt of the survey will be recorded by the research nurses assigned to the study, but completion is not mandatory. Quality of life surveys will be sent to the patients' personal email address at the baseline, at the end of RT, at 1-month follow up visit and at 2-year follow up visit. Completed responses will be sent directly to our REDCAP database. The quality of life survey completion is optional.

7 Radiation Therapy

7.1 Immobilization Techniques:

Patients will be set-up for CT simulation and treatment utilizing a dedicated table designed to accommodate prone positioning for breast treatment [22].

7.2 CT simulation

A treatment planning CT of the breast will be acquired with the patient in the treatment position (prone), utilizing the same immobilization devices as will be used for treatment. CT scan thickness should be < 0.375 cm through the tumor bed region. These images will be used in treatment planning of the breast in accordance with the dose specification constraints. Contouring of tumor bed, indexed and contralateral breast tissue, thyroid, ipsilateral and contralateral lung, heart and left anterior descending artery (LAD) will be performed in order to guide beam arrangement and optimal normal tissue avoidance. The patient will be CT scanned in the supine position if the patient cannot lie prone, or if the prone plan is not acceptable. Specifically supine set up will be attempted if the dosimetry information derived from prone planning reveals exceeding normal tissue dose constraints for heart,

LAD, ipsilateral lung, or contralateral lung.

7.3 Treatment duration

The whole breast will be treated for five consecutive fractions for either three (Arm 1) or two (Arm 2) consecutive weeks.

7.4 Target Delineation

7.4.1 The PTVBreast is the entire breast volume acquired in prone or supine position based on physician's delineated fields. The PTVBreast is derived from the 50% isodose line associated with clinically determined opposed tangent fields. This is accomplished by converting the 50% isodose level to a structure, smoothing and then removing parts extending outside the 50% isodose structure with an additional 0.7 cm margin within the field borders. The lung and the heart are also excluded from the PTVBreast volume.

7.4.2 The GTV is the tumor bed, as identified on CT.

7.4.3 The PTVTumor is the GTV with an additional 1.0 cm 3D margin. PTVTumor will not extend outside of the breast tissue and, if necessary, will be consistently modified ("clipped") to be confined within PTVBreast.

7.5 Normal structure delineation

The following structures will be contoured: contralateral breast, thyroid, ipsilateral lung, contralateral lung, heart, and LAD

7.6 Technical Factors

7.6.1 Dose calculation with heterogeneity corrections must be used.

7.6.2 Nominal photon energies greater than or equal to 6 MV must be used. 16 MV photons may be used mixed with 6 MV photons in a ratio not to exceed 3:1 (16 MV: 6 MV). However, 16 MV photons may not be used for any beam in which the superficial extent of the GTV is within 0.5 cm of the skin.

7.6.3 Prone positioning requires the isocenter to be placed approx. 1.5 cm from medial edge of the breast to allow clearance between the gantry and the couch/board.

7.6.4 Hybrid Whole Breast planning - IMRT (intensity modulated radiation therapy) tangents plus non-IMRT tangents

1. Non-IMRT tangents deliver nominally 67% of prescribed dose using 6 MV or 6MV/16MV photons and include 3 cm anterior flash. The fields are wedged and weighted to obtain a uniform dose distribution, normalized to allow approximately 105% dose max.

2. IMRT tangents deliver nominally 33% of prescribed dose using 6 MV photons and include 3 cm anterior flash and use the non-IMRT tangent plan as a base for optimization.3D-CRT Whole Breast Planning

3. 3D-CRT tangents will be used to obtain a uniform dose distribution.

4. Wedges and/or field within fields can be used.

7.6.5 Boost plan

1. Non-coplanar beam arrangement is encouraged, but not required
2. Electrons, 3D-CRT or IMRT may be used
3. If the tumor bed, as visualized in the BEV (beams-eye-view), is within 1cm of the body surface, 1 cm of flash will be added to the field(s)
4. No photon beam will be directed toward heart, lung, contralateral breast, or thyroid
5. Inclusion of soft tissue not irradiated by the whole breast tangents is allowed to aid in target coverage

7.6.6 Dose Constraints

Target volume dose constraints for Whole Breast Plans: Whole breast IMRT hybrid tangents. PTVBreast max 108% (to ≥1cc) of the whole breast dose. This can be achieved with 6 MV, or 6 MV/16 MV (IMRT/3D) photons. PTVBreast: ≥95% of the volume must receive ≥100% of the whole breast dose. PTVTumor: ≥98% of the volume must receive ≥100% of the whole breast dose.

Whole breast 3D-CRT tangents PTVBreast max 112% (to >1cc) of the whole breast dose.
PTVBreast: ≥95% of the volume must receive ≥100% of the whole breast dose. PTVTumor: >98% of the volume must receive >100% of the whole breast dose.
Target volume dose constraints for Boost Plans:
IMRT Boost
Breast max 108% (to >1cc) of the boost dose. This can be achieved with 6 MV IMRT, or a hybrid approach using 6 MV/16MV (IMRT/3D) photons.
PTVTumor: >98% of the volume must receive >100% of the total boost dose.
>60% of the PTVBreast volume must not receive >50% of the total boost dose.
3D-CRT Boost
Breast max 112% (to>1cc) of the boost dose. This can be achieved with 6 MV, 16 MV, or 6MV/16 MV photons.
PTVTumor: ≥98% of the volume must receive ≥100% of the total boost dose.
> 60% of the PTVBreast volume must not receive >50% of the total boost dose
Composite of tangents and boost fields.

