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Brief Title: **Accelerated Radiation Therapy (ART) To The Breast And Nodal Stations After Neo-Adjuvant Systemic Therapy And Surgery: A Feasibility Study**

Version 6.0

Version date: 24MAR2021

IRB approval: 07FEB2024

Document History

Protocol	Version Number	Version Date
Amendment 6	**6.0**	**24MAR2021**
Amendment 5	5.0	12JAN2021
Amendment 4	4.0	06.30.2020
Amendment 3	3.0	10.11.2019
Amendment 2	2.1	05.04.2018
Amendment 1	2.0	10.09.2017
Initial Protocol	1.0	07.25.2016

ACCELERATED RADIATION THERAPY (ART) TO THE BREAST AND NODAL STATIONS AFTER NEO-ADJUVANT SYSTEMIC THERAPY AND SURGERY: A FEASIBILITY STUDY

IRB Protocol #: 1602017017
Version Date: - 24MAR2021
Version: 6.0

Principal Investigator: Silvia C. Formenti, M.D.
[redacted]

Co-Investigators: [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Nurse Practitioner:

[redacted]

Statistician:

[redacted]

Study Coordinators:

[redacted]

[redacted]

[redacted]

Participating Sites:

1. *New York-Presbyterian Weill Cornell Medical College Stich Radiation N-046 525 East 68th street, New York, NY – 10065*
2. *New York-Presbyterian Weill Cornell Medical College, 1283 York Avenue,4th floor, David H, Koch Building New York, NY-10065*
3. *New York-Presbyterian - Brooklyn Methodist Hospital 506 Sixth Street, Brooklyn, NY - 11215*
4. *New York Presbyterian - Queens Radiation Oncology 56-45 Main Street, Flushing, NY – 11355*

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.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADL	Activities of daily living
AE	Adverse event
AIMRT	Accelerated Intensity Modulated Radiation Therapy
ATM	Ataxia Telangiectasia Mutated
BED	Biologically Effective Dose
CBC	Complete blood count
CI	Confidence interval
CBCT	Cone-Beam CT
CRF	Case report/Record form
CR	Complete response
3D-CRT	3 Dimensional Conformal Radiotherapy
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical target volume
DCIS	Ductal Carcinoma In Situ
DHPLC	Denaturing High Performance Liquid Chromatography
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
FBD	Friday Boost Dose
GI	Gastrointestinal
Gy	Gray
Hgb	Hemoglobin
IBV	Ipsilateral Breast Volume
IGRT	Image Guided RadioTherapy
IMRT	Intensity Modulated RadioTherapy
IRB	Institutional Review Board
LENT/SOMA	Late Effects Normal Tissues / Subjective, Objective, Management criteria with Analytic laboratory and imaging procedures
LLN	Lower limit of normal
OS	Overall survival
PCR	Polymerase Chain Reaction
PCR-RFLP	Polymerase Chain Reaction-Restriction Fragment Length Polymorphism
PD	Progressive Disease
PFS	Progression free survival
PLT	Platelet
PR	Partial response
PTT	Protein Truncation Test
PTV	Planning Target Volume
RBV	Residual Breast Volume
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event

SD	Stable disease
TGF-beta1	Transforming Growth Factor beta-1
TV	Treatment Volume
WBD	Weekend Boost Dose

Protocol	Version Number	Version Date
Amendment 6	**6.0**	**24MAR2021**
Amendment 5	5.0	12JAN2021
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Amendment 3	3.0	10.11.2019
Amendment 2	2.1	05.04.2018
Amendment 1	2.0	10.09.2017
Initial Protocol	1.0	07.25.2016

Summary of changes: Version 6.0 dated 24MAR2021

Section(s)	Changes	Rationale
Inclusion Criteria 5.1	Criteria 5.1.5 : Expanding inclusion to allow patients with a focally positive margin.	Expanding inclusion criteria.
Changes to the Informed consent document		
Footer changes	Updating the footer to match the protocol version date. Updated consent version date 24MAR2021.	Admin changes only.

Summary of changes: Version 5.0 dated 12JAN2021

Section(s)	Changes	Rationale
Adding Network sites	Adding NYP-BMH, NYP-Q as addition sites for patient enrollments	Adding sites.
Personnel section	Adding Jessica Richman (admin amendment approved 10/19/2020) Adding Co investigators: Dr. Andrew Brandmaier, Dr. Hani Ashamalla, Dr. Steven DiBiase and Dr. Akkamma Ravi Removing : Sally Sa	Personnel changes
Informed consent document changes		
Adding network sites	Adding NYP-BMH, NYP-Q as addition sites for patient enrollments	Adding sites

Summary of changes: Version 4.0 dated 06.30.2020

Adding to the eligibility criteria:

1. To include patients who because of COVID had undergone up to 3 months neoadjuvant hormonal therapy before surgery for clinical T1/T2 BC
2. Video visits will be included as part of patient follow up.
3. Removing Viji Nagaraj from the study as she is no longer working in WCM Radiation Oncology.

Rationale for the changes: NCI wants to assure most patients who had modifications during COVID are still eligible to clinical trials.

Summary of changes: Version 3.0 dated 10.11.2019

1. Adding Dr. Encouse Golden to the study.
2. Formatting the protocol as the index is not correctly formatted.
3. Making the protocol version date consistent on the header text.

   No Changes to the informed consent.

Summary of changes: Version 2.1 dated 05.04.2018

1. Making the investigators' list consistent with eIRB.
2. Changing study coordinator to Pragya Yadav

Exclusion Criteria Section 5.2:

1. Adding: Patients with more than 5 nodes involved at axillary dissection will be excluded from this study since they will be eligible to receive radiotherapy to level I and II axilla.

This was already written in the body of the protocol (section (9.0 Radiotherapy) but was not included in the exclusion Criteria section 5.2.

Summary of Changes: Version 2.0 Dated 10.09.2017.

1. Title Change : Accelerated Radiation Therapy (Art) To The Breast And Nodal Stations After Neo-Adjuvant **Systemic Therapy** And Surgery: A Feasibility Study

   - Rationale for title change : To include neoadjuvant hormone therapy

2. Cohort 2 to include: If clinically indicated, internal mammary nodes will also be treated and a supine set up will be used

   - Rationale - To follow the most recent NCCN indications to irradiate internal mammary nodes for inner quadrants and central cancers, particularly if axillary nodes are also involved

PROTOCOL SUMMARY

Full Title:	*ACCELERATED RADIATION THERAPY (ART) TO THE BREAST AND NODAL STATIONS AFTER NEO-ADJUVANT SYSTEMIC THERAPY AND SURGERY: A FEASIBILITY STUDY*
Short Title:	*ART Protocol*
Clinical Phase:	*Phase I-II*
Principal Investigator:	*Dr. Silvia. C. Formenti*
Sample Size:	*N= 74 (37 per Arm)*
Accrual Ceiling:	*100*
Rate of subject accrual:	*Approximately 3 subjects per month or 36 patients per year*
Study Population:	*Newly diagnosed breast cancer patients with an indication for post-operative radiotherapy after neo-adjuvant chemotherapy and surgery*
Accrual Period:	*2-3 years*
Study Design:	*Prospective two cohorts study in newly diagnosed breast cancer patients. Cohort 1 patients will receive Radiation to breast and chest wall. Cohort 2 patients will receive Radiation to Breast, chest wall and Level III/SCV nodes.*
Study Duration:	*Patients will complete treatment in three weeks (15 fractions). All patients will be followed at 3 months after the completion of treatment then yearly for the next 5 years.*
Study Agent/ Intervention Description:	***Cohort 1*** *(Post-segmental Mastectomy, post-mastectomy and Post-mastectomy with expanders or final reconstruction)**:*** *Prone whole breast or chest wall 3D-CRT or IMRT at 2.7 Gy X 15 fractions (40.50 Gy) with a concomitant boost of 0.50 Gy (7.5 Gy) to the original tumor bed in post-segmental mastectomy patients or mastectomy scar in post-mastectomy patients. Patients who have undergone reconstruction will not receive concomitant boost.* ***Cohort 2:*** *In addition to receiving radiation to the original tumor bed, patients will also receive radiation to Level III axillary nodes and Supraclavicular nodes: 3D-CRT or IMRT at 2.7 Gy X 15 fraction (40.50 Gy) If clinically indicated, internal mammary nodes will also be treated and a supine set up will be used*

