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TITLE:

PHASE I-II STUDY OF CONCURRENT ADJUVANT SYSTEMIC THERAPY AND ACCELERATED RADIOTHERAPY (OVER 3 WEEKS)

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Protocol Type / Version # / Version Date *Original / Version 3.1 04/13/2015*

Summary of Changes: Protocol Version 11/02/2015

Revising the cover page to remove Nagashree Seetharamu and Maria Fenton-Kerimian- Both no longer at NYU. Adding Dr. Naamit Gerber as a CO-Investigator on the trial

Summary of Changes: protocol version 09/16/2015

Revising section 15.3 further to include the reason why anonymous data will be shared with Weill Cornell Medical College- re-location of personnel- Dr. Encouse Golden. Inclusion of statement that anonymous data will only be shared after a transfer agreement is executed.

Summary of changes: protocol version 09/01/2015

Removing Dr. Encouse Golden as Co-Investigaor
Revising section 15.3 to state anonymous data will be shared with Weill Cornell Medical College

Summary of changes: protocol version 07/02/2015

Changing Dr. Carmen Perez to Principal Investigator
Changing Dr. Encouse Golden to Co- Investigator

Summary of changes : protocol version 04/13/2015

Adding Dr. Formenti as Co-PI

Summary of changes : Version 3.0 03/24/2015

Changing the Principal Investigator to Dr. Encouse Golden

Changing informed Consent to reflect new Principal investigator

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Protocol Version 2.0 03/11/2015 :

- Increasing accrual to add two more patients in order to reach a target of 37 evaluable patients.
- Removing Dr. Mathew Volm from the investigator section, as Dr. Volm is no longer at NYU.

Section 16.3 Accrual Estimates :

- Biostatistics Section amended to reflect the new target of 37 patients.

Informed consent dated 02/02/2012 :

No changes have been made to the informed consent

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PROTOCOL SYNOPSIS

TITLE	**PHASE I-II STUDY OF CONCURRENT ADJUVANT SYSTEMIC THERAPY AND ACCELERATED RADIOTHERAPY (OVER 3 WEEKS)**
STUDY PHASE	**Feasibility**
INDICATION	**Stage I-II breast cancer**
PRIMARY OBJECTVES	**Acute toxicity**
SECONDARY OBJECTIVES	**QOL, defined by RTOG-PRO;** **Late toxicity, Fibrosis, Telangiectasia**
EXPLORATORY OBJECTIVES	**Local control; Time to Progression, Survival; Evaluation of Determinants of Breast Fibrosis**
HYPOTHESES	**FEASIBILITY OF ACCELERATED RADIOTHERAPY WITH CARBOPLATIN:** **Proportion of patients with grade II-III dermatitis is 0.25 vs. alternative that the proportion is greater than 0.25 by more than 0.24.** **< 10% Grade 3 (CTC 4.0) events chemotherapy related**
STUDY DESIGN	**Prospective, single arm**
PRIMARY ENDPOINTS AND SECONDARY ENDPOINTS	**Acute, effects of radiation (Grade II, III dermatitis** **Secondary—other acute effects of radiation, late effects of radiation, QOL-PRO** **Local control, DFS, OS**
SAMPLE SIZE BY TREATMENT GROUP	**37 patients**
SUMMARY OF SUBJECT ELIGIBILITY CRITERIA	**Newly diagnosed breast cancer patients after segmental mastectomy, HORMONAL RECEPTOR NEGATIVE, HER2 NEGATIVE (TRIPLE NEGATIVE)**
INVESTIGATIONAL PRODUCTS DOSAGE AND ADMINISTRATION	**N/A**
CONTROL GROUP	**-**
PROCEDURES	**N/A**
STATISTICAL CONSIDERATIONS	**Phase I-II**

SCHEMA

ELIGIBLE PATIENTS:
STAGE I-II BREAST CANCER PATIENTS,
HORMONAL RECEPTOR AND HER2-neu NEGATIVE,
TRIPLE NEGATIVE (TN)
ELIGIBLE FOR ADJUVANT RADIOTHERAPY
AFTER SEGMENTAL MASTECTOMY

↓

INFORMED CONSENT

↓

Carboplatin will be administered with AUC of 2.0, repeated weekly for 6 weeks

Whole Breast 3D-RT or IMRT at 2.7 Gy X 15 fractions (40.50 Gy)
(the second and third Friday, 3 Gy to the tumor bed only X 2 fractions)
Total dose to tumor bed = 46.5 Gy

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		S	M	T	W	T	F		S	M	T	W	T	F
Tx	wb*	wb	wb	wb	wb		wb	wb	wb	wb	wb	B+		wb	wb	wb	wb	wb	B+

*wb = target is whole breast, 2.7 Gy/fraction
+B = boost to tumor bed 3 Gy (second and third Friday)

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

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Additional Adjuvant Chemo
C	C/RT	C/RT	C/RT	C	C	

STUDY SYNOPSIS

Preliminary experience in the neo-adjuvant setting of Locally Advanced Breast Cancer has recently demonstrated that HR negative patients have approximately 50% chance to achieve a pathological response after concurrent chemo-radiation. In a multi-institutional collaboration of 105 patients it was found that triple negative tumor carriers achieved pathological response in 54% of the cases and that the response reflected on 5-year DFS and OS. Our group has speculated that these effects on the risk of distant recurrence could depend on the recovery of anti-tumor immunity among the patients achieving pathological response, after tumor cell death induced by concurrent chemo-radiation.

We are proposing a novel study that translates these findings to the adjuvant setting of triple negative tumors (TN). TN breast cancer is a more aggressive form of the disease often coinciding with basal-like tumors. BRCA mutated-cancer is more frequently TN.

The current protocol converges the experience NYU has developed in accelerated prone breast radiotherapy with encouraging finding from the use of concurrent chemoradiation in LABC.

We will study the feasibility of combining weekly carboplatin with concurrent 3-weeks prone breast radiotherapy in the adjuvant setting of 35 women with TN tumors, after segmental mastectomy and nodal assessment. Primary endpoint of the study is acute toxicity of the combined regimen, with a target of < 25% of grade II-III dermatitis.