TABLE 3

Target/Normal Tissue Dose specifications	
Target Volume/Normal Tissue	Dose Constraints
PTVTumor	V48 Gy ≥ 98%
PTVBreast/Chest Wall	V40.5 Gy ≥ 95%
PTVNodes	V38.5 Gy ≥ 95%
Heart	V5 Gy < 5%
Ipsilateral Lung	V10 Gy < 20%
Spinal Cord	37.5 Gy maximum*
Esophagus	36 Gy maximum*
Brachial Plexus	42 Gy maximum*

PTVTumor: >98% of the volume must receive >100% of the total dose, where total dose is the whole breast dose plus boost dose.
PTVBreast: >95% of the volume must receive >100% of the whole breast dose.
PTVBreast: no more than 60% of PTVBreast should receive > 4455 cGy
Normal tissue dose constraints:
Heart: <5% of the heart receives >5 Gy.
Ipsilateral lung: <15% of the ipsilateral lung receives >10 Gy.
Contralateral lung: <15% of the contralateral lung receives >5 Gy.LAD: maximum <1800cGy, mean <1000 cGy.

7.7 Boost Technique with Image Guidance (IGRT)

IGRT Target Localization: Cone-beam CT (CBCT) images will be acquired weekly prior to treatment. By using weekly IGRT to image the post-operative tumor bed of the breast in "real-time", the operator will be able to align the tumor bed with the treatment machine for each subsequent tumor bed treatment. If the resection cavity is not visualized then cone-beam CT images will be used to ensure optimal positioning of the breast tissue. A portal image of each boost treatment field will be acquired following CBCT.

8 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

1. Expected acute toxicities include fatigue and skin reactions within the radiation field. Erythema, dry and wet desquamation of the skin will be recorded weekly, during RT treatment. The toxicities will be graded by the research nurses assigned to the study according to Common Terminology Criteria for Adverse Events, version 5.0, and Late Effects on Normal Tissues/ Subjective, Objective, Management and Analytic criteria (LENT/SOMA) for acute and late toxicity, respectively.

2. The risks involved in using the treatment machine or the CT scanning are described in the regular informed consent given to all patients undergoing radiation therapy.

8.1 Cosmetic results assessment

Breast cosmesis will be assessed using the Breast Cancer Treatment Outcome Scale (BCTOS) patient self-reports before treatment (baseline), at the end of RT, at 1-month follow up visit and at 2-year follow up visit. This brief self-report instrument has high reliability and validity and has been used in a variety of previous studies on recovery from breast cancer treatment. [25]. The BCTOS also will be used as a primary measure to assess breast-related symptoms and treatment effects. The receipt of the survey will be recorded by the research nurses assigned to the study, but completion is not mandatory. Quality of life surveys will be sent to the patients' personal email address at the baseline, at the end of RT, at 1-month follow up visit and at 2-year follow up visit. Completed responses will be sent directly to our REDCAP database. The quality of life survey completion is optional.

8.1.1 Measuring the late toxicities of breast radiation

Radiation-induced breast fibrosis is another important late effect of radiotherapy with a commonly reported incidence of 5-15%. Clinically, radiation-induced breast fibrosis is characterized by skin retraction, atrophy, toughness to palpation, and decreased tissue compliance with associated functional limitations. Visual assessment and palpation are the most important clinical investigations of the skin in radiotherapy but they are subjective and unquantitative. The LENT/SOMA scoring system will be used in the reporting of late radiation morbidity in this protocol [24]. We will obtain measurement of breast fibrosis at baseline (prior to treatment) and at each subsequent follow-up after completing radiotherapy, scored by the research nurses assigned to the study.

9 STUDY CALENDAR

All patients will be followed a month after the completion of treatment. Our routine follow up is once a year after completion of radiation therapy. **For the purpose of protocol significance (for assessment of fibrosis), we will require at least one follow up in the department visit after the**

second year. Acute and late effects will be recorded following the criteria described in Appendix 1. At each post treatment follow-up visit, a physical exam to detect clinical recurrence will be performed. Mammographic studies and/or MRI will be performed and reviewed on an annual basis.

The degree of fibrosis assessed by palpation will be measured as per Appendix 1, late effects at 2-3 years and at 5 years. Local control at 2-3 years and at 5 years will be extracted from the medical record, and can be derived from clinical reports from medical, surgical or radiation oncologists as well as from the primary care doctor who is following the patient.