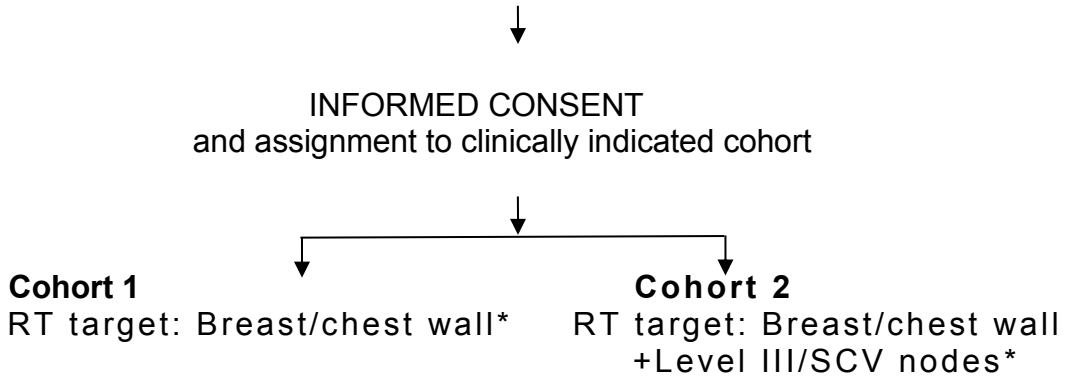
Primary Objective: *Acute Toxicity: Grade 2-3 dermatitis <25% in each cohort*

Secondary Objective: *QOL, defined by RTOG-PRO; Late toxicity, Fibrosis, Telangiectasia, Brachial Plexopathy.*

Exploratory Objectives: *Local control; Time to Progression, Survival; Evaluation of Determinants of Breast Fibrosis*

SCHEMA

Stage I-III Breast Cancer Patients, Eligible For Post-Surgical Radiotherapy After Neo-adjuvant Chemotherapy And/Or Hormonal Therapy Followed By Segmental Mastectomy Or Mastectomy



* **Radiation fields and doses:**

Cohort 1
a) Post segmental mastectomy: Prone whole breast 3D-CRT or IMRT at 2.7 Gy X 15 fractions (40.50 Gy) with a concomitant boost of 0.50 Gy (7.5 Gy) to the tumor bed.
b) Post-mastectomy: Prone whole breast 3D-CRT or IMRT at 2.7 Gy X 15 fractions (40.50 Gy) with a concomitant boost of 0.50 Gy (7.5 Gy) to the mastectomy scar on the chest wall.
c) Post-mastectomy with expanders or final reconstruction: Prone whole breast 3D-CRT or IMRT at 2.7 Gy X 15 fractions (40.50 Gy).

Cohort 2
Either a, b, c +
d) Level III axillary nodes and Supraclavicular nodes: 3D-CRT or IMRT at 2.7 Gy X 15 fractions (40.50 Gy) -If clinically indicated, internal mammary nodes will also be treated and a supine set up will be used.

All patients will be followed for toxicity and outcome (local and systemic recurrence, survival) In addition, patients will complete a self-assessment of QOL at baseline, completion of radiation treatment, at 45-60 day follow-up and at 2 year follow-up.

TREATMENT SCHEMA

Within a month from initiation	Week 1	Week 2	Week 3	Months 3	Months 12-24-36-48-60
simulation	RT	RT	RT	Follow up	Follow up
Patient education - baseline QOL Blood sample			QOL assessment Blood sample	QOL assessment	QOL assessment

STUDY SYNOPSIS

Patients undergoing primary systemic therapy, followed by surgery often receive post-operative radiation. While the targets treated post-operatively vary and depend on the initial and post-surgical stage, patients generally undergo 6-7 weeks of daily (Monday to Friday) post-operative radiation.

This approach is long and draining, particular in this population of breast cancer patients who often experience chemotherapy-induced fatigue. Our group has developed and tested a combined positioning and hypo-fractionated regimen of post-operative radiotherapy that may be particularly convenient and indicated for these women.

Specifically a prone set-up has enabled safe sparing of heart and lung while targeting the breast and, more recently, level III and supraclavicular nodes.

While we have extensively tested this approach in the classical adjuvant setting of breast cancer, until now we have not tested it after neo-adjuvant chemotherapy.

We are proposing a prospective study to test feasibility of prone breast and nodal radiotherapy in women who have undergone surgery after preoperative systemic therapy. Primary study endpoint will be acute toxicity and secondary will be late effects (with focus on radiation fibrosis) and patient's assessment of QOL with this approach. Exploratory endpoints will be 5y local control and survival.

1.0 OBJECTIVES

1.1 Primary Objectives

1.1.1. To test feasibility of accelerated radiotherapy in the post-operative setting of breast cancer patients treated by neo-adjuvant chemotherapy and surgery, by evaluating the proportion of patients who experience grade II-III dermatitis within 60 days of the end of treatment.

1.2 Secondary Objectives

1.1.2. To assess QOL of patients at baseline and after the course of treatment.

1.1.3. To assess incidence of late radiation toxicity (brachial plexopathy, fibrosis and telangiectasia) and to examine genetic determinants of breast fibrosis

1.3 Exploratory Objectives

1.1.4. To assess local control rates, distant recurrence and overall survival of at 2, 5 and 10 years follow up.

1.1.5. To prospectively validate the data on molecular signature of fibrosis.

2.0 BACKGROUND

2.1 NYU research in hypo-fractionated whole breast radiotherapy

A recent Cochrane Collaboration Intervention Review has addressed the effects of altered fractionation size on women with early breast cancer who have undergone breast conservation surgery. [1] Four prospective randomized trials that included 7095 women, selected based on tumor size less than five cm, negative pathological margin of excision and negative lymph nodes were analyzed. No difference in clinical outcome was observed when comparing traditional 6 weeks to shorter 3 weeks treatment courses. The conclusion of the review is that the use of unconventional fractionation regimens (> 2 Gy per fraction) does not affect breast appearance or late toxicity and does not adversely impact local recurrence or five-year survival rates.

Hypo-fractionation regimens enable shortening of the duration of therapy; the findings are quite relevant, since changing the standard recommendation of 30 fractions over six weeks to a 3-week regimen could result in higher compliance and cost saving.

During the past 12 years we have conducted a series of consecutive studies to optimize the safe delivery of accelerated radiotherapy to partial and whole breast. **A review of whole breast radiation research conducted so far is detailed below, as a background for the current study that targets Stage I-III breast cancer patients after neoadjuvant chemotherapy and segmental mastectomy or mastectomy.**

2.2 Experience On Accelerated Concomitant Boost Whole Breast: NYU 03-30 and 01-51

NYU 03-30. Inspired by the hypo-fractionated Canadian trial, [2] we developed a technique

that utilizes IMRT to deliver accelerated prone whole breast radiotherapy with a concomitant boost to the tumor bed. Patients with stage I or II breast cancer, excised by breast conserving surgery with negative margins, and either sentinel node biopsy or axillary dissection were eligible for this IRB-approved protocol. All patients underwent an informed consent procedure. CT simulation was performed with the patient on a dedicated prone breast board, in the exact position used for treatment. Relevant volumes contoured included the post-operative tumor bed (CTV), the ipsilateral breast volume (IBV), the heart, and the lungs. The Planning Target Volume (PTV) was defined as CTV + 1 cm. The residual breast volume (RBV) was defined as the IBV - PTV. A dose of 40.5 Gy in 15 fractions was prescribed to the IBV. An additional 0.5 Gy was delivered concomitantly to the PTV for a total dose of 48 Gy. The dose was determined by radiobiological modeling of the Biologically Effective Dose (BED), to match tumor control and risk of late effects of a standard schedule of 46 Gy to the whole breast plus a sequential boost dose of 14 Gy to the tumor bed. A value for tumor $\alpha/\beta = 4$ was used and the impact of cell proliferation during the course of treatment was taken into account. For each patient accrued to the study, blood was collected for radiation genomic studies, to explore markers predictive of late breast complications (fibrosis, retraction, and telangiectasia).

