TITLE

PHASE I - II STUDY OF PRONE ACCELERATED BREAST AND NODAL IMRT

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PROTOCOL SYNOPSIS

TITLE	Phase I - II Study of Prone Accelerated Breast and Nodal IMRT
STUDY PHASE	I - II
INDICATION	Stage II - III breast cancer (AJCC 2002)
PRIMARY OBJECTIVES	Feasibility, Acute toxicity
SECONDARY OBJECTIVES	Incidence of re-simulation supine, QOL (defined by RTOG-PRO), Late toxicity: e.g., fibrosis, telangiectasia, Local control: Time to Progression,
EXPLORATORY OBJECTIVES	Survival and evaluation of genetic determinants of breast fibrosis
HYPOTHESES	Prone IMRT to breast, level III and SCV nodes is feasible and well tolerated in a 3-week regimen
STUDY DESIGN	Prospective, single arm uncontrolled
PRIMARY ENDPOINTS	Acute, late effects, QOL-PRO
[redacted]	[redacted]
SAMPLE SIZE BY TREATMENT GROUP	104 patients. Cohort A – 30 patients
SUMMARY OF SUBJECT ELIGIBILITY CRITERIA	Newly diagnosed breast cancer patients after segmental mastectomy, and axillary dissection of at least 8 lymph nodes.
INVESTIGATIONAL PRODUCTS DOSAGE AND ADMINISTRATION	N/A
CONTROL GROUP	N/A
PROCEDURES	N/A
STATISTICAL CONSIDERATIONS	Phase I - II

SCHEMA

ELIGIBLE PATIENTS

↓

INFORMED CONSENT

↓

Whole breast/chest wall, level 1- III (includes Cohort A) and SCV nodes
IMRT at 2.7 Gy x 15 fractions

Total dose to the indexed breast = 40.50 Gy

Daily 0.5 Gy boost to the tumor bed (15 fractions)

Total dose to tumor bed = 48 Gy

All patients will be followed for toxicity and outcome (i.e., local and systemic recurrence, survival). In addition, patients will complete a Quality of Life (QOL) self-assessment at baseline, week 3, day 45-60 and 2-yr follow-ups.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADL	Activities of daily living
AE	Adverse event
ATM	Ataxia Telangiectasia Mutated
BED	Biologically Effective Dose
CBC	Complete blood count
CI	Confidence interval
CBCT	Cone-Beam CT
CRF	Case report/Record form
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
Gy	Gray
Hgb	Hemoglobin
IBV	Ipsilateral Breast Volume
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
RIF	Radiation-Induced Fibrosis
RR	Response rate
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event
SD	Stable disease
SNP	Single Nucleotide Polymorphism
SSCP	Single-Strand Conformation Polymorphism
TGF-beta1	Transforming Growth Factor beta-1
TV	Treatment Volume

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To evaluate feasibility of prone IMRT to breast, level III and supraclavicular nodes (physics and dosimetry parameters)

1.1.2 To estimate acute toxicity of prone IMRT to breast, level III and supraclavicular nodes

1.2 Secondary Objectives

1.2.1 To estimate the incidence of re-simulation to improve dosimetry after initial prone set-up

1.2.2 To evaluate changes in QOL of patients assessed at baseline and after treatment

1.2.3 To estimate incidence of late radiation toxicity (e.g., lymphedema, fibrosis and telangiectasia) and to examine genetic determinants of breast fibrosis

1.3 Exploratory Objectives

1.3.1 To estimate local recurrence rates

1.3.2 To estimate median Disease Free Survival (DFS)

1.3.3 To estimate median Time to Progression

1.3.4 To estimate median Overall Survival (OS)

1.4 Cohort A Objectives

1.4.1 To explore feasibility of treating in the prone position a comprehensive nodal volume, that includes axillary nodal levels I and II in addition to the fields already treated per this protocol (i.e., axillary nodal levels III, supraclavicular fossa and breast or chest wall tangents, depending on whether the patient has undergone segmental mastectomy or mastectomy, respectively)

2. BACKGROUND

2.1 NYU Research in Hypofractionated 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 (James Melissa, Lehman et al. 2008). 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 (greater than 2 Gy per fraction) does not affect breast appearance or toxicity, and does not seem to affect local recurrence or five years survival rates.

Hypofractionation 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. As background for the proposed study that will test a novel technique to target the breast and level III/SCV nodes in the prone position for women with 1 - 5 involved nodes, a review of the whole breast radiation research studies conducted thus far is detailed below.

2.2 NYU Experience on Accelerated Concomitant Boost Whole Breast: NYU 03-30

Inspired by the hypo-fractionated Canadian trial (Whelan, MacKenzie et al. 2002) we developed a technique that utilizes IMRT to deliver accelerated prone whole breast radiotherapy with a concomitant boost to the tumor bed. The rationale for adding a boost to the tumor cavity derived from the results of a prospective randomized trial conducted by the EORTC (Bartelink, Horiot et al. 2001). A recent update of the trial demonstrated a 10-year cumulative incidence of local recurrence of 10.2% versus 6.2% for the no boost and the boost group respectively ($p < 0.0001$) (Bartelink, Horiot et al. 2007).

Patients with stage I or II breast cancer, excised by breast conserving surgery with negative margins, and either sentinel node biopsy or axillary dissection were eligible for study NYU 03-30. CT simulation was performed with the patient on a dedicated prone breast board, in the exact position used for treatment.

From September 2003 to August 2004, the planned accrual was completed, with 90 patients treated in the protocol (mean follow-up of 39 months, range 1 - 72 months). Median age was 58 years old (range 28 – 80 yo). Median tumor size was 13 mm (range 1 - 40 mm). Acute toxicity was generally mild and is summarized in Table 1 (RTOG score). Most common toxicity was radiation dermatitis, which tended to occur the week after completion of treatment.

Table 1 - Acute Toxicity Observed from Study 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, late toxicity, and to determine cosmetic results. Because of blood collection, once sufficient time has elapsed to measure late effects, the study will enable us to explore associations between specific genomic profiles and the

occurrence of fibrosis (Formenti 2005). In addition, this trial generated preliminary data on dose sparing to the heart and lung when patients are treated prone (Darby, McGale et al. 2005).

2.3 Rationale for Prone Radiotherapy: NYU 05-181

Despite the demonstrated feasibility and advantages of the 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 the heart and lung. Since no obvious clinical characteristics predict for this exception, NYU led a subsequent 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 1 mm of margin, no more than 3 positive lymph nodes for breast cancer, at least two weeks post chemotherapy (if indicated), no history of prior or concurrent malignancy (within 3 years), and no history of active connective tissue disorders. Patients underwent CT simulation in both the prone and supine positions. Treatment followed in the optimal position that ensured the smallest volume of heart and lung respectively, in the target field.