Table 4: Study Calendar

Study	Pre Entry	Weekly‡	Post Treatment Follow-up visits
Mammogram	**X**		**X****
Lumpectomy pathology report	**X**		
Medical History	**X**		**X***
BCTOS and quality of life surveys⊕	**X**		**X**
Physical exam	**X**	**X**	**X***
Consent Form	**X**		
Randomization	**X**		
Treatment simulation	**X**		
Weekly CBCT prior to RT treatment		**X**	
Port films/ each RT dose after the first one		**X**	
Skin Assessment	**X**	**X**	**X***

‡ - performed weekly during the weeks of radiation therapy.

* Our routine follow up is once a year after completion of radiation therapy. For the purpose of protocol significance (for assessment of fibrosis), we will require at least one follow up visit after the second year.

** Standard annual mammogram (or MRI) for both breasts will be accepted as follow up data.

⊕ Quality of life surveys will be sent to the patients' personal email address. Completed responses will be sent directly to our REDCAP database. The quality of life survey completion is optional. The receipt of the BCTOS survey will be recorded by the research nurses assigned to the study, but completion is not mandatory. The BCTOS and quality of life questionaries will administer before treatment (baseline), at the end of RT, at 1-month follow up visit and at 2-year follow up visit.

10 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

- Acute and late toxicity will be reported as scheduled in the above study calendar (10.1) following the criteria in Appendix 1.

- Local recurrence will be classified as it follows:
- Local recurrence within the field of conformal radiation is defined as TRUE LOCAL RECURRENCE.

- Axillary/ intra-mammary or supraclavicular recurrence in the same side of the index lesion will be defined as REGIONAL RECURRENCE /SAME BREAST.

- At the time of local recurrence all patients will undergo disease assessment with CT of Chest/ Abdomen/ Pelvis and, if symptomatic, bone scan and/or brain MRI.

- Local/regional recurrences will be further grouped as:

- ISOLATED LOCAL/REGIONAL RECURRENCES

- CONCOMITANT LOCAL/REGIONAL AND DISTANT RECURRENCES

Patients developing local recurrences after systemic recurrence has been documented will be classified as:

- METACRONOUS LOCAL/REGIONAL RECURRENCES.

- CONTRALATERAL BREAST CANCER will also be recorded and reported as invasive and noninvasive.

11 STATISTICAL AND DATA MANAGEMENT CONSIDERATIONS

Study Design: This study is a prospective randomized controlled trial to test the hypothesis that whole breast radiotherapy to 3200cGy with a concomitant tumor bed boost to 4200 cGy in 10 fractions (Arm 2,) is not inferior to standard whole breast radiotherapy with a concomitant tumor bed boost to 4800 cGy to the tumor bed in 15 fractions (Arm 1).

A total of 400 patients will be randomized to arm 1 or 2 to test the primary hypothesis that the proportion of patients with grade ≥ 2 acute toxicity with 2 weeks regimen would not be > 5% greater than the rate of 10% with a standard 3weeks regimen, with a 1-sided a of 0.025 and power of 79%.

The trial will have 2 planned interim analyses at 80 patients (20%; rejecting the null hypothesis when $Z \leq -4.88$, or $P \leq 0$) and at 240 patients (60%; rejecting the null hypothesis when $Z \leq -2.67$, or $P \leq 0.0038$) and a final analysis at 400 patients (100%; rejecting the null hypothesis if $Z \leq -1.98$, or $P \leq 0.0238$). The secondary objective was to test whether a significant difference exists between the 2 arms for long term fibrosis or telangiectasia grade ≥ 2. The secondary objective has 1 planned interim analysis when 50% of the patients had completed 3 years of post-treatment follow-up (rejecting the null hypothesis if the hazard ratio was ≤ 0.37, or $P < 0.0031$) and a final analysis when all the patients

had completed 3 years of follow-up (rejecting the null hypothesis if the hazard ratio was ≤ 0.63, or $P < 0.049$).

The distributions of the baseline patient and disease characteristics at randomization for each arm will be summarized using descriptive statistics. Quantitative variables were summarized using the means, standard deviations, medians, and ranges; qualitative variables were summarized with frequency distributions of the nominal levels. Wilcoxon rank sum tests were used to compare the distributions of the quantitative variables between the 2 arms, and Fisher exact tests were used to compare the distributions of the qualitative variables between the 2 arms.

To summarize the safety data, distributions of toxicity grades will be provided by treatment arm. Noninferiority tests will conducted to test the primary hypothesis that the 2 weeks regimen would result in no more toxicity than did the 3 weeks regimen. Fisher exact tests will be used to compare the distributions of acute and late toxicity grades between the 2 weeks arm and the 3 weeks arm.

The comparison of the cumulative incidence of long term fibrosis or telangiectasia grade ≥ 2 between the 2 arms will be conducted using log-rank χ^2 tests. The hazard ratio between the 2 arms will be computed with the 95% confidence intervals.

Local recurrence-free survival will be estimated for both treatment arms using Kaplan-Meier curves, the relative risk will be estimated, and the 2 arms will be compared using the log-rank χ^2 tests.