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
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
QOL	Quality of Life
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
SNP	Single Nucleotide Polymorphism
SSCP	Single-Strand Conformation Polymorphism
TN	Triple negative
TGF-beta1	Transforming Growth Factor beta-1
TV	Treatment Volume
WBD	Weekend Boost Dose

1. OBJECTIVES

1.1. Primary Objectives

1.1.1. To test feasibility of combining carboplatin and accelerated radiotherapy in patients with triple negative breast cancer (HR and Her2-*neu* negative) by evaluating the proportion of patients who experience grade II-III dermatitis within 60 days of the end of treatment.

1.2. Secondary Objectives

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

1.2.2. To compare incidence of late radiation toxicity (fibrosis and telangiectasia) and to examine genetic determinants of breast fibrosis by treatment regimen.

1.3. Exploratory Objectives

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

1.3.2. To prospectively validate the data on molecular signature of BRCA methylation in triple negative cancers in this prospective series and examine possible new molecular signatures of breast cancer.

2. 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] Analysis of two prospective randomized trials that included 2644 women, selected based on tumor size less than five cm, negative pathological margin of excision and negative lymph nodes. No difference in clinical outcome was detected. The conclusion of the review is that the use of unconventional fractionation regimens (> 2 Gy per fraction) does not affect breast appearance or toxicity and does not seem to affect 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 eight years the Breast Cancer Radiotherapy Research team at NYU has 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-II breast cancer patients, s/p segmental mastectomy, found to have HR negative HER2 negative tumors (TN).**

2.2. NYU 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 to 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, 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 2 (RTOG score). Most common toxicity was radiation dermatitis, which 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%)	-	-	-

Longer follow up is required to assess local control and late toxicity, likely to determine the cosmetic result. Because of blood collection, once sufficient time has elapsed to measure late effects, the study will enable to explore association between specific genomic profiles and the occurrence of fibrosis. [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. [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 to the trial were DCIS patients 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 it either, and especially for left breast DCIS, some women were initially simulated supine and because of the large extent of lung and heart in the field were re-simulated prone and often (but

not always) were found to have better normal tissue sparing when prone and were then treated consistently. [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, NYU 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 postmenopausal 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, be 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 received a CT simulation in the prone and supine position. ***Treatment followed in the optimal position defined as that which assured the smallest volume of heart and lung respectively, 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 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 (submitted for publication).

Based on the experience gathered from NYU Protocol 05-181, it is rational for all patients to first undergo a CT Simulation in prone position. Again, we will be using 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. Only if found that conventional tangents in 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

Solid radiobiological reasons supported the introduction of a larger fraction dose before a two-day treatment break (weekend). In the context of a Phase III randomized study, we are studying two different boost schemas. The **standard arm** is a concomitant boost protocol over three weeks which has previously been evaluated in over 500 patients (NYU 03-30 and NYU 05-

181) and has shown excellent tolerance, and results. The **experimental arm** evaluates a Friday Weekly Boost Dose (FBD) regimen which may have a radiobiological advantage by counteracting tumor repopulation which can occur over the weekend break. Choice of the technique was be randomized. BED calculations for the **standard arm** using an alpha/beta ratio of 4 Gy, result in a BED for 3.2 Gy x 15 fx of 86 Gy_4. By comparison, the BEDs for possible comparative experimental arms at 2.7 Gy X 12 fx plus 3 fractions given each Friday of either 3.7 Gy, 4.2 Gy, 4.7 Gy or 5.2 Gy would be 76, 80, 85 and 90 Gy_4, respectively. Thus, the **experimental arm** delivers 2.7 Gy four times per week (Monday-Friday) during the 3 weeks (i.e., 2.7 Gy x 15 fx), but with an additional 2 Gy on each of the three Fridays to the tumor bed in addition to the 2.7 Gy whole breast dose given on that day, with the tumor bed receiving 4.7 Gy on each of the three Fridays. Preliminary results of the interim analysis are presented in Table 2. Between March 2009 and March 2010, 126 patients have enrolled to this protocol. CTCAE v3.0 defined radiation dermatitis was evaluated at two month follow-up demonstrating no statistical difference between the two arms in RT-related acute toxicity between terms of the two regimens P-value NS.

Table 2 below compares rates of radiation dermatitis among the two treatment groups.

Table 2. Comparison of acute radiation skin toxicities among patients in NYU 09-0030

	Grade 1		Grade 2		Grade 3		Total #	
	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2
Dry DesQ	3	5	0	0	0	0	3	5
Edema	23	21	3	4	1	0	27	25
Erythema	52	53	9	5	0	0	61	58
Wet DesQ	0	0	8	3	0	1	8	4

To further reduce the risk of acute and late effects during concurrent radiosensitizing chemotherapy the regimen proposed consists of a total of 17 fractions over 19 days, taking advantage of the fact that NYU Department of Radiation Oncology is open during the weekend enabling radiotherapy on Sunday. Patients will be treated with 2.7 Gy per fraction to the whole breast, prone as per our extensive experience in > 2,000 patients. A 3 Gy boost to the tumor bed will be given by IGRT on the 2nd and 3rd Friday.

2.5. Rationale for concurrent chemoRT in TN tumor carriers: the LABC experience

Triple-negative breast cancers (TNBCs) are characterized by the lack of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2). [6-7] These cancers occur in approximately 20% to 25% of all patients with breast cancer, and are associated with an unfavorable prognosis. [7-9] Patients with TNBC derive no benefit from molecularly targeted treatments such as endocrine therapy or trastuzumab, because they lack the appropriate targets for these drugs.

Liedke et al compared the outcome 255 triple negative carriers out of 1118 treated with neoadjuvant chemotherapy at MD Anderson cancer center (23%). [10] Patients with TNBC compared with non-TNBC had significantly higher pCR rates (22% vs. 11%; P <.034), but decreased 3-year progression-free survival rates (P < .0001) and 3-year Overall Survival (OS) rates (P < .0001). TNBC was associated with increased risk for visceral metastases (P < 0.0005), lower risk for bone recurrence (P < 0.027), and shorter post-recurrence survival (P < 0.0001). Recurrence and death rates were higher for TNBC only in the first 3 years. If pCR was achieved, patients with TNBC and non-TNBC had similar survival (P < 0.24). In contrast, patients with residual disease (RD) had worse OS if they had TNBC compared with non-TNBC (P <.0001). In their experience patients with TNBC had increased pCR rates compared with non-TNBC, and those with pCR had excellent survival. However, patients with RD after neoadjuvant chemotherapy had significantly worse survival if they have TNBC compared with non-TNBC, particularly in the first 3 years.