From 2006 to 2009 the study met the planned accrual of 400 patients: 200 with left and 200 with right breast cancer. Results are summarized in Table 2. Among right breast cancer patients, the prone position was optimal in sparing lung volume in 98% (195/200), reducing the volume of lung in the treatment field by a mean 107 cc (SD 75, range 463,0). In the five patients treated supine, the choice for supine treatment was based on patient's preference since there was no significant difference in lung sparing between the two positions. For left breast cancer patients, the prone position was optimal in 85% (170/200), with lung volume reduced by a mean of 93 cc (SD 72, range 334, 9) and heart volume reduced by a mean of 11 cc (SD 23, range 0,220). However, in 15% of left breast patients, the best position was supine reducing the amount of heart in the treatment field by a mean of 6 cc (SD 8, range 0,41).

Table 2 - Protocol 05-181 - Interim Results: Left/Right Breast Cancer by Supine/Prone Positioning

	Supine	Prone	Total
Left	30	170	200
Right	5	195	200

The experience gathered from the NYU 05-181 study provides support for all patients to first undergo a CT simulation in the prone position when the breast is to be irradiated. An additional supine set up will be attempted only if the dosimetry information derived from prone planning

reveals that it exceeds the following normal tissue dose constraints:

a. Heart: ≥ 5% of the heart volume receives greater than 5 Gy.
b. Ipsilateral lung: ≥15% of the ipsilateral lung receives greater than 10 Gy.
c. Contralateral lung: ≥15% of the contralateral lung receives greater than 5 Gy.

2.4 Rationale for Treating Axillary Level III and Supraclavicular Nodes

After breast surgery and an adequate axillary dissection (i.e., at least 8 nodes retrieved in the axillary dissection specimen from level I and II) it is possible to identify patients with 1 - 5 positive nodes who require radiotherapy to both the indexed breast/chest wall and the draining nodal stations that the surgeon did not include in the traditional level I - II axillary dissection, i.e., level III and supraclavicular stations. **We are proposing to test a new technique that extends prone set up to also include these lymph node regions.**

Limiting treatment to the supraclavicular fossa and level III axilla in patients with an adequately dissected axilla is supported by several published studies. Regional nodal recurrences are rare (occurring in 1 - 5%) in patients with early stage invasive breast cancer who have undergone breast conserving therapy (Fisher, Anderson et al. 2002; Moran and Haffty 2002; Harris, Hwang et al. 2003). Several institutions choose to treat only the level III axilla and supraclavicular nodal stations in patients who have undergone surgical treatment of level I/II axilla. This technique was documented recently by Liengsawangwong, who utilized CT-delineated nodal stations to improve target coverage of SCV and level III axillary nodes (Liengsawangwong, Yu et al. 2007) in patients who had undergone axillary level I/II dissection and were found to have positive lymph nodes.

Locoregional recurrences have been extensively studied in post-mastectomy patients as well. After chest wall recurrences, nodal failures in the undissected axillary level III or supraclavicular fossa are the second most common type of regional recurrence and occur more commonly in patients with four or more positive lymph nodes (Table 3) (Taghian, Jeong et al. 2004).

Table 3 - Locoregional Recurrence Rates in Post-mastectomy Patients without Radiotherapy

Table 6. Ten-Year Cumulative Rates of Locoregional Failure With or Without Distant Failure According to Number of Positive Lymph Nodes (LN+)

Number LN+	1-3 LN+ (%)	≥ 4 LN+ (%)	Median No. of LN Dissected	Chemotherapy Used
Danish trial 82b[6]	30	42	7	CMF
Danish trial 82c[7]	31	46	7	CMF
Canadian[5]*	33	46	11	CMF
ECOG[9]†	13	29	15	CMF
MDA[10]‡	14	25-34‖	17	Doxorubicin based
IBCSG,[11]† premenopausal	19.7§	30-38§‖	≈15¶	CMF**
IBCSG,[11]† postmenopausal	16§	29-35§‖	≈15¶	CMF or tamoxifen††
NSABP†	13	24-32‖	16	Doxorubicin/CMF‡‡

Abbreviations: LN, lymph nodes; LN+, positive lymph nodes; CMF, cyclophosphamide, methotrexate, and fluorouracil; ECOG, Eastern Cooperative Oncology Group; MDA, M.D. Anderson Cancer Center; IBCSG, International Breast Cancer Study Group; NSABP, National Surgical Adjuvant Breast and Bowel Project.
*Fifteen-year actuarial rate.
†Ten-year cumulative incidence.
‡Ten-year actuarial rate.
§Rate of LRF ± DF calculated from Table 5 from Wallgren et al.[11]
‖Rate of LRF ± DF for patients with four to nine LN+ and ≥ 10 LN+, respectively.
¶Forty-seven percent of patients had 15 or more lymph nodes removed.
**All patients received at least three courses of CMF chemotherapy.
††All patients received at least three courses of CMF chemotherapy or tamoxifen for 1 to 5 years.
‡‡The percentage of patients who received doxorubicin-based chemotherapy was 90.3%.

The impact of extracapsular extension on outcome of post-mastectomy patients is controversial. Some studies report higher risk of distant recurrence, but no change in locoregional recurrence (Donegan, Stine et al. 1993) while others document higher rates of locoregional recurrence in patients with extracapsular extension (Garg, Strom et al. 2004; Huang, Tucker et al. 2005).

There may be a subset of high-risk patients who would benefit from adjuvant radiotherapy to the entire previously-dissected axilla. For example, an axillary boost to treat levels I/II decreased nodal recurrence, although it did not affect overall survival in a cohort of breast cancer patients with ten or more positive lymph nodes treated with breast conservation therapy (Chang, Feigenberg et al. 2007).

In summary, for some patients, the toxicity of any nodal radiotherapy will outweigh the benefit, while other patients have superior outcomes when the entire axilla and supraclavicular fossa are treated. There is likely a subset of breast cancer patients who could benefit from the advantage of limiting nodal radiotherapy to axillary level III and supraclavicular nodes after adequate axillary level I/II lymph node dissection, without impairing their chances of loco-regional control. Based on the previously referenced studies, we propose utilizing an approach of limited nodal treatment in patients with invasive breast cancer treated by breast conservation therapy or mastectomy with one to five involved lymph nodes after adequate dissection of level I/II axilla. These patients could also be studied to explore the feasibility and safety of an accelerated regimen of 3 weeks to the prone breast (or chest wall), and level III and supraclavicular nodes.

2.5 Late Radiation Effects and Assessment of Risk

For patients who require regional nodal irradiation, an accelerated regimen of three weeks is very appealing, but in the past it has generally been discouraged because of concerns regarding the morbidity of larger doses to normal tissue, including lymphedema and brachial plexus

injury. The current protocol is likely to overcome some concerns of lymphedema by avoiding irradiation of the axillary stations where a surgical dissection was performed. Nevertheless, a field that includes axillary level III and the supraclavicular nodes will also include most of the ipsilateral brachial plexus, warranting cautious radiobiological modeling of late effects of radiotherapy to this target.

The severity of late effects is known to be dependent on both total dose and fraction size. In the linear-quadratic model, sensitivity to fraction size is expressed by the alpha/beta ratio, with a lower ratio indicating increased sensitivity. In a recent review, Kurtz summarized known alpha/beta values for tissues irradiated in breast cancer treatment (Table 4) (Kurtz 2005).

Table 4 - A Review of Results Summarized by Kurtz et al.