11.1 Data management:

Data Management will be carried out by staff of the Department of Radiation Oncology at WCMC under the direction of Dr. Formenti. Randomization will occur from a randomization list provided by Karla Ballman's team and allocation to each arm will be performed, after consent is acquired, by the research team in the department of Radiation Oncology. The Randomization will be a manual process where the data manager will enter the consented patient's name in a sequential order in the Randomization list provided. Data will be entered into the JCTO Clinical database management system maintained by the JCTO according to the procedures of WCM. Patients will be followed every 12 months to evaluate their status with respect to recurrence. Recurrences will be evaluated using standard criteria in the Dept. of Radiation Oncology that are provided in the protocol. Data will be transferred from the Clinical database to the Division of Biostatistics for analysis. The Principal Investigator, Research Nurse and Data Manager have access to data collected.

Analysis: Patient characteristics at randomization will be summarized by treatment group using descriptive statistics and graphical displays.

12 REGISTRATION GUIDELINES

At the time of registration, informed consent form must be signed by the patient, and the treating physician obtaining the consent. The Consent is then scanned to the patient's chart in EPIC and a scanned copy is sent to the Rad.Onc Clinical Trials office for patient registration. Please email rocto@med.cornell.edu the scanned informed consent and the completed eligibility document.

- At the time of registration, the eligibility registration worksheet will be completed. A complete Eligibility document will be required before randomization can occur.

- Patients will be registered in the Department of Radiation Oncology enrollment log in

REDCAP and in the JCTO oncore system. Registration confirmation emails will be sent out by the CancerCTregistrar after the consent and eligibility is reviewed by the Cancer CT registration team from JCTO. Any questions or concerns regarding registration should be directed to CancerCTRegistrar@med.cornell.edu.

ROCTO will also send out an enrollment notification email to all radiation oncology personnel involved in the study including the billing team.

- Patient will be marked as "Research" in ARIA and subsequently the protocol specific Pre-CRFS will be populated for the patient in the clinical trial database in REDCAP.

12.1 Confidentiality

All data and medical information obtained once a patient has decided to participate in this research, will be kept confidential to the extent permitted by law and will not be released without the patient's written permission except as described in this paragraph. In all study forms, patients will be identified only by their initials and patient number. Patient names will not be reported in any publication; only the data obtained as a result of their participation in this study will be made public.

12.2 Registration information for sub-sites:

Once the patient is consented, the sub-site should email the WCMC radiation oncology research team at rocto@med.cornell.edu the following documents within 24 hours :

1 Eligibility checklist/randomization
2 Enrollment form -sent via email
3 Online enrollment form (via REDCAP) when ready

WCMC research study team will assign a trial ID number and randomize patients to one of the 2 arms of the study. Since this is a randomized study, we request that the sites notify WCMC immediately.

13 Adverse Event Reporting and Medical Monitor

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

13.1 Reporting adverse events

13.1.1 Adverse events

Adverse events will be recorded for the duration of a patient's participation in the trial. All adverse events (except grade 1 and 2 laboratory abnormalities unless a dose treatment modification, delay or therapeutic intervention is required), regardless of causal relationship, are to be recorded in the case report form and source documentation. Pre-existing conditions at baseline will be recorded. If a pre-existing condition does not change, it does not have to be reported on subsequent cycles.
The investigator must determine the toxicity of adverse events according to the CTCAE version 5.0 (Appendix 1) and their causal relationship.

13.1.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure.
CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Attribution of the AE:

- 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.

13.1.3 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

13.1.4 Recording of Adverse Events

All adverse events will be recorded on a patient specific AE log. The AE log will be maintained by the research staff and kept in the patient's research chart. The AEs are documented in REDCAP database.

13.1.5 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:

http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2 Definition of SAE

SAE's include death, life threatening adverse experiences, prolonged hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:

http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.p df.

13.2.2 Serious adverse events

Adverse events classified as serious require expeditious handling and reporting to comply with regulatory requirements. All serious adverse events, whether considered to be drug-related or not, require that a Serious Adverse Event Report Form be completed within 24 hours of the investigator becoming aware of the event. The investigator must immediately report all unexpected serious adverse events to the Institutional Review Board in writing.

Serious adverse events will be reported to:

Silvia C. Formenti, M.D. 525 East 68th Street, Box 169, New York, NY - 10065 Phone number: (212) 746-3608 Fax number: (212) 746-8068

14 Sub Sites:

Sub-sites participating in the trial will be given access to REDCAP e-CRFs to document adverse events based on CTCAE v5.0 in REDCAP routinely. We request that the sites complete the REDCAP baseline e-CRFs within 7 days from enrolling the patients. Adverse events have to be documented in REDCAP routinely during every follow-up visit.

Serious adverse events will be documented as per sub-site's institutional guidelines. We request sub-sites to notify Dr. Silvia C. Formenti within 24 hours of the sub-site becoming aware of the event. Serious Adverse Events will be reported to WCMC's data safety monitoring board every 6 months.