From September 2003 to August 2004, the planned accrual was completed, with 90 patients treated in the protocol (mean follow-up of 13 months, range 1-23 months). Median age was 58 (range 28-80). Median tumor size was 13 mm (range 1-40 mm). Acute toxicity was generally mild and is summarized in Table 1 using the RTOG score. Radiation dermatitis was the most common toxicity and tended to occur the week after completion of treatment.

Table 1. Acute Toxicity NYU 03-30

	Grade 1	Grade2	Grade 3	Grade 4
Dermatitis	38 (42%)	9 (10%)	2 (2%)	-
Fatigue	15 (17%)	-	-	-
Breast edema	7 (8%)	-	-	-
Breast pain	4 (4%)	-	-	-

Because of blood collection, the study also started an annotated repository to enable exploration of the association between specific genomic profiles and the occurrence of fibrosis, once there has been sufficient follow up to assess late effects. [3] In addition, this trial has generated an invaluable repository of physics information from the planning and volume inclusion by the technique adopted, offering the opportunity for an in-depth investigation of the effect of laterality when patients are treated prone. This information is relevant in terms of optimization of normal tissue sparing, particularly the heart and lung, both organs susceptible to risk of fatal late effects of radiation [4].

01-51: Accelerated Radiotherapy for DCIS

This protocol aimed at testing the use of accelerated whole breast radiotherapy in women with ductal carcinoma in situ. Eligible patients were women with DCIS who refused conventional 5-week radiotherapy. The trial consisted of 15 daily fractions of 2.8 Gy, over three weeks, to a total dose of 42 Gy. While the protocol did not require prone positioning it did not exclude this technique either. In some instances, women who were initially simulated supine were re-simulated in the prone position due to the large extent of lung and heart in the field. They were often (but not always) found to have better normal tissue sparing when prone and were then treated in

that position. [5]

2.3 Rationale For Prone Radiotherapy: Nyu 05-181

Despite the demonstrated feasibility and advantages of a prone set up, in our experience of more than 3,000 cases, occasional patients appear to be better treated supine, in order to optimally spare heart and lung. Since no obvious clinical characteristics predict for this exception, we led an organized prospective effort of comparing supine versus prone breast setup in a consecutive cohort of 200 right and 200 left breast cancer patients. Again, intensity modulated radiotherapy with an accelerated, daily concomitant boost approach was used, the same regimen originally pilot-tested for prone IMRT. NYU Protocol #05-181, "Accelerated Intensity Modulated Radiation Therapy (AIMRT) to the Breast after Segmental Mastectomy: Identification of Optimal Individual Positioning" was opened in 2005 to pre- and post-menopausal women with stage 0-IIB breast cancer who had received breast conserving surgery. Patient eligibility criteria included the requirement of at least 1mm of margin, no more than 3 positive lymph nodes for breast cancer, at least two weeks post chemotherapy (if indicated), with no history of prior or concurrent malignancy (within 3 years), and with no history of active connective tissue disorders. Patients underwent CT simulation in the prone and supine positions. Treatment followed in the optimal position defined as that which assured the smallest volume of heart and lung in the target field.

Among right breast cancer patients, the prone position was optimal in sparing lung volume in all women, reducing the in-field lung volume by a mean 104.6cc (95%CI: 94.01 – 115.16) compared to supine set-up. For left breast cancer patients, the prone position was optimal in 85%, with in-field heart volume reduced by a mean of 9.9cc (95%CI: 7.37 – 12.45) and in-field lung volume reduced by a mean of 95.2cc (95%CI: 84.27 – 106.13). In the 30 left breast patients best treated supine, the in-field heart volume was reduced by a mean of 6.2cc (95%CI: 2.97 – 9.33). Only 32% of the women with breast volume <750 cc were better treated supine. Prone set-up reduced the amount of lung volume irradiated in all patients and reduced the amount of heart volume irradiated in 85% of left breast cancer patients. Prone positioning was also superior to supine treatment for the majority of small-breasted women, contrary to the common opinion that it should be reserved for large breast size patients (6).

Based on the experience gathered from NYU Protocol 05-181, it is rational for all patients to first undergo a CT Simulation in the prone position. In this protocol, we will again use 2.5 mm slice thickness with the patient positioned on a dedicated breast mattress that allows the index breast to freely fall through an opening. If it is found that conventional tangents in the prone position include **any** volume of heart and/or > 5% of lung volume, a second simulation will be required in supine position to assess which position best minimizes the amount of heart and lung in the treatment fields to be chosen for treatment.

2.4 NYU 09-0300: A Prospective Randomized Trial Aimed At Establishing The Optimal Boost Schedule

Radiobiological evidence supported the introduction of a larger fraction dose before a two-day treatment break (weekend). We studied two different boost schemas in a randomized trial of 400 patients. The **standard arm** was a concomitant boost protocol over three weeks which had previously been evaluated in over 500 patients (NYU 03-30 and NYU 05-16 of 60

181) and had shown excellent tolerance, and results. In addition to the 2.7 Gy whole breast dose, an additional 2 Gy was delivered to the tumor bed on each of the three Fridays, with the tumor bed receiving 4.7 Gy on each of the three Fridays.

At a median follow-up of 45 months, there were no deaths related to breast cancer. The weekly boost regimen produced no more grade ≥ 2 acute toxicity than the daily boost regimen (8.1% vs 10.4%; non-inferiority $Z = -2.52$; $p = 0.006$). There was no statistical difference in cumulative incidences of long term fibrosis or telangiectasia grade ≥2 between the two arms (log-rank p=0.923). There were 2 local and 2 distant recurrences in the daily boost arm. There were 3 local and 1 distant recurrences in the weekly arm, with no difference in 4-year RFS between the two arms (98% in both arms). In addition, extensive QOL assessment between the 2 arms demonstrated comparable results with regard to the patient's experience during and after radiotherapy. In conclusion, the trial demonstrated that a tumor bed boost delivered either daily or weekly is similarly tolerated during accelerated prone breast radiotherapy, with excellent control of disease and comparable cosmetic results (7).

2.5 Prone Breast And Nodal Radiotherapy

The results of NYU- 09– 0623, a prospective trial of prone breast radiotherapy with inclusion of level III axillary and supraclavicular nodes was recently reported (8). Eligibility required surgical dissection of ≥ 8 axillary lymph nodes and negative surgical margins of ≥ 1 mm at the primary site. An interval of 60 days from surgery was allowed. RT started ≥ 2 weeks and <60 days following completion of chemotherapy. Exclusion criteria included pregnancy, prior ipsilateral breast RT, or >5 involved nodes at dissection. Following either segmental or total mastectomy with axillary node dissection, patients were treated to a dose of 40.5 Gy/15 fractions with a concomitant daily boost to the tumor bed of 0.5 Gy (total dose, 48 Gy). In post-mastectomy patients, the same treatment was prescribed, but without a tumor bed boost. The primary endpoint was incidence of grade 2 acute skin toxicity. The secondary endpoints were feasibility of treatment using prone set-up, compliance with protocol-defined dosimetric constraints, and incidence of late toxicity.

Sixty nine patients accrued to the study (one with bilateral breast cancer), for a total of 70 prone treatments of breast/chest wall, level III and supraclavicular nodes: 54/70 breast cancers were staged as N1 and 16 as N2. Fifty-five of the 69 patients (79%) underwent adjuvant chemotherapy, usually after radiotherapy was completed.

The results of this trial are encouraging, since no patients experienced grade >2 acute skin toxicity according to the Common Terminology Criteria for Adverse Events, version 3.0, meeting the primary endpoint. At a median follow up of 36 months, no ipsilateral breast local recurrence, regional nodal recurrence, or contralateral breast cancer have developed. Three patients have developed distant failures, 1 after 9 months and 2 after 18 months post-treatment. Currently, there have been 4 deaths, 2 from breast cancer, resulting in a 3-year breast cancer–specific survival of 95.6%.