End-point	Author (reference)	Alpha/beta (Gy)
Telangiectasia	Turesson et al. [14]	4.2
Chest wall fibrosis	Bentzen et al. [6]	1.9
Shoulder stiffness	Bentzen et al. [5]	3.5
Brachial plexus injury	Powell et al. [12]	1.5–2.0
Rib fractures	Overgaard [11]	1.8–2.8
Breast cosmesis (fibrosis)	Van Limbergen et al. [16]	2.5

Due to low alpha/beta ratios for most of these tissues, it is possible that higher rates of late complications could be observed with an accelerated regimen. To clinically evaluate the impact of hypofractionation on brachial plexus injury, Powell et al. reported their experience with an accelerated schedule in a seminal paper published in 1990, describing the late effects of a group of 449 patients irradiated to the breast and regional lymph nodes with mean brachial plexus dose 45.9 Gy in 15 fractions (3 Gy per fraction) versus 54 Gy in 30 fractions (1.8 Gy per fraction) (Powell, Cooke et al. 1990). He noted a cumulative actuarial incidence of radiation-induced brachial plexus injury at 5.5 years of 5.9% versus 1.0% for the large and small fraction size group, respectively. It is important to note that the dose was higher than our proposed dose of 40.50 Gy given in 2.7 Gy daily fractions and that the fields included the entire axilla.

Lymphedema is another late complication sensitive to fraction size. Hayes documented rates of lymphedema in 2,579 patients followed at a single institution who underwent breast conservation therapy between 1970 and 2005. In patients receiving radiotherapy to the breast, breast + SCV, and breast + SCV + axillary boost, lymphedema occurred in 16%, 23%, and 31%, respectively (Hayes, Freedman et al. 2008). In a large phase III randomized trial, 46% of mastectomy patients experienced arm swelling at some point after radiotherapy (Deutsch, Land et al. 2008). For radical mastectomy patients, total mastectomy and radiotherapy patients, and total mastectomy patients in this trial, arm edema was recorded at least once in 58.1%, 38.2%, and 39.1% of patients, respectively ($p < 0.001$) and at last recorded measurement in 30.7%, 14.8%, and 15.5%, respectively ($p \leq 0.001$). We anticipate that reduction of the size of the field for nodal radiation will reduce rates of lymphedema despite an accelerated treatment regimen.

Most patients experience lymphedema within the first years after treatment, but it can continue to increase in severity for more than five years after treatment in over 50% of patients (Bar Ad, Cheville et al. 2009). Therefore, subjects will need to be carefully followed for progressive lymphedema, for at least five years after radiotherapy is completed.

2.6 Dose Selection for Treating Breast and Nodal Stations

The linear-quadratic model (Lea 1942) can be used to determine whether the proposed IMRT protocol should result in a roughly equal probability of tumor control compared with a standard schedule, but without increasing the potential for normal tissue damage. The equation describing the single dose survival curve (Douglas and Fowler 1976) using this model is

$$-\ln S = (\alpha D + \beta D^2)$$

where S is the surviving fraction, D is the total dose and α and β are tissue specific parameters. If the total radiation dose is delivered in a series of n fractions of dose d, rather than a single exposure, then the surviving fraction can be described as

$$-\ln S = n(\alpha d + \beta d^2)$$

which can be called the biological effect E. This equation can be rewritten as

$$E = (nd)(\alpha+\beta d) = (\alpha)(nd)(1+d/\alpha/\beta)$$

If this equation is divided through by α, then $E/\alpha = (nd)(1+d/\alpha/\beta)$. The quantity E/α has been termed the biologically effective dose (15) or BED that is similar to the previously suggested extrapolated response dose (Barendsen 1982).

Hence,

$$BED = (nd)(1+d/\alpha/\beta)$$

This equation was used to calculate the BEDs for early and late responses, and tumor control for a standard schedule representing twenty-three 2 Gy fractions delivered once per day to the whole breast plus seven 2 Gy boost fractions to the tumor bed over a 39 day period. The proposed AIMRT schedule consists of fifteen IMRT fractions of 2.7 Gy to the whole breast and regional nodes and 3.2 Gy to the tumor bed delivered over an 18-day period. These calculations assume full repair takes place during the 24-hour or greater interval between fractions. Table 5 lists the BEDs for tumor control in addition to the early responses, erythema and desquamation, as well as the late responses, telangiectasia and fibrosis. The α/β values used for these computations were reported in previous studies (Steel, Deacon et al. 1987; Matthews, Meeker et al. 1989; Turesson and Thames 1989; Thames, Bentzen et al. 1990; Archambeau, Pezner et al. 1995; Yamada, Ackerman et al. 1999).

Table 5 - Biologically Effective Doses

Normal Tissue Responses				
	α/β (Gy)	Standard Schedule	Standard Schedule	AIMRT Schedule
		(2 Gy x 23 in 39 days)	(2 Gy x 25 in 39 days)	(2.7 Gy x 15 in 18 days)
Brachial plexus injury	2	92 Gy_2	100 Gy_2	95 Gy_2
Fibrosis	2	92 Gy_2	100 Gy_2	95 Gy_2
Telangiectasia	4	69 Gy_4	75 Gy_4	68 Gy_4
Erythema	8	58 Gy_8	63 Gy_8	54 Gy_8
Desquamation	11	54 Gy_{11}	59 Gy_{11}	50 Gy_{11}
Tumor Control				
	α/β (Gy)	Standard Schedule	AIMRT Schedule	AIMRT Schedule
		(2 Gy x 30 in 44 days)	(3.2 Gy x 15 in 18 days)	(2.7 Gy x 15 in 18 days)
Tumor	2	120 Gy_2	125 Gy_2	95 Gy_2
Tumor*	2	116 Gy_2	125 Gy_2	95 Gy_2
Tumor	4	90 Gy_4	86 Gy_4	68 Gy_4
Tumor*	4	86 Gy_4	86 Gy_4	68 Gy_4
Tumor	10	72 Gy_{10}	63 Gy_{10}	51 Gy_{10}
Tumor*	10	68 Gy_{10}	63 Gy_{10}	51 Gy_{10}

*Taking into account cell proliferation during the course of treatment.

In terms of normal tissue responses, it can be observed from Table 5 that the BED values for the IMRT treatment are generally lower than the BEDs for the standard treatment for the early responses of erythema and desquamation. In addition, the BEDs are similar for the late responses of telangiectasia and fibrosis and brachial plexus injury. Hence, it would appear unlikely that the IMRT treatment will result in a greater risk of complications compared with the standard protocol.

With respect to tumor control, the classic dilemma typically encountered when a hypo-fractionated protocol is substituted for a standard treatment plan, is either a reduced probability of tumor control or an increased risk for late complications. This is due to the observation that fractionation generally results in greater sparing of late responding tissues compared with tumors. This finding is reflected in the relatively large α/β values derived for tumors and small α/β values for late responses (Thames and Hendry 1987).