15 Medical Monitor

This study will be monitored by the WCM Data Safety Monitoring Committee according to the procedures of the WCM Data Safety Monitoring Plan. The DSMB will be monitoring Grade 3 and above adverse events throughout the course of the study. In addition, the DSMB will also be reviewing SAE reports submitted by the study team, based on the DSMB guidelines. The WCM DSMB committee will be the medical monitor of the study.

15.1 Sub-sites:

Sub-sites will monitor the study locally and must follow sub-site's institutional guidelines. Waivers, exceptions and serious adverse events must be reported to the WCM team as and when the event occurs.

15.2 DSMB safety Review

The protocol will be reviewed by the Data Safety Monitoring Board (DSMB) on a Semi-annual basis. Safety reports will be submitted to the DSMB every six months.

15.3 Stopping Rules

For patients experiencing Grade 3 and above adverse events, treatment will be suspended until the resolution of the adverse events to baseline.

15.4 Sub-sites:

Sub-sites should use the local Data safety Monitoring board to monitor the studies. Data safety reports and approvals must be sent to the WCM team for regulatory purposes.

16 RESEARCH CONFLICT OF INTEREST

There are no conflicts of interest to report.

17 COST TO SUBJECTS

Each subject or their insurance company will be charged and held responsible for the costs of care provided as part of this study. Radiotherapy is a standard treatment for breast cancer and will be billed to subjects and their insurance companies.
There will be no monetary compensation for participating in this study.

18 APPENDIX 1 - LENT/SOMA Criteria: Late Reactions

Table 1. RTOG/EORTC and LENT/SOMA classification of late effects

RTOG/EORTC	Grade 1	Grade 2	Grade 3	Grade 4
Skin	Slight atrophy, pigmentation change, some hair loss	Patchy atrophy, moderate telangiectasia, total hair loss	Marked atrophy, gross telangiectasia	Ulceration
Subcutaneous tissue	Slight induration (fibrosis), and loss of subcutaneous fat	Moderate fibrosis, but asymptomatic; slight field contracture, ≤10% linear reduction	Severe induration and loss of subcutaneous tissue, field contracture, ≥10% linear reduction	Necrosis
LENT/SOMA				
Breast				
Subjective				
Pain	Occasional and minimal Hypersensation, pruritus	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Objective				
Telangiectasia	<1 cm^2	1–4 cm^2	>4 cm^2	
Fibrosis	Barely palpable, increased density	Definite increased intensity and firmness	Very marked density, retraction, and fixation	
Edema	Asymptomatic	Symptomatic	Secondary dysfunction	
Retraction, atrophy	10–25%	>25–40%	>40–75%	Whole breast
Ulcer	Epidermal only, <1 cm^2	Dermal only, >1 cm^2	Subcutaneous	Bone exposed, necrosis
Lymphedema, arm circumference	2–4-cm increase	>4–6-cm increase	>6-cm increase	Useless arm
Skin				
Pigmentation change	Transitory, slight	Permanent, marked	—	—

Abbreviations: RTOG = Radiation Therapy Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; LENT = Late Effects Normal Tissue Task Force; SOMA = subjective, objective, management, and analytic.

Please, refer to the following link for the Common Terminology Criteria for Adverse Events, version 5.0

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

19 Appendix 2 - Toxicity Tracking Form

PHYSICIAN'S PROGRESS NOTE

Fraction: ☐ 1-5 ☐ 6-10 ☐ 11-15 ☐ 1 mo F/U ☐ 3 mo F/U

The following critical elements of the patient's weekly exam have been covered:

☐ *Chart & Dosimetry, Treatment set up & positioning review*

☐ *Port Film or image review*

☐ *Examination of patient for evaluation and progress of treatment (see notes below)*

Progress note: _____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Please indicate Toxicity due to Radiation Treatment on the following chart:

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
FATIGUE	☐ No change	☐ Mild fatigue over baseline	☐ Moderate or causing difficulty performing some ADL	☐ Severe fatigue interfering with ADL	☐ Disabling
RADIATION DERMATITIS	☐ No change	☐ Faint erythema or dry desquamation	☐ Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	☐ Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	☐ Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site
PAIN (Breast)	☐ No pain	☐ Mild pain not Interfering with function	☐ Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	☐ Severe pain; pain or analgesics severely interfering with ADL	☐ Disabling

Attending Signature: _____ Date: _____

20 Appendix 3 – Quality Of Life Questionnaires

20.1 Appendix 3.1 Quality of Life questionnaire used at baseline

Form QLB (01-25-2005) Page 1 of 7

Quality of Life Questionnaire - Baseline

Patient Initials ☐ , ☐ ☐ (*Last* *First* *Middle*)

Patient Study ID ☐☐☐☐☐☐☐☐☐

Participants should complete this questionnaire at baseline (after consent and prior to randomization). The first page is to be completed by a clinical staff member. Fill in the items listed on this page, print the patient's study ID at the top of pages 2 through 7 and give the questionnaire to the patient for completion. After the patient has completed the questionnaire, verify that the date has been recorded at the top of page 2.

Please administer the questionnaire at an office visit if possible. If that is not possible, mail the questionnaire to the patient, then call to ask for the patient's responses over the phone. If all efforts to administer the scheduled questionnaire fail, a B-39 QMD form should be submitted instead.