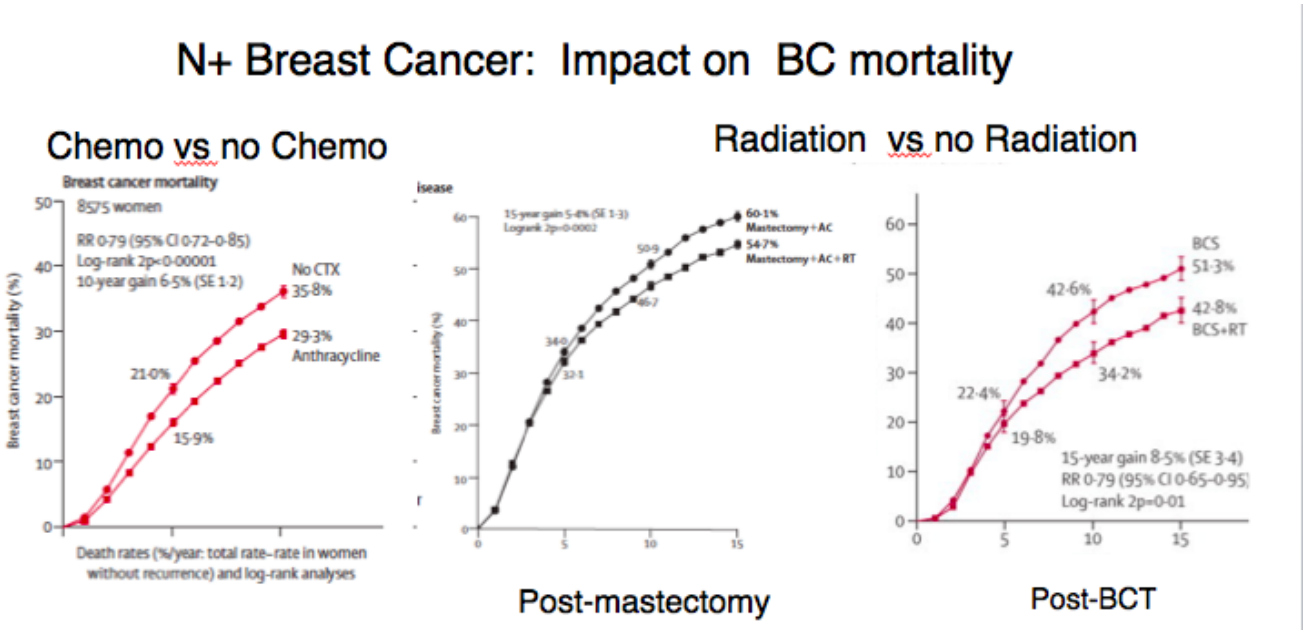
The results of this trial warrant testing of the same approach after neo-adjuvant chemotherapy and surgery, the scope of this protocol.

2.6 Benefit Of Post-Operative Radiotherapy In The Adjuvant Setting

Several consecutive meta-analyses have demonstrated the additional benefits of post-operative/adjuvant radiotherapy distinct from those of systemic therapy (9) in both the breast conservation and post-mastectomy settings (10,11,12). Noticeably, for node positive patients, adding radiotherapy confers a statistically significant survival advantage that is comparable to that derived from the addition of anthracycline-based chemotherapy (figure 1). The data from the meta-analyses have changed the practice of oncology by establishing a central role for post-operative

breast cancer radiotherapy.

Figure 1 (from references 9-12)



2.7 Post-Operative Radiotherapy After Neo-Adjuvant Chemotherapy

Neo-adjuvant/preoperative chemotherapy is usually reserved for high-risk breast cancer patients, whether because of locally advanced stage, an inflammatory breast cancer diagnosis or aggressive tumor biology. In such settings neo-adjuvant chemotherapy is considered standard care. Alternatively, a preoperative investigational approach can be tried as part of a "window of opportunity" clinical protocol, testing the effect of a novel targeted therapy. The latter choice is commonly offered in the setting of biologically more aggressive breast cancers, like triple negative breast cancer, tumors overexpressing HER2 positivity or in oestrogen receptor-positive tumors with clinically positive nodes. The majority of patients given preoperative chemotherapy subsequently undergo a mastectomy (13). Generally these patients are offered the choice of breast reconstruction and most North American patients elect to undergo reconstructive surgery. However, nowadays approximately a third of patients treated with preoperative systemic therapy undergo breast conservation surgery (BCS).

Based on the evidence for a benefit in the adjuvant setting, radiotherapy is often offered to women treated neo-adjuvantly, after surgery. Traditionally, women are treated with a supine set up that includes the breast (or chest wall / reconstructed breast) and draining nodes, over 6-7 weeks of daily visits (Monday-Friday).

Recently, the concept that the pathological response to neoadjuvant chemotherapy might be used to exclude patients from postoperative RT or to at least reduce the fields of radiotherapy has emerged. NSABP B-51/RTOG 1304 is an Intergroup clinical trial currently exploring the effects of excluding post-operative radiation or reducing the radiotherapy fields among patients who present with involved axillary nodes (documented by fine needle aspiration or core needle biopsy) and are found to have a negative sentinel node or axillary dissection after chemotherapy. The trial

randomizes patients treated with preoperative chemotherapy and mastectomy to receive or not receive post-mastectomy chest wall and regional nodal RT. Those who have been treated with segmental mastectomy are randomized to receive post-segmental mastectomy radiation to the breast alone versus breast and regional nodal RT.

In conclusion, at this time, most breast cancer patients who have undergone neo-adjuvant radiotherapy are offered post-operative radiotherapy with standard dose and fractionation resulting in a course duration of approximately 6-7 weeks. **We propose testing the feasibility of accelerated radiotherapy after neo-adjuvant systemic therapy and surgery. We will utilize the same 3 weeks accelerated regimen used to treat the breast and draining nodes in the prone position that we have extensively tested in the adjuvant setting of breast cancer (6, 8)**

3.0 Background For Primary Objective

3.1 Measuring Acute Toxicity

The Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI) Common Toxicity Criteria (CTC) was developed in 1982 for use in adverse drug experience reporting, study AE summaries, Investigational New Drug (IND) reports to the Food and Drug Administration (FDA), and publications. The CTCAE v4.0 is the first uniform and comprehensive dictionary of AE grading criteria available for use by all modalities used in the treatment of cancer. A grading (severity) scale is provided for each AE term.

The terms considered in this trial are specific to radiation toxicity and include fatigue, radiation dermatitis and brachial plexopathy. This information will be collected by the treating physician using a specific tracking form (see appendix 3). Acute Toxicity will be scored using the CTCAE v4.0 (see Appendix 1).

4.0 Correlative Studies Background

4.1 Quality of Life Assessment

Patients' quality of life assessments will be performed at regular intervals (baseline, last week of radiation treatment, 45-60 days from starting radiotherapy and 2-year follow-up). QOL will be evaluated in several ways.

First, cosmetic results will be examined using the Breast Cancer Treatment Outcome Scale (BCTOS) using patient self-reports. 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. [14] The BCTOS also will be used as a primary measure to assess breast-related symptoms and treatment effects. Specifically, the BCTOS will be augmented with a brief set of additional items that focus on radiotherapy-relevant symptoms (e.g., reports of skin problems, tenderness/pain in the breast, and hardness in the breast due to enhanced fibrosis). Second, we will use the MOS SF-36 Vitality Scale, a widely used measure with high reliability and validity, will assess fatigue. [15-16]

4.2 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% [17-18]. Manifestations of radiation-induced breast fibrosis include pain, cosmetic deformities, and diminished quality of life. 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.

Hoeller et al. recently reported a careful comparison of The Radiation Therapy Oncology Group (RTOG) and Late Effects Normal Tissue Task Force subjective, objective, management, and analytic (LENT/SOMA) scores for late breast toxicity after radiation in a group of breast cancer patients. [19] In comparison, when LENT/SOMA criteria were used, telangiectasia and pigmentation were upgraded in 34% and 36%, respectively, and telangiectasia was downgraded in 45%. Inter-observer variability was similar for both classification systems and ranged from Cohen's kappa 0.3 (retraction) to 0.91 (telangiectasia). The authors concluded that LENT/SOMA criteria seem to be the better in grading and recording late radiation toxicity compared with the RTOG scale. Specifically, fibrosis scores correlated well with the LENT/SOMA scoring system (Spearman's rho 0.78, $p = 0.01$).