In contrast to this generalization, evidence exists that breast cancer cells display a relatively low α/β. This comes from in vitro studies in which α/β values determined for breast cancer cell lines were generally about 4 Gy (Steel, Deacon et al. 1987; Matthews, Meeker et al. 1989; Yamada, Ackerman et al. 1999). The way in which this problem is diminished for this study is

through the use IMRT to limit the dose to the whole breast. Therefore, for the AIMRT protocol, the tumor bed will receive 3.2 Gy per fraction, whereas the breast and level III and supraclavicular will receive 2.7 Gy per fraction.

An even lower α/β of 2 Gy can be calculated using the results of a prospective randomized trial (Baillet, Housset et al. 1990) in which a standard treatment of twenty-five 1.8 Gy fractions resulted in approximately the same level of tumor recurrence as a hypo-fractionated protocol of two 4.5 Gy plus two 6.5 Gy fractions. Therefore, if it is assumed that the BEDs for the two treatments were roughly equal, this yields an α/β value of 2 Gy. Although there is evidence in the papers cited to support the use of these relatively low α/β values for BED calculations, tumors on average exhibit greater α/β values in the range of 10 Gy (Williams, Denekamp et al. 1985; Thames and Hendry 1987).

Viewing the results of the BED calculations for tumor control presented in Table 5, if the α/β values are assumed to be in the range of 4 - 10 Gy, then there would appear to be only a small loss in BED for the AIMRT treatment, while for the 2 Gy α/β value, the BED value for the alternate treatment actually is greater than the standard. In addition, it should be noted that the hypo-fractionated treatment also represents an accelerated protocol in which the total dose is delivered in only 18 days. Therefore, little or no tumor proliferation is likely to occur during the course of this proposed treatment as opposed to the standard treatment in which it is probable that tumor proliferation will take place thereby decreasing the chances for tumor control.

In order to take into account tumor proliferation for the BED calculation, it can be estimated that the number of clonogenic cells in the tumor (N) is related to the initial number of clonogens (N_0) by the expression

$$\ln(N/N_0) = \lambda(T-T_k)$$

where λ is a constant related to the potential doubling time T_{pot} of the tumor by the expression, $\lambda = \ln 2/T_{pot}$, T is the total treatment time, and T_k (the "kick-off" time) is the time at which accelerated repopulation begins (15,26) (Travis and Tucker 1987; Fowler 1989). Note, this relationship is only valid for values of T greater than T_k. Therefore,

$$\ln(N/N_0) = (\ln 2/T_{pot})(T-T_k)$$

Hence, the biological effect for a fractionated treatment should be *decreased* to take into account the increase in the number of cells due to repopulation and becomes:

$$E = n(\alpha d+\beta d^2) - (\ln 2/T_{pot})(T-T_k)$$

If this equation is divided through by α, then the BED equation results and is given by

$$E/\alpha = [(nd)(1 + d/\alpha/\beta)] – [\ln 2(T-T_k)/\alpha(T_{pot})]$$

Hence, it is necessary to determine values for α, the initial slope of the cell survival curve, as well as for T_{pot} and T_k. However, this may be either difficult or impossible to accomplish. Therefore, estimates are often made for these values in order to calculate the BED. For the purpose of these calculations, values of 0.3 for α, (Steel, Deacon et al. 1987; Matthews, Meeker et al. 1989) 13 days for T_{pot} (Stanton, Cooke et al. 1996; Haustermans, Fowler et al. 1998) and 21 days for T_k were used. However, it must be stressed that the actual values for any given patient may differ significantly. Nevertheless, an effort was made to correct for tumor proliferation even though these calculations may be somewhat imprecise, as they still provide a better estimate of BED than a determination of this parameter performed in the absence of any cell proliferation correction factor.

As presented in Table 5, the equation above which incorporates a cell proliferation correction factor produces small decreases in the BEDs for the standard treatment. Therefore, taking into consideration tumor proliferation during treatment, the IMRT schedule results in BED values greater to or equal to the standard treatment for α/β values of either 2 or 4 Gy and is only slightly lower when a 10 Gy α/β value is used. In addition, it must be kept in mind that there is a range of T_{pot} values for a population of tumors. Therefore, the accelerated nature of the AIMRT treatment may have a particularly beneficial effect for those patients whose tumors are characterized by relatively short T_{pot} values.

Of course, if cell proliferation is taken into account, this also diminishes the BEDs and lessens the severity of the anticipated early responses for the standard schedule compared with the AIMRT schedule. This should not affect late responses because the T_k is generally greater than the total treatment time for late responding tissues as compensatory proliferation usually does not begin until after completion of a standard protocol. However, even if the BEDs were decreased to take into account cell proliferation, this would probably result in only slightly diminished BEDs for erythema and desquamation for the standard schedule, resulting in BEDs comparable to the AIMRT schedule.

2.6.1 Rationale for this Approach

The proposed treatment approach entails radiotherapy to axillary level III and SCV, defined by CT imaging obtained in a prone position using IMRT technique. We anticipate that this will improve target coverage, toxicity, and tolerability for several reasons. First, by avoiding radiotherapy to level I and II axillary lymph nodes in a previously dissected axilla, we anticipate reduced risk of lymphedema. Additionally, treatment in the prone position has been shown to reduce dose to heart and lungs (Formenti, Gidea-Addeo et al. 2007), which may decrease late toxicity to these organs. Finally, while standard 3-field and 4-field techniques provide inadequate lymph node coverage in the prone position (refer to preliminary data in Section 2.6.2), use of IMRT technique will enable prone target coverage while maintaining low doses to normal tissues.

2.6.2 Preliminary Data

To evaluate the dosimetric feasibility of the prone IMRT treatment approach and to compare its dosimetric performance compared to other standard techniques, we explored six treatment planning techniques to target the breast and axillary level III and supraclavicular nodes.

The CT images of 10 breast cancer patients (7 left, 3 right) who underwent simulation in both prone and supine positions were used for planning. Supraclavicular and level III axillary lymph node regions, breast tissue, tumor bed, heart, and ipsilateral lung were manually contoured. Six treatment plans were created for each patient; all utilized tangential fields to target breast tissue. A three-dimensional conformal radiotherapy (3DCRT) plan with a single anterior-oblique field, a 3DCRT plan with anterior-oblique and posterior axillary boost fields, and an intensity-modulated radiotherapy (IMRT) plan were utilized to target regional nodes in both prone and supine positions. Dose-volume histograms were compared to evaluate lymph node coverage and normal tissue dose. Two-tailed student t-test was used to identify statistically significant differences between planning techniques. Nodal target and normal tissue doses from the six techniques are summarized below in Tables 6 - 8.