Mark Circles Like This: → ●

Institution Name / Affiliate Name

_____ / _____

Staff Member Administering Form

_____ _____ _____

Last Name First Name Phone

Are data amended? O Yes (If yes, circle the amended items.)

Time point for this questionnaire (Do not mark in this box.)

● Baseline (after consent, before randomization)

Last week of radiation therapy
45-60 days after starting radiotherapy
Two years after adjuvant raditation therapy

This form is being filled out: (*Mark one.*)

O By participant in doctor's office
O By participant not in doctor's office
O By clinical staff, on phone with participant
O Other

Record the participant's study ID on each of the remaining pages before giving the questionnaire to the participant.

Patient Study ID

Date this questionnaire is completed: Month Day Year

(For example, if you were completing the questionnaire on September 8, 2004, you would write 09 08 2004 in the boxes.)

Thank you for completing this questionnaire.
We are interested in your evaluation of your physical appearance and functioning since you have been treated for breast cancer. Please rate the following items on this four-point scale, according to your evaluation at this point in time.

	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

BCTOS

Patient Study ID | | | | | | | | | |

We are interested in your personal reactions to the surgery you have received for your breast cancer. Please answer the following questions by circling one (1) number. Please note that the response options are labeled at the end-points only. However, you can and should use all of the points on the scale as appropriate to best convey your response.

1. To what extent has your surgery **disrupted** your normal daily activities?

0	1	2	3	4	5	6	7	8	9	10
Not at all										A lot

2. To what extent has your surgery **disrupted** your normal recreational activities?

0	1	2	3	4	5	6	7	8	9	10
Not at all										A lot

3. To what extent has your surgery **disrupted** your normal activities with your family and friends?

0	1	2	3	4	5	6	7	8	9	10
Not at all										A lot

4. To what extent has your surgery **disrupted** your normal sleep pattern?

0	1	2	3	4	5	6	7	8	9	10
Not at all										A lot

5. To what extent has your surgery **reduced** your enjoyment of life?

0	1	2	3	4	5	6	7	8	9	10
Not at all										A lot

6. To what extent has your surgery **disrupted** your regular activities at work (e.g., need to take time off, not getting done as much as you'd like)? If you do not work outside the home for pay, please check this box ☐ and go to the next question.

0	1	2	3	4	5	6	7	8	9	10
Not at all										A lot

7. How **satisfied** are you with the length of time your treatment has taken to this point in time?

0	1	2	3	4	5	6	7	8	9	10
Not at all										A lot

8. How **disruptive** has your surgery been to the other important people in your life (e.g., family and close friends)?

0	1	2	3	4	5	6	7	8	9	10
Not at all										A lot

Patient Study ID | | | | | | | | | |

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
1. Did you feel full of life?	1	2	3	4	5
2. Did you have a lot of energy?	1	2	3	4	5
3 Did you feel worn out?	1	2	3	4	5
4. Did you feel tired?	1	2	3	4	5

5. Rate your pain at its worst in the past four weeks. (Circle one number.)

0	1	2	3	4	5	6	7	8	9	10

No pain — Pain as bad as you can imagine

6. Rate your pain at its least in the past four weeks. (Circle one number.)

0	1	2	3	4	5	6	7	8	9	10

No pain — Pain as bad as you can imagine

7. Rate your pain on average in the past four weeks. (Circle one number.)

0	1	2	3	4	5	6	7	8	9	10

No pain — Pain as bad as you can imagine

8. Rate how much pain you have right now. (Circle one number.)

0	1	2	3	4	5	6	7	8	9	10

No pain — Pain as bad as you can imagine

9. Are you currently receiving treatments or taking medications for your pain?
Circle one: Yes No

Patient Study ID | | | | | | | | | |

By circling one (1) number per line, please indicate how much you have been bothered by each of the following problems <u>in the past four weeks</u>.

	Not bothered at all	A little bit bothered	Some-what bothered	Bothered quite a bit	Bothered very much
Fever or shivering (shaking, chills)	0	1	2	3	4
Swelling of breast (breast feels larger)	0	1	2	3	4
Breast heaviness	0	1	2	3	4
Breast warm to touch	0	1	2	3	4
Breast skin is red	0	1	2	3	4
Breast skin is tanned	0	1	2	3	4
Breast skin or area around nipple is pale in color	0	1	2	3	4
Breast skin is flaking or peeling	0	1	2	3	4
Bleeding or fluid leakage from breast	0	1	2	3	4
Breast itching	0	1	2	3	4
Blisters on the breast (or breast skin moist and raw)	0	1	2	3	4
Coughing	0	1	2	3	4
Difficulty breathing	0	1	2	3	4
Muscle aches	0	1	2	3	4
Rib or chest wall pain	0	1	2	3	4
Infections	0	1	2	3	4
Slow healing of breast wounds	0	1	2	3	4
Visible small blood vessels (spider veins)	0	1	2	3	4
Pockmarks or puncture wounds on breast	0	1	2	3	4
Thickening of breast skin	0	1	2	3	4
Hardening of breast	0	1	2	3	4
Breast or nipple numbness	0	1	2	3	4
Sharp shooting pains or twinges in the breast	0	1	2	3	4

SCL

Patient Study ID | | | | | | | | | |

By circling one (1) number per line, please indicate how much you have been bothered by each of the following problems in the past four weeks.