Brachial plexopathy is a potential toxicity associated with nodal irradiation. This side effect can significantly impair arm/shoulder function and worsen quality of life due to pain and paresthesia. Early trials of hypofractionated nodal irradiation conducted in Australia and Sweden in the 1960s revealed a 73% and 63% rate of neuropathy, respectively. However, the Australian regimen consisted of 63 Gy delivered in 12 fractions while the Swedish trial used 44 Gy in 11 fractions. Decades of experience have improved our understanding of the relationships between the volume of a critical structure treated, dose, fractionation and subsequent brachial plexus injury. We will also report this adverse effect using the LENT/SOMA scoring system.

4.3 Genetics Of Radiation-Induced Breast Fibrosis

Since the most likely long-term toxicity of accelerated radiation is soft tissue fibrosis and skin telangiectasia the preliminary recognition of genetic predispositions to these complications enables the exclusion of high-risk carriers from the trials of accelerated/hypo-fractionated radiation. In other words, similar to the impact of pharmacogenomics in medical oncology, the field of radiation-genomics is also rapidly emerging, permitting to identify individuals with genetic predisposition to inferior repair of the damage caused by ionizing radiation.

A recent study from Quarmby et al has shed some light on the genetic risk of developing breast fibrosis post-ionizing radiation. To investigate whether single nucleotide polymorphisms (SNP) of transforming growth factor beta-1 (TGF-beta1) were associated with the susceptibility of breast cancer patients to severe radiation-induced normal tissue damage Quarmby et al performed Polymerase Chain Reaction-Restriction Fragment Length Polymorphism- (PCR-RFLP) assays for TGF-beta1 gene polymorphisms on DNA obtained from 103 breast cancer patients who received radiotherapy. [21] The G-800A, C–509T, T+869C and G+915C polymorphic sites were examined, and genotype and allele frequencies of two subgroups of patients were calculated and compared. The investigators found that the less prevalent –509T and +869C alleles were significantly associated with a subgroup of patients who developed severe radiation-induced normal tissue fibrosis (n=15) when compared with those who did not (n=88) (odds ratio=3.4, p=0.0036, and 2.37, p=0.035, respectively). Furthermore, patients with the –509TT or +869CC genotypes were between seven and 15 times more likely to develop severe fibrosis. These findings imply a role for the -509T and +869C alleles in the biological mechanisms underlying susceptibility to radiation-induced fibrosis.

4.4 Blood Collection For Genomic Studies

The purpose of this portion of the study will be to collect blood from each subject accrued to the study and willing to donate a specimen of blood for research, to study the –509C□T and +869T□C TGF-β1 polymorphisms that have been reported to be correlated with the development of fibrosis following radiotherapy for treatment of breast cancer. [21]

For the purpose of this trial blood will be collected to enable genomic analysis for this polymorphism to explore association with the incidence of grade 3 and 4 late complications at 3 years follow up. Results of the blood test will be de-identified and will not be part of the patient's care. It will not be included in the medical record, but it will be maintained at the research office of the Department of Radiation Oncology at WCMC. When the study information is disclosed outside of WCMC as part of the research, the information that can identify the patient will be removed and the patient's records will be assigned a unique number. WCMC will not disclose the code key, except as required by law.

5.0 Patient Eligibility

5.1 Inclusion Criteria

5.1.1 Age older than 18
5.1.2 Pre- or post-menopausal women with Stage I-III breast cancer
5.1.3 Status post neoadjuvant systemic therapy
5.1.4 Status post-chemotherapy breast surgery
5.1.5 Original biopsy-proven invasive breast cancer, excised with negative margins of at least 1 mm (patients with focally positive margin are not excluded).
5.1.6 Status post segmental mastectomy or mastectomy, with either negative sentinel node biopsy and/or axillary node dissection (at least 6 nodes removed).
5.1.7 Patient needs to be able to understand and demonstrate willingness to sign a written informed consent document

5.2 Exclusion Criteria

5.2.1 Previous radiation therapy to the ipsilateral breast and/or nodal area
5.2.2 Active connective tissue disorders, such as lupus or scleroderma requiring flare therapy
5.2.3 Pregnant or lactating women
5.2.4 Concurrent chemotherapy, with the exception of anti HER2neu therapies
5.2.5 Inadequate axillary dissection in a setting of positive sentinel node
5.2.6 Patients with more than 5 nodes involved at axillary dissection will be excluded from this study since they will be eligible to receive radiotherapy to level I and II axilla.

6.0 Registration Procedures

6.1 General Guidelines

Patients will have completed breast cancer surgery prior to accrual into this protocol in order to establish eligibility criteria. Final pathology margins must be at least 1 mm in all directions to be eligible. The patient may undergo re-excision if the initial margins are involved or close (<

1 mm).

AJCC staging criteria will be used to identify original Clinical Stage of breast cancer patients eligible to this study. All eligible women who are referred to the Radiation Oncology Department at Weill Cornell Medicine for radiation following neo-adjuvant systemic therapy and surgery for breast cancer will be offered the opportunity to participate in this experimental protocol.

6.2 Registration Process

Before any protocol specific procedures can be carried out, investigators/staff will fully explain the details of the protocol, the study procedures and the aspects of patient privacy regarding research information. Patients will be provided a comprehensive explanation of the proposed treatment including the type of therapy, the rationale for treatment on the protocol, alternative treatments that are available, any known adverse events, the investigational nature of the study and the potential risks and benefits of the treatment. The Informed Consent document will meet all requirements of the Institutional Review Board. All subjects/patients are informed in the Consent that participation or refusal to participate in the research study will not affect any of the clinical treatment or services to which they would otherwise be entitled.

The physicians who may obtain informed consent are listed on the title page of this protocol. The Informed Consent form will be signed by the participant and the registering physician. Once signed, a copy will be given to the patient and one will be maintained with the patient's medical record. Once eligibility is confirmed and Informed Consent is documented, the patient will be registered by the study coordinator/data manager.

6.3 Randomization Process

This study is a Phase I-II non-randomized trial. Patients will be registered within 2 cohorts defined by requirement for nodal radiation (yes =Cohort 2/no= Cohort 1).

7.0 Treatment Plan

7.1 General Concomitant Medication and Supportive Care Guidelines

During radiation treatment, all patients will be prescribed daily application of Calendula lotion, to prevent skin dryness and reduce erythema.

7.2 Duration of Therapy

The treatment will consist of 15 fractions, Monday to Friday, for 3 weeks total time (over a total of 19-21 days, depending on the start day), see study calendar in Section 13.

7.3 Duration of Follow Up

Patients will be seen for follow-up at day 45-60 and then yearly thereafter for 5 years, see study calendar in Section 13.

7.4 Alternatives

At the time of study accrual, all patients will be offered access to the standard six weeks of radiotherapy.

7.5 Compensation

No compensation is available for participating in the study.

8.0 Surgery

Patients will have completed all surgical procedures related to breast cancer surgery prior to accrual into this protocol in order to establish eligibility criteria. Final pathology margins must be at least 1 mm in all directions to be eligible. The patient may undergo re-excision if the initial margins are involved or close (< 1mm). If the patient meets the eligibility criteria after re-excision, she may be entered onto the study. Patients undergoing reconstructive surgery are eligible either after maximum expansion of tissue expanders or after completion of breast reconstruction.

While currently women with a variety of clinical presentations of breast cancer are offered a neo-adjuvant systemic approach (stage I-III), eligibility to this protocol will require assessment of nodal status at surgery, either by sentinel node and/or axillary dissection (minimum 6 nodes).