Table 6 - Prone Compared to Supine Positioning

	mean (st dev, range)	mean (st dev, range)	p-value
	3-field supine	**3-field prone**	
PTV-V50	53.96% (18.20, 25.70-75.00)	34.10% (21.91, 4.50-73.10)	0.0407559
Lung-V40	14.70% (4.84, 8.30-24.40)	3.81% (4.41, 0.10-14.40)	0.0000530
Lung-V20	22.98% (5.23, 16.50-33.80)	9.52% (5.98, 2.10-21.20)	0.0000434
Lung-V5	31.57% (5.82, 24.00-42.10)	13.57% (6.83, 4.90-27.90)	0.0000056
Heart-V20	0.15% (0.30, 0.00-0.80)	0.04% (0.08, 0.00-0.20)	0.2687512
Heart-V5	0.72% (1.07, 0.00-2.70)	0.38% (0.44, 0.00-1.20)	0.3436903
Spinal cord-Dmax	1131.90 cGy (333.38, 782.00-1712.00)	889.60 cGy (273.04, 263.00-1258.00)	0.0922816
	IMRT supine	**IMRT prone**	
PTV-V50	94.59% (0.32, 94.00-95.00)	95.48% (0.69, 94.80-97.00)	0.0016879
Lung-V40	15.28% (3.06, 11.90-21.80)	6.54% (1.98, 3.50-9.00)	0.0000005
Lung-V20	27.22% (6.88, 18.60-37.80)	12.48% (3.29, 8.20-17.90)	0.0000089
Lung-V5	43.73% (7.47, 32.30-56.90)	24.18% (5.09, 19.50-33.40)	0.0000021
Heart-V20	0.12% (0.26, 0.00-0.70)	0.37 (0.72, 0.00-2.00)	0.3011538
Heart-V5	0.62% (0.93, 0.00-2.40)	0.93% (1.08, 0.00-3.70)	0.6524424
Spinal cord-Dmax	3490.70 cGy (765.64, 1963.00-4266.00)	2805.20 cGy (953.84, 1762.00-4112.00)	0.0932683
	4-field supine	**4-field prone**	
PTV-V50	60.77% (12.56, 36.90-83.50)	38.93% (20.65, 1.80-78.60)	0.0104802
Lung-V40	12.29% (7.38, 0.70-25.30)	5.59% (4.70, 0.00-15.60)	0.0262689
Lung-V20	20.53% (8.34, 2.20-34.10)	10.93% (6.65, 2.10-26.30)	0.0107219
Lung-V5	29.78% (10.27, 5.60-43.70)	16.40% (8.19, 5.90-36.50)	0.0047406
Heart-V20	0.50% (1.05, 0.00-2.80)	0.06% (0.10, 0.00-0.20)	0.2870816
Heart-V5	1.84% (3.09, 0.10-8.50)	0.53% (0.42, 0.20-1.20)	0.2864321
Spinal cord-Dmax	836.20 cGy (225.60, 560.00-1258.00)	739.10 cGy (134.95, 418.00-872.00)	0.2580200

These results indicate that all 3DCRT plans had inadequate lymph node coverage, with mean planning target volume (PTV) V50 Gy 54% supine and 34% prone (3-field 3DCRT), and 61% supine and 39% prone (4-field 3DCRT). Compared to these techniques, IMRT significantly improved nodal coverage, with mean PTV V50 Gy 95% supine and 95% prone ($p < 0.001$, two-

tailed t-test). Prone positioning resulted in significantly lower ipsilateral lung doses: mean V20 Gy was 10% prone versus 23% supine (3-field 3DCRT, $p < 0.001$, two-tailed t-test); 21% supine versus 11% prone (4-field 3DCRT, $p = 0.01$, two-tailed t-test); and 12% prone versus 27% supine (IMRT, $p < 0.001$, two-tailed t-test). Among the 7 left breast cancer patients, there was no statistically significant difference in mean heart V20 Gy or V5 Gy ($p > 0.05$, two-tailed t test).

Table 7 - Supine IMRT Compared to Supine 3F/4F

	mean	mean	p-value
	3-field supine	**IMRT supine**	
PTV-V50	53.96	94.59	0.0000014
Lung-V40	14.70	15.28	0.7525528
Lung-V20	22.98	27.22	0.1382071
Lung-V5	31.57	43.73	0.0007318
Heart-V20	0.15	0.12	0.8059355
Heart-V5	0.72	0.62	0.8108750
Spinal cord-Dmax	1131.90	3490.7	0.00000005
	4-field supine	**IMRT supine**	
PTV-V50	60.77	94.59	0.0000001
Lung-V40	12.29	15.28	0.2521097
Lung-V20	20.53	27.22	0.0027134
Lung-V5	29.78	43.73	0.0027134
Heart-V20	0.5	0.12	0.4401863
Heart-V5	1.84	0.62	0.4509997
Spinal cord-Dmax	836.2	3490.7	0.000000004

Table 8 - Prone IMRT Compared to Prone 3F/4F

	Mean	mean	p-value
	3-field prone	**IMRT prone**	
PTV-V50	34.10	95.48	0.0000001
Lung-V40	3.81	6.54	0.0909352
Lung-V20	9.52	12.48	0.1876868
Lung-V5	13.57	24.18	0.0009626
Hrt-V20	0.04	0.37	0.1577367
Hrt-V5	0.38	0.93	0.2202274
Cord-Dmax	889.60	2805.20	0.0000091
	4-field prone	**IMRT prone**	
PTV-V50	38.93	95.48	0.0000001
Lung-V40	5.59	6.54	0.5635124
Lung-V20	10.93	12.48	0.5172072
Lung-V5	16.4	24.18	0.0200405
Hrt-V20	0.06	0.37	0.2744447
Hrt-V5	0.53	0.93	0.2089303
Cord-Dmax	739.1	2805.20	0.0000024

2.7 Quality of Life Assessment

Quality of life (QOL) assessments will be performed by patients at regular intervals (i.e., baseline, last week of treatment, 45 - 60 days from starting radiotherapy and 2-year follow-up). Patients status post mastectomy will be asked to answer applicable questions only in the QOL assessment. This trial will use the QLB and QLF questionnaires from the RTOG.

The QLB and QLF questionnaires are derived from a validated integration of parts of the BCTOS and MOS SF 36. BCTOS is a validated questionnaire that measures cosmetic results based on 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 (Stanton, Krishnan et al. 2001). MOS SF36 is a common QOL questionnaire used in cancer patients (Shelbourne 1992; Ware and Sherbourne 1992).

2.8 Measuring the Late Toxicities of Breast and Nodal Radiation

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 (Hoeller, Tribius et al. 2003). In comparison, when LENT/SOMA criteria were used, telangiectasia and pigmentation were upgraded in 34% and 36% of patients, respectively, and

telangiectasia was downgraded in 45% of patients. 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 tool in grading and recording late radiation toxicity as compared to the RTOG scale. Specifically, fibrosis scores correlated well with the LENT/SOMA scoring system (Spearman's rho 0.78, $p = 0.01$). The LENT/SOMA scoring system will be used in the reporting of late radiation morbidity in this protocol.

2.8.1 Quantitative Measurement of Thyroid Function

Patients undergoing radiotherapy for invasive breast cancer are at higher risk of hypothyroidism. One recent study documented hypothyroidism in 18% of patients with stage II/III invasive breast cancer who had undergone radiotherapy, compared to only 6% ($p < 0.001$) of an age-matched control group from the general population (Reinertsen, Cvancarova et al. 2009).

As such, patients will undergo thyroid function testing, including measurement of serum thyroid stimulating hormone (TSH) and free T_4 levels, at baseline and at yearly intervals after completion of radiotherapy.