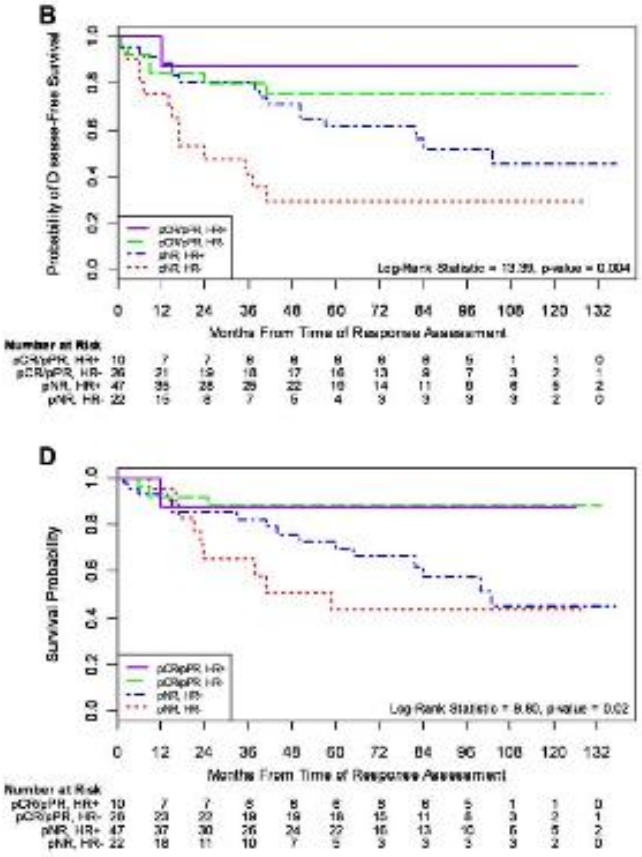
Derived from a protocol of concurrent paclitaxel and radiation originally developed by Dr. Formenti at USC, three institutions, USC, NYU and Vanderbilt reported the five years experience on 105 patients with LABC (White 46%, Non-White 54%) treated with paclitaxel (30 mg/m$_2$ intravenously twice a week) for 10-12 weeks. Daily radiotherapy was delivered to the breast, axillary and supraclavicular lymph nodes during weeks 2-7, at 1.8 Gy per fraction to a total dose of 45 Gy with a tumor boost of 14 Gy at 2 Gy/fraction. Post-operative treatment was left to the discretion of the treating physician. Pathological response (pCR and pPR) after neoadjuvant chemoradiation was achieved in 36/105 patients (34%, 95% CI: 25%-44%). Achievement of pathologic response was associated with significantly better DFS and OS. Patients with pathologic response had a lower risk of recurrence or death compared with non-responders (hazard ratio =0.35, 95% CI: 0.15-0.80, log-rank p-value=0.01). At a median follow-up of 60 months, the median survival for the entire group has not been reached. The estimated 5-year disease-free (DFS) and overall survival (OS) are 61.4% (95% CI: 50.1-70.8%) and 71.6% (95% CI: 60.5-80.1%), respectively.

Table 3. Pathological response and Receptor status

Subtype	Total	Proportion of patients who received trastuzumab	Proportion of patients with pathologic response (pCR+pPR)
Entire Cohort (n = 105)			
HR positive	57	5/57 (2 with pathologic response)	10/57 (17.5%)
HR negative	48	3/48 (3 with pathologic response)	26/48 (54.2%)
Cohort with Her2 status available (n = 85)			
HR positive/Her2 negative	34	N/A	6/34 (17.7%)
HR positive/Her2 positive	13	5/13 (2 with pathologic response)	3/13 (23.1%)
HR negative/Her2 positive	14	3/14 (3 with pathologic response)	7/14 (50.0%)
HR negative/Her2 negative (triple negative)	24	N/A	13/24 (54.2%)

Abbreviations: HR: hormone receptor, Her2: human epidermal growth factor receptor, pCR: pathologic complete response, pPR: pathologic partial response

Figure 1. Outcome at five years of 105 LABC patients treated pre-operatively by concurrent paclitaxel and radiation: DFS and OS results based on pathological response and HR status



Approximately half of HR negative tumor carriers achieved a pathological response: the incidence of pathological response was 54% in TN tumor carriers. Importantly, in this study the 5 year outcome of the patients was plotted based on receptor status and pathological response. As demonstrated in figure 1, HR negative tumor carriers achieving a pathological response did as well at 5 years as the HR positive tumor carriers who had achieved a pathological response.

However, the main insight from the results of this multi-institutional trial is the fact that a pathological response after single agent concurrent chemo-radiation is prognostically similar to that achieved with protocols of much more intense multi-agent, dose-dense chemotherapy.

We speculated that that the recruitment of an effective immune response may reflect in the survival

benefit that some patients gain after a pathologic response following chemoradiation, supported by the fact that response to therapy was associated with certain immune signatures. [11] A superior outcome after concurrent versus sequential chemotherapy and radiation has been demonstrated in other settings. [12-16] Standard anti-cancer modalities such as certain chemotherapy agents and radiotherapy are thought to generate an immunogenic cell death, converting the original tumor into an *in situ* immunogenic hub. [17-21] The consequent anti-tumor immune response might also control micro-metastatic foci. Alternatively, it is possible that in patients achieving a pathologic response, concurrent chemoradiation successfully eradicated CD44+/CD24-/low or aldehyde dehydrogenase 1 (ALDH1)+ tumor cells, shown to possess tumor-initiating potential if they persist after treatment. [22-23] RT and chemotherapy when given alone can enrich the population of breast cancer stem- like cells, which are resistant to either single modality [23-26], suggesting that perhaps they are sensitive to concurrent chemoradiation. Finally, the concurrent combination of chemoradiation could have successfully eliminated the subset of cancer cells later destined to become circulating cells with seeding potential. [27] **The relevance of these findings to TN tumors, found to be potentially more immunogenic than the other subtypes of breast cancer, has justified the design of this protocol**.

2.5.1. Rationale for carboplatin and radiation

Triple negative breast cancer represents approximately 15% of breast cancer of all breast cancer cases. [28] Though the sensitivity of these tumors to platinum drugs was debated for a number of years only recently the abundance of both basic science and limited clinical data lead to a consensus that these drugs play a crucial role in the treatment of these tumors both as management of metastatic and locally advanced disease. Patients with TN tumors have demonstrated sensitivity to platinum compounds, possibly because of their inherent chromosomal fragility and impairment of DNA repair pathways. [29]

The possible interaction of platinum agents and PARP inhibitors especially in cancers related to the BRCA mutation. So far there is paucity of data investigating the role of platinums in the adjuvant management of breast cancer.