9.0 Radiotherapy

Radiotherapy schedule for Cohort 1 and Cohort 2

WEEK	WEEK 2						WEEK 3							WEEK 4					
DAY #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
	M	T	W	T	F			M	T	W	T	F			M	T	W	T	F
Tx	wb/c	wb/c	wb	wb	wb			wb	wb	wb	wb	wb			wb	wb	wb	wb	wb
	w*	w	TB	TB	TB			TB	TB	TB	TB	TBB			TB	TB	TB	TB	TB
	TB+	TB										BBb							B

*wb = target is whole breast, chest wall or reconstructed breast, 2.7 Gy/fraction
+TB = target is the original tumor bed or mastectomy scar in post-mastectomy patients without reconstruction, 3.2 Gy/fraction

Cohort 2 will follow the same schedule like Cohort 1 but level III axillary and SCV nodes will also be treated daily, at 2.7 Gy per fraction, to a total dose of 40.50 Gy.

9.1 Radiotherapy target

Patients with sentinel node negative or axillary node dissection negative results will be assigned to cohort 1. Patients with sentinel node positive or axillary node dissection positive results will be assigned to cohort 2. Patients with more than 5 nodes involved at axillary dissection will be excluded from this study since they will be eligible to receive radiotherapy to level I and II axilla.

9.2 Dose Specification

Patients will receive 15 daily radiation fractions of 2.7 Gy, to the entire breast, to a total dose of 40.5 Gy to the breast, and an additional .50 Gy to the tumor bed or chest wall scar daily to a total dose of 48 Gy to the tumor bed or chest wall scar. The whole breast or chest walland boost volume will be treated for five consecutive fractions Monday to Friday for 3 weeks. Patients undergoing nodal RT will also receive 2.7 Gy to the nodal targets, daily, Monday to Friday to a total dose of 40.50 Gy.

All patients will be CT scanned in the prone position on a specially designed board that allows the indexed breast tissue to fall freely below the board, granting unobstructed access to the breast and lymph nodes through radiation ports from multiple beam angles. CT slice thickness should be 5 mm or less. Prior to the patient lying prone on the table for scanning, the borders of the field will be marked with radio-opaque CT fiducial markers. The chest wall scar will also be delineated using radio-opaque fiducial markers.

These markers will be used to outline the treatment volume according to conventional treatment guidelines. Borders of the fields will be set medially at mid-sternum, laterally at the anterior edge of latissimus dorsi, superiorly at the bottom of the clavicular heads and inferiorly 2 cm from the infra-mammary fold. Patients will be tattooed with leveling marks for setup alignment with room lasers and for positioning the isocenter of the beams. A tattoo will be placed on the lateral breast tissue as a landmark for planning and positioning.

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 (see section 8.7.8.4)

9.3 Target Delineation

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. 3-dimensional/intensity modulated RT (IMRT) tangents will include the breast/chest wall, and coverage of breast will be ensured by placing the posterior edge of the field on a plane connecting the midline to the anterior extent of the latissimus dorsi. Planning target volume (PTV) of the breast/chest wall will be created from the volume contained in the tangent fields with an additional 6 mm subtracted in all directions. The tumor bed/boost volume will be contoured with a 10-mm expansion. The regional nodal clinical target volume includes ipsilateral supraclavicular and level III axillary lymph nodes, with a 5-mm expansion (PTV nodes), but cropped 6 mm from the skin. We anticipate that coverage will require 3 IMRT fields (2 anterior/1 posterior). All target volume and normal tissue constraints are shown in Table 1. Portal images of orthogonal set-up fields will be acquired on days 1 through 3, then weekly. Portal imaging of each treatment field will occur once during the first 3 days of treatment. Cone beam computed tomography of PTV nodes is acquired on days 1 through 3.

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

9.3.2 The PTVTumor is the GTV with an additional 1.0 cm3D margin.

9.3.3 PTVTumor will not extend outside of the breast tissue and, **Table 3.**

if necessary, will be consistently modified ("clipped") to be confined within PTVBreast.

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*

9.4 Normal structure delineation

The following structures will be contoured: contralateral breast, thyroid, ipsilateral lung, contralateral lung, heart, and LAD. If nodes are treated spinal cord, esophagus and brachial plexus will also be contoured Table 3 describes the constraints.

Technical Factors

9.5.1 Dose calculation with heterogeneity corrections must be used.

9.5.2 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.

9.5.3 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.

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

9.5.4.1 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.

9.5.4.2 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.

9.5.5 3D-CRT Whole Breast Planning

9.5.5.1 3D-CRT tangents will be used to obtain a uniform dose distribution. Wedges and/or field within fields can be used.

9.5.6 Boost plan

9.5.6.1 Non-coplanar beam arrangement is encouraged, but not required

9.5.6.2 Electrons, 3D-CRT or IMRT may be used

9.5.6.3 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)

9.5.6.4 No photon beam will be directed toward heart, lung, contralateral breast, or thyroid

9.5.6.5 Inclusion of soft tissue not irradiated by the whole breast tangents is allowed to aid in target coverage

9.5.7 Composite plan is created with all fields. Dose Constraints

9.5.7.1 Target volume dose constraints for Whole Breast Plans:
9.5.7.2 Whole breast IMRT hybrid tangents
9.5.7.3 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.
9.5.7.4 PTVBreast: ≥95% of the volume must receive ≥100% of the whole breast dose.
9.5.7.5 PTVTumor: ≥98% of the volume must receive ≥100% of the whole breast dose.
9.5.7.6 Whole breast 3D-CRT tangents
9.5.7.7 PTVBreast max 112% (to >1cc) of the whole breast dose.
9.5.7.8 PTVBreast: ≥95% of the volume must receive ≥100% of the whole breast dose.
9.5.7.9 PTVTumor: >98% of the volume must receive >100% of the whole breast dose.
9.5.7.10 Target volume dose constraints for Boost Plans:
9.5.7.11 IMRT Boost
9.5.7.12 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.
9.5.7.13 PTVTumor: >98% of the volume must receive >100% of the total boost dose.
9.5.7.14 >60% of the PTVBreast volume must not receive >50% of the total boost dose.
9.5.7.15 3D-CRT Boost
9.5.7.16 Breast max 112% (to>1cc) of the boost dose. This can be achieved with 6MV, 16 MV, or 6MV/16 MV photons.
9.5.7.17 PTVTumor: ≥98% of the volume must receive ≥100% of the total boost dose.
9.5.7.18 > 60% of the PTVBreast volume must not receive >50% of the total boost dose
9.5.7.19 Composite of tangents and boost fields
9.5.7.20 PTVTumor: >98% of the volume must receive >100% of the total dose, where total dose is the whole breast dose plus boost dose.
9.5.7.21 PTVBreast: >95% of the volume must receive >100% of the whole breast dose.
9.5.7.22 PTVBreast: no more than 60% of PTVBreast should receive > 4455 cGy
9.5.7.23 Normal tissue dose constraints:
9.5.7.24 Heart: <5% of the heart receives >5 Gy.
9.5.7.25 Ipsilateral lung: <15% of the ipsilateral lung receives >10 Gy.
9.5.7.26 Contralateral lung: <15% of the contralateral lung receives >5 Gy.
9.5.7.27 LAD: maximum <1800cGy, mean <1000 cGy.

9.6 Boost Technique with Image Guidance (IGRT)

IGRT Target Localization: Cone-beam CT (CBCT) images will be acquired weekly prior to each boost treatment. By using IGRT to image the post-operative tumor bed of the breast in "real-time", the operator may automatically align the tumor bed with the treatment machine on each day of treatment of the tumor bed. 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.

9.7 Dosing Delays/Dose Modifications

For radiation toxicity: In case of grade 3 acute skin toxicity occurring during the course of the 3 weeks radiotherapy treatment, the dose per fraction of the remaining treatment fractions will be reduced to 2 Gy/fraction to the whole breast (and 2 Gy to the boost area on boost days) until completion of the total prescribed dose. No interruptions are planned. No other grade 3 toxicity is expected.

10.0 Adverse Events: List And Reporting Requirements

10.1 Adverse Events and Potential Risks List

Expected toxicities include fatigue and skin reactions within the radiation field. Erythema, dry and moist desquamation of the skin will be recorded weekly as described in Appendix 1. Breast edema and tenderness are additional possible acute side effects. Acute and late toxicity will be reported as scheduled in the study calendar.
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 trial medication will be followed until resolution even if this occurs post-trial.