2.8.2 Quantitative Measurement of Lymphedema

Patients will be assessed for lymphedema at baseline, end of treatment, and at yearly intervals after completion of radiotherapy. Arm circumference at sites 10 cm above and below the antecubital fossa will be obtained. Mild, moderate, and severe lymphedema is defined as a difference of 0.5 to 2 cm, 2.1 to 3 cm, and greater than 3 cm, respectively, of arm circumference at one or more measurement sites on the treated versus untreated side. Lymphedema progression is defined as transition from lower to higher grade at any time point. Similar lymphedema classification systems have been used in previously published studies (Keramopoulos, Tsionou et al. 1993; Bar Ad, Cheville et al. 2009).

2.8.4 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 identification of 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 (Quarmby, Fakhoury et al. 2003). 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.

2.8.5 Blood Collection for Future Genomic Studies

The purpose of this portion of the study will be to collect blood from each subject accrued to the study for 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 (Quarmby, Fakhoury et al. 2003).

It is first important to note that Dr. Rosenstein's (co-investigator) laboratory has extensive experience in the detection of genetic alterations using Denaturing High Performance Liquid Chromatography (DHPLC) (Atencio, Iannuzzi et al. 2001; Iannuzzi, Atencio et al. 2002; Bernstein, Teraoka et al. 2003). In addition, our group is part of the WECARE consortium of four laboratories that is in the process of using DHPLC to screen 2100 breast cancer patients for mutations and SNPs in a variety of genes associated with DNA repair and radiation responses. Hence, our laboratory has substantial expertise performing genetic analysis using DHPLC and will therefore be able to immediately implement this portion of the project.

For the purpose of this trial blood will be collected to enable future genomic analysis for this polymorphism to explore association with the incidence of grade 3 and 4 late complications at 3 years follow up and for other related research studies. Methods details of DHPLC are covered in Section 10.4.

3 PATIENT SELECTION

For Cohort A : Include patients who have undergone SLNB without completion ALND)

3.1 Inclusion Criteria

3.1.1 Pre- or post-menopausal women with stage II - III breast cancer (AJCC 2002)

3.1.2 Biopsy-proven invasive breast cancer, excised with negative margins of at

least 1 mm

3.1.3 Status post segmental mastectomy or mastectomy and axillary node dissection with removal of at least 8 nodes

3.1.4 One to 5 involved lymph nodes identified at axillary staging

3.1.5 At least 2 weeks from last chemotherapy or before chemotherapy

3.1.6 No more than sixty days from final surgery to simulation if no systemic therapy (includes chemotherapy and Hormonal therapy) is given

3.1.7 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 More than 5 involved nodes identified at axillary staging

3.2.3 Current treatment for active connective tissue disorders, such as lupus or scleroderma

3.2.4 Pregnant or lactating women

3.2.5 Less than 35 years old

3.2.6 Prior concurrent malignant other than basal or squamous cell carcinoma or carcinoma in situ of cervix unless disease free > 3years

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 II - III 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 or their legal guardians 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 (IRB). 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.

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 or equivalent, to prevent skin dryness and reduce erythema.

5.2 Duration of Therapy

The treatment will consist of 15 fractions, with one fraction daily for five days a week, for 3 consecutive weeks.

5.3 Duration of Follow-up

Patients will be seen for follow-up at 45 - 60 days from first radiotherapy treatment, and then yearly for up to 5 years.

5.4 Alternatives

At the time of study accrual, all patients will be offered access to standard six weeks radiotherapy, including 5 weeks of treatment to the whole breast or chest wall and regional lymph nodes using a standard 4-field plan, followed by a boost to the tumor bed or scar if required.

5.5 Compensation

No compensation is available for participating in the study.

6 SURGERY

Patients will have completed all breast cancer 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 onto the study. Patients must also undergo lymph node dissection of axillary levels

I/II with removal of at least 8 nodes.

7 RADIOTHERAPY SPECIFICATIONS

7.1 Treatment Planning using Hybrid IMRT Technique

In the context of a Phase I/II prospective study, this protocol will test whole breast and regional nodal radiotherapy using a hybrid approach. Patients will receive whole breast radiotherapy in a prone position with a concomitant daily boost to the tumor bed over three weeks, a technique which has previously been evaluated in over 500 patients (NYU 03-30 and NYU 05-181) and has shown excellent tolerance and results. In addition, an intensity modulated radiation therapy (IMRT) technique will be used to deliver concomitant radiotherapy to axillary level III and supraclavicular lymph nodes. In patient Cohort A, axilliary levels I and II will also be part of the radiation target. Patients status post mastectomy will receive whole reconstructed breast/chest wall radiotherapy and nodal irradiation. A concomitant boost to the scar region will be offered only to patients without reconstruction.

7.2 Dose Specification

Patients will receive 15 daily radiation fractions of 2.7 Gy, Monday to Friday for three weeks, to the entire breast/chest wall and axillary level III and supraclavicular nodes with a daily concomitant boost of 0.5 Gy to the tumor bed, for a total daily dose of 3.2 Gy to the tumor bed (2.7 Gy + 0.5 Gy). The overall dose will be 40.5 Gy to the breast/chest wall, axillary level III and supraclavicular nodes, and 48.0 Gy to the tumor bed.

7.3 CT Simulation

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 3.75 mm or less. Prior to the patient lying prone on the table for scanning, the borders of the breast/chest wall fields will be marked with radio-opaque CT fiducial markers. These markers will be used to outline the breast/chest wall 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. Patients status post mastectomy will also be simulated prone with similar field borders. In addition, the chest wall scar will carefully be marked with radio-opaque CT fiducial markers.

Contouring of breast tumor bed, axillary level III nodes, supraclavicular nodes, indexed and contralateral breast tissue, ipsilateral brachial plexus, esophagus, heart, right and left lung, spinal cord, spinal cord plus 5 mm margin and right and left lobes of the thyroid will be

performed in order to guide beam arrangement and optimal normal tissue avoidance. In patients who have undergone pre-operative breast MRI, the breast glandular tissue will be contoured with the help of a radiologist co-investigator (Drs. Moy and Newburg), to better inform the design of the treatment fields.

The patient will be CT scanned and treated in the supine position if the patient cannot lie prone, or if the prone plan fails to satisfy the dose constraints specified in Section 7.5.6

7.4 Target Delineation

7.4.1 The physician designs tangent fields to encompass the whole breast. The PTVBreast is created from the 50% isodose line associated with the tangent fields. Technically 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 0.6 cm margin. The PTVBreast volume overlapping the heart and lung is excluded.

7.4.2 PTVTumor is the tumor bed, as identified on CT with an additional 1.0 cm 3D margin. Post-mastectomy PTVTumor is the tumor bed and depending on clinical judgement may or may not include the scar.

7.4.3 PTVTumor Eval is the PTVTumor cropped 0.6 cm from the skin.

7.4.3 PTVNodes includes axillary level III and supraclavicular lymph nodal regions as identified on CT with an additional 0.5 cm 3D margin.For patients in Cohort A PTVNodes will include axillary levels I-III and supraclavicular nodal regions as identified on CT with an additional 0.5 cm 3D margin, However, the PTV will not be expanded medially to better spare the esophagus.