The main platinum agent established in the management of triple negative breast cancer is Cisplatin, fewer clinical studies utilized carboplatin in the setting of triple negative disease.

Over the last decade the difference between the 2 platinum drugs have been debated. The carboplatin toxicity especially vis-a vis nephrotoxicity and gastrointestinal (nausea and vomiting) is significantly less pronounced compared to equivalent doses of cisplatin. In other malignancies (testicular, ovarian cancer etc) the equivalency in efficacy are well established.

The role of adjuvant chemoradiation in breast cancer has been studied mostly in small studies and in combinations with CMF, anthracyclines and taxanes. The possibility of better locoregional control is debated as well as higher toxicities (fatigue, skin toxicity).

In the current protocol we propose the combination of platinum containing chemoradiation as adjuvant therapy for patients with triple negative breast cancer.

The 3 week radiation extensively studied in the adjuvant regimens will be combined with weekly carboplatin at a dose of AUC of 2 per week.

2.6. Background for Primary Objective

2.6.1. 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 v3.0 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 pain. 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 v3.0 (see Appendix 1).

2.7. Correlative Studies Background

2.7.1. 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. [30] 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, 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. [31-32]

2.7.2. 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%. [33-34] 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. [35] 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, $p = 0.01$).

The Delfin MoistureMeter D is a portable, non-invasive device that measures the dielectric constant of the skin and subcutaneous fat that can be used to provide a quantitative assessment of radiation-induced breast fibrosis. A report by Nuutinen et al. demonstrates that two years post irradiation, the dielectric constant of the irradiated skin increases with increasing clinical findings of subcutaneous fibrosis. Since the dielectric constant of biological tissues is related to tissue water content, these results demonstrate that the free water content and thus the extracellular fluid increases in irradiated skin. [36]

The LENT/SOMA scoring system will be used in the reporting of late radiation morbidity in this protocol as well as quantifiable measurements using the MoistureD device. Patients will be assessed with the MoistureD device, as part of their physical examination at baseline and during the follow up visits.

Measurements will be obtained at the tumor bed (B1) and at the indexed breast (B2) away from the surgical bed and at the two symmetrical, corresponding areas in the contralateral breast (CB1 and CB2), with a total of four areas of assessment per patient. For each area, the measurement will be repeated three times, and the average value and standard deviation calculated. We will obtain measurement of breast fibrosis at baseline (prior to treatment) and at each subsequent follow-up after completing radiotherapy.

2.7.3. 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. [37] 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.

2.7.4. 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. [37]

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 data office of New York University School of Medicine (NYUSM). When the study information is disclosed outside of NYUSM 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. NYUSM will not disclose the code key, except as required by law.

3. PATIENT SELECTION

3.1. Inclusion Criteria

- **3.1.1.** Age older than 18.
- **3.1.2.** Pre- or post-menopausal women with Stage I and II breast cancer, triple negative tumors (upper limit of positivity <10% for estrogen receptors, <20% for progesterone receptors)
- **3.1.3.** Biopsy-proven invasive breast cancer, excised with negative margins of at least 1 mm
- **3.1.4.** Status post segmental mastectomy, after sentinel node biopsy and/or axillary node dissection (Tumors < 5 mm in size do not require nodal assessment) or after mastectomy.
- **3.1.5.** No previous chemotherapy
- **3.1.6.** Patient needs to be able to understand and demonstrate willingness to sign a written informed consent document

3.2. Exclusion Criteria

- **3.2.1.** Previous radiation therapy to the ipsilateral breast
- **3.2.2.** Active connective tissue disorders, such as lupus or scleroderma
- **3.2.3.** Pregnant or lactating women

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Patients will have completed all breast surgical procedures 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). If the patient meets the eligibility criteria after re-excision, she may be

entered into the left or right breast cancer strata. AJCC staging criteria will be used to identify Clinical Stage I, II breast cancer patients eligible to this study. All eligible women who are referred to the Radiation Oncology Department at NYU School of Medicine for radiation following surgery for breast cancer will be offered the opportunity to participate in this experimental protocol.

4.2 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.

4.3 Randomization Process

This study is a Phase I-II non-randomized trial. Patients will be registered within strata defined by menopausal status (pre/post) and by nodal status (yes/no).

5. TREATMENT PLAN

5.1. 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.

5.2. Duration of Therapy

The treatment will consist of 17 fractions, Monday to Friday, week 2, Sunday to Friday week 3 and Sunday to Friday week 4, for 3 weeks total time (over a total of 19 days), see study calendar in Section 13.

5.3. Duration of Follow Up

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

5.4. Alternatives

At the time of study accrual all patients will be offered access to standard six weeks radiotherapy. If patients are stage I and are carrier of node negative breast cancer they will be offered the option to be treated with an established accelerated whole breast radiotherapy regimen (3 weeks Canadian trial). [2]

5.5. Compensation

No compensation is available for participating in the study.

6 SURGERY

Patients will have completed all breast surgical procedures 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. All patients with tumors > 5 mm in diameter require nodal assessment, by sentinel node biopsy and/or axillary dissection.

7 CHEMOTHERAPY

7.1 Carboplatin Administration

Carboplatin will be administered with AUC of 2.0 which will be repeated weekly for 6 weeks. **Carboplatin (NSC 241240), other names:** Paraplatin®

7.2 Formulation

Carboplatin Injection is a premixed aqueous solution of 10 mg/mL Carboplatin.

Carboplatin Injection, 10 mg/mL can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP.

When prepared as directed, Carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C). Since no antibacterial preservative is contained in the formulation, it is recommended that Carboplatin aqueous solutions be discarded 8 hours after dilution.

How Carboplatin is Supplied

Carboplatin Injection, 10 mg/mL is available in multi-dose vials, individually carton:

NDC 0703-4244-01	10 mg/mL, 5 mL Vial
NDC 0703-4246-01	10 mg/mL, 15 mL Vial
NDC 0703-4248-01	10 mg/mL, 45 mL Vial
NDC 61703-0339-56	10 mg/mL, 60 mL Vial

Storage

Unopened vials of Carboplatin Injection, 10 mg/mL are stable to the date indicated on the package when stored at 25°C (77°F) excursions permitted from 15°–30°C (59°–86°) [see USP Controlled Room Temperature] Protect from light.