	Not bothered at all	A little bit bothered	Some-what bothered	Bothered quite a bit	Bothered very much
Breast aches	0	1	2	3	4
Breast tenderness	0	1	2	3	4
Decrease or lack of arousal on breast	0	1	2	3	4
Any other problems? (Specify below)	0	1	2	3	4

Specify other problems:

You have been treated with breast conserving therapy for breast cancer. As you know, a reason for choosing this treatment is to keep a breast that looks and feels as close to normal as possible. Your opinion concerning the appearance of your breast is valuable to us. Circle the number next to the word that best describes how your breast looks now.

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.

My satisfaction about the treatment and results is: (Select the phrase that best describes your satisfaction.)

☐ Totally satisfied ☐ Somewhat satisfied ☐ Neither satisfied nor dissatisfied ☐ Somewhat dissatisfied ☐ Totally dissatisfied

SCL and RTOG PQ

Patient Study ID | | | | | | | | | |

Before any treatment to your breast, the size of your breasts was: (Select the phrase that best describes your breast size prior to treatment.)

☐ Larger on left ☐ The same on both sides ☐ Larger on right

The size of your breasts now is: (Select the phrase that best describes your breast size now.)

☐ Larger on left ☐ The same on both sides ☐ Larger on right

Thank you for completing this questionnaire!

21 Appendix - Quality of Life questionnaire used for follow-up visits

Form QLF(01-25-2005) Page 1 of 6

Quality of Life Questionnaire - Follow-up

Patient Initials ☐ , ☐ ☐ (Last, First, Middle) **Patient Study ID** ☐☐☐☐☐☐☐☐☐

For patients who receive both radiation and chemotherapy, this should be completed at day 45-60 following start of radiation and at 2-year follow-up.

Patients who experience a documented cancer recurrence or second primary cancer are not expected to complete questionnaires after that event. Patients who discontinue therapy for other reasons are expected to complete all the quality of life assessments.

The first page is to be completed by a clinical staff member. Fill in the items listed on this page, print the patient's study ID at the top of pages 2 through 6 and the assessment time point at the bottom of pages 1 through 6 and give the questionnaire to the patient for completion. After the patient has completed the questionnaire, verify that the date has been recorded at the top of page 2.

Please administer the questionnaire at an office visit if possible. If that is not possible, mail the questionnaire to the patient, then call to ask for the patient's responses over the phone. If all efforts to administer the scheduled questionnaire fail, a B-39 QMD form should be submitted instead.

Institution Name / Affiliate Name

_____ / _____

Staff Member Administering Form

Last Name | First Name | Phone

Are data amended? O Yes (If yes, circle the amended items.)

This form is being filled out: (*Mark one.*)

O By participant in doctor's office
O By participant not in doctor's office
O By clinical staff, on phone with participant
O Other

Mark Circles Like This: → ●

assessment time point O last week RT O day 45-60 O 2 years

Record the assessment time point and participant's Study ID on each of the remaining pages before giving the questionnaire to the participant.

Patient Study ID | | | | | | | | | |

Date this questionnaire is completed: | | | Month | | | Day | | | | Year

(*For example, if you were completing the questionnaire on September 8, 2004, you would write 09 08 2004 in the boxes.*)

Thank you for completing this questionnaire.
We are interested in your evaluation of your physical appearance and functioning since you have been treated for breast cancer. Please rate the following items on this four-point scale, according to your evaluation at this point in time.

	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

assessment time point O last week RT O day 45-60 O 2 years

BCTOS

Patient Study ID | | | | | | | | | |

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
1. Did you feel full of life?	1	2	3	4	5
2. Did you have a lot of energy?	1	2	3	4	5
3 Did you feel worn out?	1	2	3	4	5
4. Did you feel tired?	1	2	3	4	5

5. Rate your pain at its worst in the past four weeks. (Circle one number.)

0	1	2	3	4	5	6	7	8	9	10

No pain — Pain as bad as you can imagine

6. Rate your pain at its least in the past four weeks. (Circle one number.)

0	1	2	3	4	5	6	7	8	9	10

No pain — Pain as bad as you can imagine

7. Rate your pain on average in the past four weeks. (Circle one number.)

0	1	2	3	4	5	6	7	8	9	10

No pain — Pain as bad as you can imagine

8. Rate how much pain you have right now. (Circle one number.)

0	1	2	3	4	5	6	7	8	9	10

No pain — Pain as bad as you can imagine

9. Are you currently receiving treatments or taking medications for your pain?
Circle one: Yes No

assessment time point O last week RT O day 45-60 O 2 years

Patient Study ID | | | | | | | | | |

By circling one (1) number per line, please indicate how much you have been bothered by each of the following problems in the past four weeks.