7.4.4 PTVNodesEval is the PTVNodes cropped 0.6 cm from the skin.

7.5 Technical Factors

7.5.1 Dose calculations will include heterogeneity corrections.

7.5.2 Whole Breast fields – 3D tangents plus IMRT tangents

1. The prone position requires careful placement of the isocenter during planning to avoid collision between the gantry and the breast board, couch, or patient.
2. 3D tangents deliver nominally 67% of the whole breast dose, using 6 MV photons and including 2-3 cm flash. The fields are wedged and weighted to obtain a uniform dose distribution, normalized to allow approximately 105% maximum dose. 16 MV photons may be used for patients with large separations to reduce magnitude of dose maximum.
3. IMRT tangents deliver nominally 33% of the whole breast dose, using 6 MV photons and including 2-3 cm flash. The 3D tangents are used as a base for optimization.

7.5.3 Axillary level I-III and supraclavicular nodes (PTVNodes)

1. Three or more IMRT fields.

7.5.4 PTVTumor fields

1. Non-coplanar beam arrangement is encouraged, but not required.
2. Integrated boost within the IMRT tangents is allowed.
3. Electron therapy may be utilized.
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.
6. If the PTVTumor, as visualized in the beams-eye-view (BEV), is within 1 cm of the body surface, 1 cm of flash will be added to the field(s), painting fluence for IMRT fields.

7.5.5 IMRT Optimization

IMRT optimization is performed either by using the 3D tangents plan as a base plan for all IMRT fields, or by using a plan with all tangent fields (IMRT and 3D) as a base for the IMRT nodal fields. Regardless, a single plan is created with 3D breast tangent fields, IMRT breast tangent fields, boost fields if used, and IMRT axillary level III and supraclavicular nodal fields.

7.5.6 Dose Constraints

The dose constraints below represent acceptance criteria for the resulting dose distribution.

1. Target volume dose constraints:
    - PTVTumor: V 48 Gy $\geq$ 98%
    - PTVBreast: V 40.5 Gy $\geq$ 95%
    - PTVNodesEval: V 38.5 Gy $\geq$ 95%
2. Normal tissue dose constraints:
    a. Heart: V 5 Gy < 5%
    b. Ipsilateral lung: V 10 Gy < 20%
    c. Contralateral lung: V 5 Gy < 15%
    d. Spinal cord: 37.5 Gy maximum
    e. Spinal cord plus 0.5 cm margin: 40 Gy maximum
    f. Thyroid: contralateral lobe 15 Gy maximum
    g. Esophagus: V 30 Gy < 50%, 40.5 Gy maximum
    h. Ipsilateral brachial plexus: 42 Gy maximum
    i. Contralateral breast: Efforts should be made to keep the contralateral breast completely outside the primary beams

7.6 Portal Imaging

Portal images of orthogonal setup fields will be acquired on days 1, 2, and 3 then weekly thereafter. In addition, portal images will be acquired of each treatment field (except where geometrically impractical) during the first three days of treatment.

Cone beam CT (CBCT) of the nodal region will be acquired once on a day when orthogonal setup fields are imaged. No alignment adjustment will be made based on the CBCT.

8 DOSE MODIFICATIONS AND STOPPING CRITERIA

8.1 Dose Modification

In case of grade 3 acute skin toxicity occurring during the course of the 3-week treatment, the dose per fraction of the remaining treatment fractions will be reduced to 2 Gy/fraction until completion.

8.2 Stopping Criteria

Regional nodal recurrences occur in 1 - 5% of patients with early stage breast cancer who have undergone mastectomy or breast conserving therapy (Fisher, Anderson et al. 2002; Moran and Haffty 2002; Harris, Hwang et al. 2003). While most nodal recurrences occur within the first five years after treatment, nodal recurrences have been documented for more than twenty years after completion of treatment (Lukens, Vapiwala et al. 2009).

Based on this data, a stopping rule for regional node recurrences will be implemented with an evaluation after every 21 patients are observed for at least 1 year post treatment. The schema is described in Section 14. This rule allows early stopping based on an excess of incidence of regional node recurrences (greater than 5% of patients).

9 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

9.1 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. Breast edema and tenderness are additional possible acute side effects. Acute ($\leq$ 60 days after first day of treatment) and late toxicity ($>$ 60 days after first day of treatment) will be reported as scheduled in the study calendar. This study will utilize the descriptions and grading scales as described in *Common Terminology Criteria for Adverse Events v3.0 (CTCAE)* for acute toxicity and in the LENT/SOMA classification for late toxicities (appendix 1). Toxicities will be tracked using the Toxicity Tracking Form (appendix 2).

9.2 Expedited Adverse Event Reporting

Expedited AE reporting will utilize the descriptions and grading scales as described in *Common Terminology Criteria for Adverse Events v 3.0 (CTCAE)*. 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 and to the NYU Clinical Trials Office for reporting to the NYUCI Data Safety Monitoring Committee.

9.3 Routine Adverse Event Reporting Guidelines

The IRB Reportable Events Forms (available electronically at http://irb.med.nyu.edu/sites/default/files/irb2/app.reportable.event_.2012.03.07.docx) will be used for all adverse events

10 CORRELATIVE/SPECIAL STUDIES

10.1 Blood Collection for TGF-beta 1 Polymorphism Determination

Approximately 30 mL 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 specimen will be aliquoted and stored for future testing of other polymorphisms and other related research studies.

10.2 Lymphocyte Isolation, DNA Extraction, PCR Amplification and DNA Sequencing

The lymphocyte isolation and DNA extraction and DHPLC procedures will be performed as previously described (Iannuzzi, Atencio et al. 2002) using the Wave™ DNA Fragment Analysis System manufactured by Transgenomic. Any samples that appear, based upon the DHPLC screening, to be homozygous for either the –509C→T or +869T→C TGF-β1 polymorphism, will be subjected to DNA sequencing using an automated DNA sequencer.

10.3 Test Method

The products of the PCRs will be subjected to DHPLC analysis with the 96 well plate placed in the DHPLC apparatus. The Wave™ DNA Fragment Analysis System (Transgenomic), which will be used for this project, represents a complete unit for the automated DHPLC analysis of PCR products using a DNASep cartridge specifically designed for separation of DNA fragments. DHPLC is a high throughput technique in which large numbers of DNA samples can be rapidly screened for base sequence alterations and relies upon the physical changes in DNA molecules induced by mismatched heteroduplex formation during reannealing of wild type and mutant DNA.

In this method, a portion of a gene is amplified using standard PCR conditions and the products analyzed using DHPLC. Material from a homozygous sample will only form one species, the wild-type homoduplex. However, when the PCR products produced from a sample

heterozygous for a base sequence alteration are heated to 95°C, and then slowly cooled, the DNA strands separate and randomly reanneal to form a mixture of four species; a mutant homoduplex, two heteroduplexes and a wild type homoduplex. When mutant and wild-type DNA strands reanneal to form a heteroduplex, the molecule is physically altered. At the region of base pair mismatches, a "bubble" forms yielding a short linear region of single-stranded DNA. This structural alteration provides the basis for separation of heteroduplex from homoduplex species and ultimately identifies samples with mutant alleles. The basis of this technique is that by heating the column during separation, it is possible to partially denature the sample and elute the homoduplexes and heteroduplexes separately. Heteroduplexes, having a greater percentage of single-stranded DNA than homoduplexes in the mismatch region at a given temperature, will elute first from the column. Therefore, if the DNA sample does not possess a base sequence alteration, only homoduplexes will form and there will be only one peak on the chromatogram representing the homogenous nature of the fragment. A sample that contains a heterozygous mutation will appear as 2, 3 or 4 peaks representing the two homoduplex and heteroduplex populations.