Definitions of adverse events
Adverse event (AE)
Any untoward medical occurrence in a clinical investigation patient administered a treatment that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can, therefore, be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of an investigational procedure, whether or not related to the investigational procedure.

Serious adverse event (SAE)
An adverse event occurring at any dose that results in any of the following outcomes:
-death
-a life-threatening adverse experience
-inpatient hospitalization or prolongation of existing hospitalization excluding those for administration, transfusional support, disease staging/re-staging procedures, thoracentesis/paracentesis, or placement of an indwelling catheter, unless associated with other serious events.
-persistent or significant disability/incapacity, or
-congenital anomaly/birth defect.
Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug experiences when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.
Death, regardless of cause, which occurs within 30 days of the last dose of or after 30 days and is a result of delayed toxicity due to administration of the , should be reported as a serious adverse event.
Unexpected adverse event
An adverse event that is not mentioned in the informed consent or the specificity or severity of which is not consistent with the study's informed consent.
Life-threatening
Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

Reporting adverse events
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 CTC version 4.0 (Appendix 1) and their causal relationship.
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 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:

Name 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

10.2 Medical Monitor

This study will be monitored by the WCMC Data Safety Monitoring Committee according to the procedures of the WCMC Data Safety Monitoring Plan. The WCMC DSMB committee will be the medical monitor of the study.

10.3 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.

10.4 Expedited Adverse Event Reporting

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. Expedited AE reporting will utilize the descriptions and grading scales as presented in Appendix 1. The rest of the events (SAE or any other) will be brought to attention of the Data Safety Monitoring Committee. The IRB would need to see their regular reports as a result of analysis of all SAEs and AEs.

11.0 Correlative/Special Studies

11.1 Blood collection for TGF-beta 1 polymorphism determination

Approximately 30 cc of blood will be obtained by venipuncture once before starting treatment and once on the last day of treatment, after the last dose of radiation. The specimens will be aliquoted to store part of them for future testing of other polymorphisms and other related research studies.

12.0 Storage Of Samples

All blood samples will be processed immediately and stored indefinitely for later analysis in a locked -80°C freezer in WCMC for research purposes only. These specimens will not be linked to any clinical data and will be de-identified in the clinical research database, only the Principal investigator and the data manager will have access to the master list with the patient name and an identification number. This master list will be secured in a locked cabinet at the WCMC. Only the investigators listed on this protocol will have access to these samples. After blood samples are analyzed at a later date, any unutilized samples will be preserved indefinitely in WCMC for potential future research.

All patients enrolled will be given a unique identifier (study ID number). Only the data manager will know the code linking patient and study ID number. Patients will be assigned a unique code number. All specimens collected will be de-identified and assigned the same unique study number of the corresponding patient and will also be marked with the collection time point. Clinical information regarding toxicities and response will likewise be stored in a de-identified database using only the unique identifier (study ID number).

All blood samples will be stored indefinitely until appropriate funding has been obtained to perform correlative studies or until subject withdraws consent for banking of study specimens. If consent is withdrawn by the study subject, samples will be destroyed as per standard practices.
The storage of blood is optional and subject may withdraw consent for the banking of these specimens at any time. The subject may make this request by writing to the Principal Investigator Silvia C. Formenti, M.D. at New York –Presbyterian Weill Cornell Medical Center, Stich Radiation N-046, 525 East 68th Street, New York, NY- 10065.

12.1 Research Conflict Of Interest

There are no conflicts of interest to report.

12.3 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.

12.4 Optional Genetic Research

Part of the blood samples will be stored for DNA/RNA related studies. As with all research samples obtained in this study, patient samples will be de-identified and coded with a unique # that allows only the researchers of this study to gather information about patients if necessary.

The Principal Investigator and the data manager will know the code linking patients and study ID number through a master list; this master list will be kept in a secured, locked cabinet at the WCMC. No one outside of this study will have access to the patients' samples.

Patients will not be notified of the results of the future research. The results of the future research might be used in presentations and publications without any identifiers that might link results directly to patients.

Patients may choose to withdraw their permission to use the samples in the future research, and may do so at any time by writing to the Principal Investigator Silvia C. Formenti, M.D. at New York –Presbyterian Weill Cornell Medical Center, Department of Radiation Oncology, 525 East 68th Street, Box 169, New York, NY- 10065.

12.5 Coding of Samples

Specimens will be given a Study ID number and will be otherwise de-identified for privacy protection. The study data manager will keep the list of samples.

13.0 Study Calendar

Study	Pre Treatment	Weekly	Last week	Post Treatment (day 45-60)	Post Treatment (once/year)
History & Physical	X				
Toxicity evaluation	X	X		X	X
CBC with differential	X	X			
Comprehensive metabolic	X	as clinically indicated			
Mammogram and/or breast MRI[a]	X				X
Lumpectomy pathology report	X				
BREAST-focused exam, KPS	X	X		X	X
Blood for TGF-BETA polymorphisms	X		X[b]		
Quality of Life Questionnaires[c]	X		X	X	X
LENT/SOMA assessment[d]					X[c]

a. Standard mammogram or MRI for both breasts.
b. Last day of treatment, after last dose of radiation
c. QOL will be assessed using the Breast Cancer Treatment Outcome Scale (BCTOS) [30] MOS SF- 36 Vitality Scale (see appendix 4) at baseline, last week of radiation treatment, 45-60 days from starting radiotherapy and 2 year follow-up.
d. Patients will be seen after completion of treatment (at day 45-60) and then yearly for five years to assess long term sequelae by LENT/SOMA scale.

14.0 Measurement Of Effect

14.1 Response Review

Since the first main endpoint of this study is to compare the toxicity profile of the regimen, the study nurse will assess the acute toxicity for radiation by recording the findings on the form attached in Appendix 3.

15.0 Data Reporting / Regulatory Considerations

The WCMC Data and Safety Monitoring Committee (DSMC) is the central monitoring board for this study. The WCMC Cancer Institute Data and Safety Monitoring Committee (DSMC) is the local monitoring board for WCMC patients.

15.1 Monitoring plan

This study will be conducted in accordance with the guidelines in the 2001 NCI approved data Safety and Monitoring plan for the WCMC Cancer Institute and with the WCMC approved data Safety and Monitoring plan for the WCMC Cancer Institute. Monitoring will occur on a yearly basis from the date the first patient is enrolled. Reports to the Data Safety and Monitoring Committee will include the following information: accruals, targets, responses, adverse events and evidence of reporting to appropriate review committees. The WCMC Data and Safety Monitoring Board (DSMB) will review the IRB approved protocol, the data and safety monitoring plan and any stopping guidelines during protocol initiation. During the course of the study, the DSMB will review cumulative study data twice a year to evaluate safety, efficacy, study conduct, and scientific validity and integrity of the trial. The WCMC DSMB may also convene as needed if stopping criteria are met or other safety issues arise that the Principal Investigator and/or IRB would like the WCMC DSMB to address.

15.2 Stopping rules

Treatment will be held if patients experience > Grade 2 radiation dermatitis. Patients will be monitored until the resolution of the adverse event. Based on PI's discretion, patients will resume or be withdrawn from the study. Adverse Events will be recorded based on CTCAE v4.03.

If safety concerns arise, the DSMC will identify these concerns and recommend modification or termination of the clinical trial. There is no formal interim analysis for this trial.

15.3 Data management

Data will be entered into the REDCap database and maintained at WCM by trained Radiation Oncology data managers.

The system provides audit trails that track creation and modification of records that include user ID and timestamp. Once entered, the data is subjected to validation procedures that are executed either immediately or upon saving the eCRF page or during the batch validation process. Validation failures that are identified before the page is saved can be corrected immediately. Validation failures during saving of the eCRF page and during batch validation processes will generate a discrepancy. Depending on the database account privileges, the data managers may be able to correct a discrepancy or if not, route it to the project data manager at WCM who can take appropriate action to correct the problem. Data clarification forms can also be printed out when necessary to be sent to the project data manager. Once the discrepancy is closed, by marking "resolved" or "irresolvable", the data is marked clean and an audit trail is generated by the system.