Carboplatin injection, 10 mg/mL multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Solutions for infusion should be discarded 8 hours after preparation.

Handling and Disposal

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. NOTE: Aluminum reacts with Carboplatin causing precipitate formation and loss of potency, therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of Carboplatin.

7.3 Pharmacokinetic information

Carboplatin is an alkylating agent which covalently binds to DNA; possible crosslinking and interference with the function of DNA. Distribution: Vd: 16 L/kg; into liver, kidney, skin, and tumor tissue. Protein binding: 0%; however the platinum from carboplatin becomes 30% irreversibly bound. Metabolism: Minimally hepatic to aquated and hydroxylated compounds. Half-life elimination: Terminal: 22 – 40 hours. In patients with creatinine clearance > 60 mL/minute: 2.5-5.9 hours. Excretion: Urine (~60% - 90%) within 24 hours.

7.4 Dosing of Carboplatin

The dose will be calculated to reach a target area under the curve (AUC) of concentration x time according to the Calvert formula using an estimated glomerular filtration rate (GFR) from Cockcroft- Gault formula.

- *The initial dose of carboplatin must be calculated using GFR. In the absence of new renal obstruction or other renal toxicity greater than or equal to CTCAE grade 2 (serum creatinine >1.5 x ULN), the dose of carboplatin will not be recalculated for subsequent cycles, but will be subject to dose modification as noted.*
- *In patients with an abnormally low serum creatinine (less than or equal to 0.6 mg/dl), due to reduced protein intake and/or low muscle mass, the creatinine clearance should be estimated using a minimum value of 0.7 mg/dl. If a more appropriate baseline creatinine value is available within 4 weeks of treatment that may also be used for the initial estimation of GFR.*
- *Calvert Formula: Carboplatin dose (mg)= target AUC x (GFR +25)*
- **NOTE: the GFR used in the Calvert formula to calculate AUC-based dosing should be capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.**
- **Maximum** carboplatin dose (mg) = target AUC(mg·min/mL) x 150 mL/min

- The maximum carboplatin dose should not exceed target AUC(mg·min/mL) **x** 150 mL/min, but it may be less. Many trials have a target carboplatin AUC of 6 which would result in a maximum dose of 900 mg. Highly specific settings like bone marrow transplant or pediatric studies may target a higher AUC (see table below).

Maximum AUC-based Carboplatin Dose	
AUC	**Maximum Carboplatin Dose**
6	900 mg
5	750 mg
4	600 mg

- For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft- Gault using the following formula:

$$\textbf{Creatinine Clearance (mL/min)} = \frac{\textbf{[140-Age (years)] x Weight (kg) x 0.85}}{\textbf{72 x serum creatinine (mg/dl)}}$$

Notes:

Weight in kilograms (kg): In general, actual weight should be used for estimation of GFR. However, it is also acceptable to utilize **adjusted** weight, when concerned about safety in a specific patient, in accordance with local institutional policy. Suggested ideal and adjusted weight calculations:
Ideal weight (kg) = (((Height (cm)/2.54) – 60) x 2.3) + 45.5
Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight

The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).

At the time of a dose modification for toxicity:

If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

If the dose of carboplatin (mg) at the time of dose modification, is higher than the previous dose due to the use of the Cockcroft-Gault formula [when the previous dose was calculated using the Jelliffe formula and IDMS to "non-IDMS" conversion (if applicable)], use the same method that was used to calculate the previous dose [Jelliffe formula and IDMS to "non-IDMS" conversion (if applicable)], to calculate the dose of carboplatin (mg) at the time of dose reduction. This will ensure that the patient is actually receiving a dose reduction.

7.5 Potential Drug Interactions

Increased Effect/Toxicity: Aminoglycosides increase risk of ototoxicity and/or nephrotoxicity. When administered as sequential infusions, observational studies indicate a

potential for increased toxicity when platinum derivatives (carboplatin, cisplatin) are administered before taxane derivatives (docetaxel, paclitaxel).

7.6 Adverse Effects of Carboplatin

Common known potential adverse events: >10%: Central nervous system: Pain.
Endocrine & metabolic: Hyponatremia, hypomagnesemia, hypocalcemia, hypokalemia.
Gastrointestinal: Nausea, vomiting, abdominal pain. Hematologic: Myelosuppression is dose related, schedule related, and infusion-rate dependent (increased incidences with higher doses, more frequent doses, and longer infusion times) and, in general, rapidly reversible upon discontinuation. (dose related and dose limiting; nadir at ~21 days with q 3 weeks dosing recovery by ~28 days), leukopenia, anemia, neutropenia, thrombocytopenia. Hepatic: Alkaline phosphatase increased, AST increased. Neuromuscular & skeletal: Weakness. Renal: Creatinine clearance decreased, BUN increased.

Less common known potential adverse events, 1% - 10%: Central nervous system: Neurotoxicity
Dermatologic: Alopecia. Gastrointestinal: Constipation, diarrhea, stomatitis/mucositis, taste dysgeusia. Hematologic: Hemorrhagic complications. Hepatic: Bilirubin increased. Local: Pain at the injection site. Neuromuscular & skeletal: Peripheral neuropathy. Ocular: Visual disturbance. Otic: Ototoxicity. Renal: Creatinine increased. Miscellaneous: Infection, hypersensitivity.

Rare known potential adverse events, <1% (Limited to important or life-threatening): Anaphylaxis, anorexia, bronchospasm, cardiac failure, cerebrovascular accident, embolism, Erythema, fever, hemolytic uremic syndrome, hyper-/hypotension, malaise, necrosis (associated with extravasation), nephrotoxicity, neurotoxicity, pruritus, rash, secondary malignancies, urticaria, vision loss.

7.7 Adverse Events Reporting

Adverse events to be reported based on CTC AE 4.0 version and RTOG toxicity criteria and reported to the NYU IRB as well as medwatch based on the NYU SAE reporting guidelines.
The Study will be monitored by NYU Cancer Institute Data Monitoring and Safety Committee as per DSMC chapter and Internal Audit Committee as per institutional SOPs.

8 RADIOTHERAPY SPECIFICATIONS

8.1 Treatment Planning Using either 3D-CRT or Hybrid IMRT Technique

In the context of this study, this protocol will implement accelerated whole breast radiotherapy using either 3D-CRT or a hybrid IMRT approach.