	Not bothered at all	A little bit bothered	Some-what bothered	Bothered quite a bit	Bothered very much
Fever or shivering (shaking, chills)	0	1	2	3	4
Swelling of breast (breast feels larger)	0	1	2	3	4
Breast heaviness	0	1	2	3	4
Breast warm to touch	0	1	2	3	4
Breast skin is red	0	1	2	3	4
Breast skin is tanned	0	1	2	3	4
Breast skin or area around nipple is pale in color	0	1	2	3	4
Breast skin is flaking or peeling	0	1	2	3	4
Bleeding or fluid leakage from breast	0	1	2	3	4
Breast itching	0	1	2	3	4
Blisters on the breast (or breast skin moist and raw)	0	1	2	3	4
Coughing	0	1	2	3	4
Difficulty breathing	0	1	2	3	4
Muscle aches	0	1	2	3	4
Rib or chest wall pain	0	1	2	3	4
Infections	0	1	2	3	4
Slow healing of breast wounds	0	1	2	3	4
Visible small blood vessels (spider veins)	0	1	2	3	4
Pockmarks or puncture wounds on breast	0	1	2	3	4
Thickening of breast skin	0	1	2	3	4
Hardening of breast	0	1	2	3	4
Breast or nipple numbness	0	1	2	3	4
Sharp shooting pains or twinges in the breast	0	1	2	3	4

assessment time point O last week RT O day 45-60 O 2 years

SCL

Patient Study ID | | | | | | | | | |

By circling one (1) number per line, please indicate how much you have been bothered by each of the following problems <u>in the past four weeks</u>.

	Not bothered at all	A little bit bothered	Some-what bothered	Bothered quite a bit	Bothered very much
Breast aches	0	1	2	3	4
Breast tenderness	0	1	2	3	4
Decrease or lack of arousal on breast	0	1	2	3	4
Tattoos on breast placed for radiation therapy	0	1	2	3	4
Any other problems? (Specify below)	0	1	2	3	4

Specify other problems:

You have been treated with breast conserving therapy for breast cancer. As you know, a reason for choosing this treatment is to keep a breast that looks and feels as close to normal as possible. Your opinion concerning the appearance of your breast is valuable to us. <u>Circle the number</u> next to the word that best describes how your breast looks <u>now</u>.

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.

assessment time point O last week RT O day 45-60 O 2 years

SCL and RTOG PQ

Patient Study ID | | | | | | | | | |

My satisfaction about the treatment and results is: (Select the phrase that best describes your satisfaction.)

☐ Totally satisfied	☐ Somewhat satisfied	☐ Neither satisfied nor dissatisfied	☐ Somewhat dissatisfied	☐ Totally dissatisfied

Before any treatment to your breast, the size of your breasts was: (Select the phrase that best describes your breast size prior to treatment.)

☐ Larger on left	☐ The same on both sides	☐ Larger on right

The size of your breasts now is: (Select the phrase that best describes your breast size now.)

☐ Larger on left	☐ The same on both sides	☐ Larger on right

Thank you for completing this questionnaire!

assessment time point	O last week RT	O day 45-60	O 2 years

RTOG PQ

22 Appendix - Form for missing Quality of Life information

Form QMD (01-25-2005) Page 1 of 1

Missing Data Form for Quality of Life Questionnaire

Submit this form whenever a protocol-scheduled Quality of Life (QOL) Questionnaire (i.e., Form QLT, QLP, or QLF) is not filled out by the patient and the assessment cannot be obtained by phone or mail. No missing data form is required for partially completed QOL forms or patients who have died or had a documented breast cancer recurrence or a second primary cancer.

Patient Initials ☐, ☐☐ (Last, First, Middle) **Patient ID** ☐☐☐☐☐☐☐☐☐

Institution Name / Affiliate Name _____ / _____

Person Completing Form Last Name First Name Phone

Today's Date ☐☐ Month ☐☐ Day ☐☐☐☐ Year

Are data amended? (*check box if yes, and circle amended items*) ☐ Yes

Time Point for this Form (*mark one*)

- O Form QLT: Last week of radiation therapy
- O Form QLP: 45-60 days after starting radiation therapy
- O Form QLF: 2 years after adjuvant therapy (radiation and/or chemotherapy)

Reason QOL was Not Assessed During Clinic Visit
(*Mark the main reason and add comments below.*)

- O Staff oversight or understaffing
- O Staff concerned for patient's medical or emotional condition
- O Patient stated that she was too ill or upset to complete questionnaire
- O Patient refused to complete questionnaire for reason other than illness or upset
- O Patient was unavailable (e.g., scheduling or transportation difficulties)

Reason QOL was Not Obtained by Phone or Mail
(*Mark all that apply and add comments below.*)

- O Staff oversight or understaffing
- O Patient's medical or emotional condition
- O Patient refused to complete questionnaire
- O Staff was unable to contact patient by phone
- O Questionnaire was mailed to patient but she did not return it (for any reason)

Comments

_____

_____

Mark Circles Like This: → ●

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