All key end points will be source verified by a second person and errors will be corrected. Once the data is verified and all discrepancies are closed, the data can be locked/frozen. Locking

and freezing can be done at different granular levels and will follow institutional SOPs and any specific requirements for the project.

Security measures that will be taken in order to protect patient data will include firewall technology and database level security which will be achieved by assigning roles and privileges to different levels of users and by requiring that the users authenticate themselves using user ID and password. Additional security for data transfer between remote clients and servers will be achieved by using digital certificates/SSL. All data will be backed-up to tape periodically according to the Institutional SOPs. All data will be stored for at least 5 years following the termination of this study.

15.4 Confidentiality

The medical, hospital and research records associated with this study are considered confidential. Members of the treating team and designated study assistants will have access to the records as required to administer treatment and comply with the protocol. Neither the name nor any other identifying information for an individual will be used for reporting or publication regarding this study. All laboratory and baseline data will be de-identified and transferred via secure links to the Study Biostatisticians. Patient records will be made available for inspection to auditing agencies to satisfy regulatory requirements.

16.0 Statistical Considerations

This trial is designed to test the feasibility of the combined regimen, defined as limitation of the acute effects to < 10% Grade 3 events.

16.1 Endpoints

16.1.1 Primary endpoint

The primary endpoint for the study is acute toxicity occurring within 60 days after treatment; the proportion of patients with grade II or III acute skin toxicity.

16.1.2 Secondary endpoints

Acute toxicities, Quality of Life of patients before during and after treatment
Late toxicity 60 days post treatment including brachial plexopathy, fibrosis and telangiectasia; the proportion of patients with grades 2 or higher toxicity

16.1.3 Exploratory endpoints

Local recurrence
Distant recurrence/metastases
Survival

16.2 Analysis Populations

All registered patients will be included in these analyses (intent to treat).

Statistical Considerations Sample Size and Interim Analysis Plans

16.3 Accrual estimates

Two distinct cohorts will be tested in this study. Based on the algorithm presented in study design (Page 9) some patients will need post-operative radiation to the breast/chest wall alone

(cohort 1) or to the breast and level III /SCV nodes (cohort 2). Since the fields of accelerated radiation are different the 2 cohorts will be accrued separately and analyzed separately.

Estimated number of eligible patients for the trial is 2-4/month. Therefore, we estimate that the required 74 patients (37 per cohort) will be recruited within 24-36 months.

With 37 patients, we can detect a difference of 18% from a baseline rate of 25% (grade II-III acute dermatitis) with a 2-sided $\alpha = 0.05$ and power of 80% using an exact binomial test. If we observe 15 or more events among these 37 patients, the null hypothesis that the rate is 25% will be rejected. Calculations from PASS 2008, NCSS.

16.4 Criteria for future studies

N/A

16.5 Interim analyses

None planned

16.6 Statistical Analysis

16.6.1 Primary Endpoint

The primary endpoint is the occurrence of grade II or greater dermatitis within 60 days of the end of the treatment. The proportion of patients who experience this grade II or greater dermatitis will be estimated with exact 95% confidence intervals.

Patient demographic and disease characteristics at registration will be summarized using frequency distributions for qualitative data and summary statistics (means, medians, standard deviations, etc.) and graphical displays (e.g., Boxplots). Treatment data will be summarized similarly. Descriptive analyses will report the primary endpoint in subgroups defined by radiation regimen and other characteristics.

16.6.2 Secondary Endpoints

See primary endpoint.

16.6.3 Exploratory Endpoints

Local recurrence rates will be reported along with 95% confidence intervals. Kaplan Meier curves will be used to estimate recurrence free and overall survival.

Appendix 1. – Common Toxicity Criteria

Acute Toxicity from *Common Terminology Criteria for Adverse Events v4.0 (CTCAE)*, Published: May 28, 2009

	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	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

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.

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: _____

Appendix 3 – Quality Of Life Questionnaires

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 <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
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.

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

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!

Appendix 3.2 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 <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

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

Appendix 3.3 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: → ●

REFERENCES

1. James Melissa, L., et al. (2010) Fraction size in radiation treatment for breast conservation in early breast cancer. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD003860.pub3.
2. Whelan, T., et al., Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst, 2002. **94**(15): p. 1143-50.
3. Formenti SC, Gidea-Addeo D, Goldberg JD, Roses DF, Guth A, Rosenstein BS, DeWyngaert KJ. Phase I-II trial of prone accelerated intensity modulated radiation therapy to the breast to optimally spare normal tissue. J Clin Oncol. 2007 Jun 1;25(16):2236-42.
4. Darby, S.C., et al., Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. Lancet Oncol, 2005. **6**(8): p. 557-65.
5. Constantine, C., et al., Feasibility of accelerated whole-breast radiation in the treatment of patients with ductal carcinoma in situ of the breast. Clin Breast Cancer, 2008. **8**(3): p. 269-74.
6. Formenti SC, DeWyngaert JK, Jozsef G, Goldberg JD. Prone vs supine positioning for breast cancer radiotherapy. JAMA. 2012 Sep 5;308(9):861-3.
7. Cooper BT, et al; Prospective Randomized Trial of Prone Accelerated Intensity Modulated Breast Radiation Therapy With a Daily Versus Weekly Boost to the Tumor Bed. Int Journal Of Radiation Oncology Biology and Physics, in press
8. Shin SM, No HS, Vega RM, Fenton-Kerimian M, Maisonet O, Hitchen C, Keith DeWyngaert J, Formenti SC. Breast, chest wall, and nodal irradiation with prone set-up: Results of a hypofractionated trial with a median follow-up of 35 months. Pract Radiat Oncol. 2015 Nov 9. pii: S1879-8500(15)00398-7.
9. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365: 1687–1717.
10. Clarke M, Collins R, Darby S, et al.; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;366(9503):2087–2106
11. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effect of radiotherapy after breast conserving surgery on 10-year recurrence and 15- year breast cancer death: Meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 378:1707-1716, 2011
12. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: Meta-analysis of individual patient data for 8135 women in 22 randomized trials. Lancet 383:2127-2135, 2014
13. Delpech Y, Coutant C, Hsu L, et al. Clinical benefit from neoadjuvant chemotherapy in oestrogen receptor-positive invasive ductal and lobular carcinomas.Br J Cancer. 2013;108(2):285–291
14. Stanton, A.L., L. Krishnan, and C.A. Collins, 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, 2001. **91**(12): p. 2273-81.
15. Shelbourne, C.D., Measuring functioning and well-being: the medical outcomes study approach, ed. A.L. Stewart and J.E. Ware. 1992, Durham: Duke University Press. xxiii,

449 p.

16. Ware, J.E., Jr. and C.D. Sherbourne, The MOS 36-item short-form health survey (SF-36).Conceptual framework and item selection. Med Care, 1992. **30**(6): p. 473-83
17. Overgaard, M., et al., The value of the NSD formula in equation of acute and late radiation complications in normal tissue following 2 and 5 fractions per week in breast cancer patients treated with postmastectomy irradiation. Radiother Oncol, 1987. **9**(1): p. 1-11.
18. Bentzen, S.M., M. Overgaard, and H.D. Thames, Fractionation sensitivity of a functional endpoint: impaired shoulder movement after post-mastectomy radiotherapy. Int J Radiat Oncol Biol Phys, 1989. **17**(3): p. 531-7.
19. Hoeller, U., et al., Increasing the rate of late toxicity by changing the score? A comparison of RTOG/EORTC and LENT/SOMA scores. Int J Radiat Oncol Biol Phys, 2003. **55**(4): p. 1013-8.
20. Nuutinen, J., et al., A dielectric method for measuring early and late reactions in irradiated human skin. Radiother Oncol, 1998. **47**(3): p. 249-54.
21. Quarmby, S., et al., Association of transforming growth factor beta-1 single nucleotide polymorphisms with radiation-induced damage to normal tissues in breast cancer patients. Int J Radiat Biol, 2003. **79**(2): p. 137-43.