8.2 Radiotherapy schedule

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		S	M	T	W	T	F		S	M	T	W	T	F
Tx	wb*	wb	wb	wb	wb		wb	wb	wb	wb	wb	B+		wb	wb	wb	wb	wb	B+

*wb = target is whole breast, 2.7 Gy/fraction
+B = target is the original tumor bed, 3 Gy/fraction

8.3 Radiotherapy target

Defined above.

8.4 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 2 daily radiation fractions of 3.0 Gy to the tumor bed to a total dose of 6.0 Gy to the tumor bed. The whole breast will be treated for five consecutive fractions Monday to Friday the first week of RT, then for an additional five fractions from Sunday to Thursday the second week of RT and finally for another five fractions Sunday to Thursday the last week of RT. The second and third Fridays of RT the patient will be treated only to the tumor bed with a 3 Gy fraction. Consequently, the tumor bed will receive a total dose of 46.5 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 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. 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)

8.5 Target Delineation

8.5.1 The PTVBreast is the entire breast volume acquired in prone or supine position based on physician's delineated fields. The PTVBreast is derived from the 50% isodose line associated with clinically determined opposed tangent fields. This is

accomplished by converting the 50% isodose level to a structure, smoothing and then removing parts extending outside the 50% isodose structure with an additional 0.7 cm margin within the field borders. The lung and the heart are also excluded from the PTVBreast volume.

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

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

8.6 Normal structure delineation

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

8.7 Technical Factors

8.7.1 Dose calculation with heterogeneity corrections must be used.

8.7.2 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.

8.7.3 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.

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

1. Non-IMRT tangents deliver nominally 67% of prescribed dose using 6 MV or 6MV/16MV photons and include 3 cm anterior flash. The fields are wedged and weighted to obtain a uniform dose distribution, normalized to allow approximately 105% dose max.
2. IMRT tangents deliver nominally 33% of prescribed dose using 6 MV photons and include 3 cm anterior flash, and use the non-IMRT tangent plan as a base for optimization.

8.7.5 3D-CRT Whole Breast Planning

1. 3D-CRT tangents will be used to obtain a uniform dose distribution.
2. Wedges and/or field within fields can be used.

8.7.6 Boost plan

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

8.7.7 Composite plan is created with all fields.

8.7.8 Dose Constraints

1. Target volume dose constraints for Whole Breast Plans:
    a. Whole breast IMRT hybrid tangents
        - PTVBreast max 108% (to ≥1cc) of the whole breast dose. This can be achieved with 6 MV, or 6 MV/16 MV (IMRT/3D) photons.
        - PTVBreast: ≥95% of the volume must receive ≥100% of the whole breast dose.
        - PTVTumor: ≥98% of the volume must receive ≥100% of the whole breast dose.
    b. Whole breast 3D-CRT tangents
        - PTVBreast max 112% (to >1cc) of the whole breast dose.
        - PTVBreast: ≥95% of the volume must receive ≥100% of the whole breast dose.
        - PTVTumor: >98% of the volume must receive >100% of the whole breast dose.
2. Target volume dose constraints for Boost Plans:
    a. IMRT Boost
        - Breast max 108% (to >1cc) of the boost dose. This can be achieved with 6 MV IMRT, or a hybrid approach using 6 MV/16MV (IMRT/3D) photons.
        - PTVTumor: >98% of the volume must receive >100% of the total boost dose.
        - >60% of the PTVBreast volume must not receive >50% of the total boost dose.
    b. 3D-CRT Boost
        - Breast max 112% (to>1cc) of the boost dose. This can be achieved with 6 MV, 16 MV, or 6MV/16 MV photons.
        - PTVTumor: ≥98% of the volume must receive ≥100% of the total boost dose.
        - > 60% of the PTVBreast volume must not receive >50% of the total boost dose
3. Composite of tangents and boost fields
    a. PTVTumor: >98% of the volume must receive >100% of the total dose, where total dose is the whole breast dose plus boost dose.
    b. PTVBreast: >95% of the volume must receive >100% of the whole breast dose.
    c. PTVBreast: no more than 60% of PTVBreast should receive > 4455 cGy
4. Normal tissue dose constraints:
    a. Heart: <5% of the heart receives >5 Gy.
    b. Ipsilateral lung: <15% of the ipsilateral lung receives >10 Gy.
    c. Contralateral lung: <15% of the contralateral lung receives >5 Gy.
    d. LAD: maximum <1800cGy, mean <1000 cGy.

8.8 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 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.

For Carboplatin toxicity, please see table below:

Criteria for Dose Modification of carboplatin	
Toxicity	**Actions**
Non-hematological Toxicity	
Grade 3	Decrease Carboplatin to AUC 1. 5. If grade 3 toxicity continues with an AUC of 1.5, decrease Carboplatin to AUC of 1. If grade 3 toxicity continues with an AUC of 1, discontinue study regimen.
Grade 4	Decrease Carboplatin to AUC of 1.5. If grade 4 toxicity continues with an AUC of 1.5, decrease Carboplatin to AUC of 1. If grade 4 toxicity continues with an AUC of 1, discontinue study regimen.
Hematological Toxicity	
Grade 2 Thrombocytopenia (platelets < 75.0- 50.0 x 10^9/L)	Hold until platelet recovers to 100 x10^9/L and decrease Carboplatin to AUC of 1.5. If grade 2 toxicity continues with an AUC of 1.5, decrease Carboplatin to AUC of 1. If grade 2 toxicity continues with an AUC of 1, discontinue study regimen.
Grade 3 Thrombocytopenia (platelets < 50.0 – 25.0 x 10^9/L)	Hold until platelet recovers to 100 x10^9/L and decrease Carboplatin to AUC of 1.5. If grade 3 toxicity continues with an AUC of 1.5, decrease Carboplatin to AUC of 1. If grade 3 toxicity continues with an AUC of 1, discontinue study regimen.
Grade 4 Thrombocytopenia (platelets < 25.0 x 10^9/L)	Hold until platelet recovers to 100 x10^9/L and decrease Carboplatin to AUC of 1.5. If grade 4 toxicity continues with an AUC of 1.5, decrease Carboplatin to AUC of 1. If grade 4 toxicity continues with an AUC of 1, discontinue study regimen.
Grade 3 Neutropenia (neutrophils < 1.0 – 0.5 x 10^9/L)	Hold the treatment until ANC < 1.5 – 1.0 x10^9/L.
Grade 4 Neutropenia (neutrophils < 0.5 x 10^9/L)	Use GMCSF per treating physician discretion.
Any hematological or non-hematological toxicity requiring interruption for ≥ 3 weeks	Discontinue carboplatin.

10 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.

10.2 Expedited Adverse Event Reporting

Expedited AE reporting will utilize the descriptions and grading scales as presented in Appendix 1. SAEs that occur in this study must be promptly reported to the study P.I. (Dr. Carmen Perez) as well as to the NYU IRB, if they fall under the policy of reportable events to IRB (see 10.3) (550 First Avenue, Veteran's Administration Hospital, 10th floor, West Wing, New York, NY 10016) and to the NYU Clinical Trials Office (462 First Avenue, New York, NY 10016) for reporting to the NYUCI Data Safety Monitoring Committee. The rest of the events (SAE or any other) will be brought to attention of the DSMP. The IRB would need to see their regular reports as a result of analysis of all SAEs and AEs.

10.3 Routine Adverse Event Reporting Guidelines

The IRB Reportable Events Forms (available electronically at http://irb.med.nyu.edu/files/irb/attachments/Reportable_event_11-09_0.doc) should be used for all adverse events

11 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."

11.2 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.

12 INVESTIGATOR RESOURCES

12.1 Qualifications

Drs. Adams, Novick, Speyer, Volm and Tiersten and Huppert will be responsible for the

accrual and care of study patients. Maria Fenton-Kerimian, N.P. will be in charge of study screening, eligibility checklist and will participate in the process of acquisition of an informed consent, after the faculty has discussed the trial with the patient. Ms. Fenton-Kerimian will also provide the research nursing component of the study, including supervising the QOL assessment of the patients.

Drs. DeWyngaert and Joszef provide the necessary expertise in physics to conduct the proposed study. Dr. Goldberg will participate in the design of the study and oversee the statistical analysis and interpretation of the data. Linda Rolnitzky will participate in the development of the study data collection forms and the ongoing data review and monitoring as well as conduct the analyses as required. Martin Donach will be the study coordinator for the study.

12.2 Use of NYU Facilities

Therapy will be administered in the Department of Radiation Oncology at the Clinical Cancer Center and at Tisch Hospital.

12.3 Conflict of interest

There are no conflicts of interest to declare.

13 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
Moisture-D assessment	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 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 DATA REPORTING / REGULATORY CONSIDERATIONS

15.1 Monitoring plan

The NYU PRMC Data and Safety Monitoring Committee (DSMC) is the monitoring board for this study. The Committee will review safety at scheduled intervals (not less than once/year) and at the time of the final analysis according to the NYU Data Safety Monitoring Plan Charter.

Stopping rules - 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.

15.2 Data management

Data will be entered into the NYUCI Oracle Clinical database and maintained at NYUSOM by trained Radiation Oncology data managers.

The Oracle 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 NYU 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.

15.3 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. Anonymous data will be shared with Weill Cornell Medical College due to the relocation of study personnel so that a paper may be published on the findings of this study. The anonymous data will only be shared with Weill Cornell Medical College after a transfer agreement is fully executed.

16. 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 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

Estimated number of eligible patients for the trial is 3-5/month. Therefore, we estimate that the required 35 patients will be recruited within 12 months. With 35 patients, we can detect a difference of 18% from a baseline rate of 25% (grade II-III acute dermatitis) with a 2-sided α = 0.05 and power of 80%. If we observe 14 or more events among these 35 patients, the null hypothesis that the rate is 25% will be rejected.

Amendment: 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 α = 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.

APPENDICIES and Informed Consent Template

APPENDIX 1. – Common Toxicity Criteria

Acute Toxicity from *Common Terminology Criteria for Adverse Events v3.0 (CTCAE)*, Published: August 9, 2006

	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 - Informed Consent Template

Attach a copy of the protocol informed consent form.

APPENDIX 3 - Toxicity Tracking Form

Department of Radiation Oncology
NYU Hospitals Center
550 First Avenue
New York, NY 10016

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 4 – Quality of Life Questionnaires

Appendix 4.1 Quality of Life questionnaire used at baseline

R#10-01969 PHASE I-II STUDY OF CONCURRENT ADJUVANT SYSTEMIC THERAPY AND ACCELERATED RADIOTHERAPY (OVER 3 WEEKS)

Form QLB (01-25-2005) **Quality of Life Questionnaire - Baseline** Page 1 of 7

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

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

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

Mark Circles Like This: → ●

Institution Name / Affiliate Name

_____ / _____

Staff Member Administering Form

Last Name _____ First Name _____ Phone _____

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

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

● Baseline (after consent, before randomization)

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

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

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

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

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

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

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

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

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

BCTOS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

0	1	2	3	4	5	6	7	8	9	10

No pain — Pain as bad as you can imagine

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

0	1	2	3	4	5	6	7	8	9	10

No pain — Pain as bad as you can imagine

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

0	1	2	3	4	5	6	7	8	9	10

No pain — Pain as bad as you can imagine

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

0	1	2	3	4	5	6	7	8	9	10

No pain — Pain as bad as you can imagine

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

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

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

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

SCL

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

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

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

Specify other problems:

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

1	**EXCELLENT:** when compared to the untreated breast or the original appearance of the breast, there is minimal or no difference in the size or shape of the treated breast. The way the breast feels (its texture) is the same or slightly different. There may be thickening, scar tissue or fluid accumulation within the breast, but not enough to change the appearance.
2	**GOOD:** there is a slight difference in the size or shape of the treated breast as compared to the opposite breast or the original appearance of the treated breast. There may be some mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes only a mild change in the shape or size.
3	**FAIR**: obvious differences in the size and shape of the treated breast. This change involves a quarter or less of the breast. There can be moderate thickening or scar tissue of the skin and the breast, and there may be obvious color changes.
4	**POOR:** marked change in the appearance of the treated breast involving more than a quarter of the breast tissue. The skin changes may be obvious and detract from the appearance of the breast. Severe scarring and thickening of the breast, which clearly alters the appearance of the breast, may be found.

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

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

SCL and RTOG PQ

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

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

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

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

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

Thank you for completing this questionnaire!

RTOG PQ

Appendix 4.2 Quality of Life questionnaire used for follow-up visits

R#10-01969 PHASE I-II STUDY OF CONCURRENT ADJUVANT SYSTEMIC THERAPY AND ACCELERATED RADIOTHERAPY (OVER 3 WEEKS)

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 4.3 Form for missing Quality of Life information

R#10-01969 **PHASE I-II STUDY OF CONCURRENT ADJUVANT SYSTEMIC THERAPY AND ACCELERATED RADIOTHERAPY (OVER 3 WEEKS)**

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

_____

_____

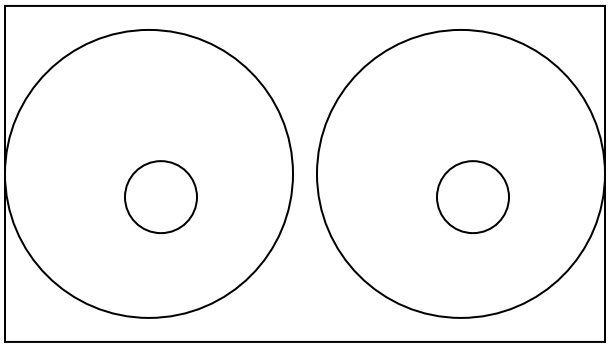
Mark Circles Like This: → ●

NYU Comprehensive Cancer Center
Fibrosis Measurement Device: Moisture meter D

Date:_____ Treatment Site:_____
Treatment Completion Date:_____ Treatment Dose:_____
Protocol_____

Area of Fibrosis:_____

Grade of Fibrosis:_____



Moisture Meter D Measurement

Location	Right Breast	Left Breast
Upper Outer Quadrant		
Upper Inner Quadrant		
Lower Outer Quadrant		
Lower Inner Quadrant		
Nipple/ Areola Complex		

REFERENCES

1. James Melissa, L., et al. (2008) *Fraction size in radiation treatment for breast conservation in early breast cancer*. Cochrane Database of Systematic Reviews, DOI: 10.1002/14651858.CD003860.pub2.
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, S.C., *External-beam partial-breast irradiation.* Semin Radiat Oncol, 2005. **15**(2): p. 92-9.
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. Dent, R., et al., *Triple-negative breast cancer: clinical features and patterns of recurrence.* Clin Cancer Res, 2007. **13**(15 Pt 1): p. 4429-34.
7. Bauer, K.R., et al., *Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry.* Cancer, 2007. **109**(9): p. 1721-8.
8. Carey, L.A., et al., *The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes.* Clin Cancer Res, 2007. **13**(8): p. 2329-34.
9. Haffty, B.G., et al., *Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer.* J Clin Oncol, 2006. **24**(36): p. 5652-7.
10. Liedtke, C., et al., *Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer.* J Clin Oncol, 2008. **26**(8): p. 1275-81.
11. Bauer, J.A., et al., *Identification of markers of taxane sensitivity using proteomic and genomic analyses of breast tumors from patients receiving neoadjuvant paclitaxel and radiation.* Clin Cancer Res, 2010. **16**(2): p. 681-90.
12. Lorvidhaya, V., et al., *Concurrent mitomycin C, 5-fluorouracil, and radiotherapy in the treatment of locally advanced carcinoma of the cervix: a randomized trial.* Int J Radiat Oncol Biol Phys, 2003. **55**(5): p. 1226-32.
13. Zatloukal, P., et al., *Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study.* Lung Cancer, 2004. **46**(1): p. 87-98.
14. Takada, M., et al., *Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104.* J Clin Oncol, 2002. **20**(14): p. 3054-60.
15. Furuse, K., et al., *Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-*

small-cell lung cancer. J Clin Oncol, 1999. **17**(9): p. 2692-9.
16. Kwong, D.L., et al., *Concurrent and adjuvant chemotherapy for nasopharyngeal carcinoma: a factorial study.* J Clin Oncol, 2004. **22**(13): p. 2643-53.
17. Apetoh, L., et al., *Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy.* Nat Med, 2007. **13**(9): p. 1050-9.
18. Formenti, S.C. and S. Demaria, *Systemic effects of local radiotherapy.* Lancet Oncol, 2009. **10**(7): p. 718-26.
19. Formenti, S.C. and S. Demaria, *Effects of chemoradiation on tumor-host interactions: the immunologic side.* J Clin Oncol, 2008. **26**(9): p. 1562-3; author reply 1563.
20. Formenti, S.C., *Immunological aspects of local radiotherapy: clinical relevance.* Discov Med, 2010. **9**(45): p. 119-24.
21. Pfannenstiel, L.W., et al., *Paclitaxel enhances early dendritic cell maturation and function through TLR4 signaling in mice.* Cell Immunol, 2010.
22. Creighton, C.J., et al., *Residual breast cancers after conventional therapy display mesenchymal as well as tumor-initiating features.* Proc Natl Acad Sci U S A, 2009. **106**(33): p. 13820-5.
23. Yu, F., et al., *let-7 regulates self renewal and tumorigenicity of breast cancer cells.* Cell, 2007. **131**(6): p. 1109-23.
24. Phillips, T.M., W.H. McBride, and F. Pajonk, *The response of CD24(-/low)/CD44+ breast cancer-initiating cells to radiation.* J Natl Cancer Inst, 2006. **98**(24): p. 1777-85.
25. Tanei, T., et al., *Association of breast cancer stem cells identified by aldehyde dehydrogenase 1 expression with resistance to sequential Paclitaxel and epirubicin-based chemotherapy for breast cancers.* Clin Cancer Res, 2009. **15**(12): p. 4234-41.
26. Li, X., et al., *Intrinsic resistance of tumorigenic breast cancer cells to chemotherapy.* J Natl Cancer Inst, 2008. **100**(9): p. 672-9.
27. Kim, M.Y., et al., *Tumor self-seeding by circulating cancer cells.* Cell, 2009. **139**(7): p. 1315-26.
28. Pal, S.K. and J. Mortimer, *Triple-negative breast cancer: novel therapies and new directions.* Maturitas, 2009. **63**(4): p. 269-74.
29. Kreike, B., et al., *Gene expression profiling and histopathological characterization of triple-negative/basal-like breast carcinomas.* Breast Cancer Res, 2007. **9**(5): p. R65.
30. 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.
31. 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.
32. Ware, J.E., Jr. and C.D. Sherbourne, *The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.* Med Care, 1992. **30**(6): p. 473-83.
33. 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.
34. 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.

35. 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.
36. 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.
37. 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.