It is also important to note that samples homozygous for a polymorphic allele can readily be detected using DHPLC by adding a roughly equal amount of DNA to the PCR from a sample known to be homozygous for the normal allele, thus essentially creating a potentially "heterozygous" sample.

The first step in the process to detect the –509C→T and +869T→C TGF-β1 gene polymorphisms will be to design primers for amplification of these regions following which the DHPLC buffer and temperature conditions will be optimized for detection of these polymorphisms. For each sample, the PCRs will be performed first without the addition of DNA from a sample that is known to be homozygous for the normal allele, and then, depending upon the DHPLC results, with the addition of known wild type DNA.

For samples in which DNA homozygous for the normal allele was not added, one peak in the DHPLC will indicate it is homozygous for either the wild type or polymorphic allele, whereas multiple peaks will signify it is heterozygous. Next, the PCRs will be performed a second time for all of the putative homozygotes to determine for which allele they are homozygous. Thus, DNA homozygous for the normal allele will be added to the PCR. If there is still one peak in the DHPLC, this will indicate that it is homozygous for the normal allele, whereas if there are multiple peaks, this will signify that the subject is homozygous for the polymorphic allele. All samples which appear to be homozygous for the polymorphic allele will be subjected to DNA sequencing to confirm this assignment.

An important step in this process will be a determination of the appropriate amount of homozygous normal allele DNA to be added to the PCR. Therefore, a titration will be performed with different concentrations of DNA to determine the amount for clearest detection of a sample homozygous for the polymorphic allele.

10.4 Denaturing High Performance Liquid Chromatography (DHPLC)

The mutation screening technique to be used in this study will be denaturing high performance liquid chromatography or DHPLC (Huber, Oefner et al. 1993; Huber, Oefner et al. 1993; Kuklin, Munson et al. 1997; Oefner and Underhill 1998). DHPLC is a robust technique that can be used to screen any gene in a large population for single nucleotide substitutions, as well as small deletions and insertions. Subjects that are either homozygous or heterozygous for a particular allele can both be identified using DHPLC. The advantage of DHPLC is that it enables the rapid, sensitive, accurate and inexpensive identification of polymorphisms and mutations in an automated fashion. Of greatest importance for this project is the evidence that DHPLC possesses a sensitivity and specificity for mutation detection approaching 100% (Liu, Smith et al. 1998; O'Donovan, Oefner et al. 1998; Arnold, Gross et al. 1999; Choy, Dabora et al. 1999; Gross, Arnold et al. 1999; Jones, Austin et al. 1999; Wagner, Stoppa-Lyonnet et al. 1999; Nickerson, Weirich et al. 2000; Taniguchi, Krishnadath et al. 2000) and that this approach possesses greater sensitivity than gel-based assays.

The sensitivity and accuracy of DHPLC for detection of genetic alterations was probably best demonstrated by a quality control study (Bernstein, Teraoka et al. 2003) performed by the WECARE (Women's Environment, Cancer and Radiation Epidemiology) Study Collaborative Group. There are four international laboratory centers (including the laboratory of Dr. Rosenstein, a co-investigator in this project) that are in the process of screening more than 2000 breast cancer patients for mutations and polymorphisms in a variety of genes associated with DNA repair and radiation responses. The purpose of this quality control study was to investigate the sensitivity and specificity of DHPLC for the detection of *ATM* mutations and polymorphisms. A panel of 19 DNA samples consisting of 4 unaffected controls, 2 heterozygous carriers, and 13 ataxia telangiectasia patients was supplied in a blinded fashion to each of the four laboratories and screened using DHPLC. Prior screening by Single-Strand Conformation Polymorphism (SSCP) and Protein Truncation Test (PTT) had detected 19 mutations among these samples; 18 of these were detected by DHPLC, an efficiency of 95%. In addition to these 18 mutations, DHPLC screening identified 6 new mutations not detected in prior screening. No mutations were identified in control samples by DHPLC, nor were there excess mutations identified in any ataxia telangiectasia patient or carrier sample, suggesting a low rate of false positives.

10.5 Coding of Samples

Specimens will be given a Study ID number and will be otherwise de-identified for privacy protection. The study data manager will keep the list of samples. Any residual blood specimen after performing the listed laboratory studies will be destroyed.

11 INVESTIGATOR RESOURCES

11.1 Qualifications

Drs. Perez and Huppert and will be responsible for the accrual and care of study patients. Victor Ty 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. Victor Ty will also provide the research nursing component of the study, including performing the QOL assessment of the patients.

Drs. Rosenstein and DeWyngaert provide the necessary expertise in radiobiology and physics to conduct the proposed study. Dr. Goldberg will oversee the statistical analyses and collaborate in the interpretation and reporting of the study results. Benjamin Levinson will participate in the ongoing monitoring of this study and statistical analyses.

11.2 Use of NYU Facilities

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

11.3 Conflict of Interest

There are no conflicts of interest to declare.

12 STUDY CALENDAR

Study Procedure	Pre Treatment	Weekly	Last week	Post Treatment (day 45 - 60)	Post Treatment (once/year)
History & Physical	X				
Mammogram and/or breast MRI[a]	X				X[b]
Lumpectomy pathology report	X				
BREAST-focused exam, KPS	X	X		X	X
Lymphedema assessment	X		X		X
Blood for TGF-BETA Polymorphisms and other related research studies	X		X[c]		
Quality of Life Questionnaires[d]	X		X	X	X
LENT/SOMA assessment[e]					X
Thyroid Testing (TSH, T_4)	X				X

a. Standard mammogram or MRI for both breasts.
b. At each follow-up visit beginning 1 year after completion of radiation treatment a non invasive measurement of fibrosis in the treated breast will be performed using clinical breast exam.
c. Last day of treatment, after last dose of radiation
d. QOL will be assessed using the RTOG validated self-assessment questionnaires QLB & QLF (see Appendix 3) at baseline, week 3, day 45 - 60 and 2-yr follow-ups.
e. Patients will be seen after completion of treatment at day 45 - 60 and then yearly for 5 years total follow up to assess long term sequelae by LENT/SOMA scale.

13 DATA REPORTING / REGULATORY CONSIDERATIONS

13.1 Monitoring Plan

An internal Data and Safety Monitoring Committee (DSMC) of the NYUCI 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 planned interim analyses described in Section 9 according to the NYUCI DSMC Charter.

13.2 Stopping Rules (for the individual patient and for the study as a whole)

If safety concerns arise, the DSMC will identify these concerns and recommend modification or termination of the clinical trial. In case of grade 3 acute skin toxicity, the dose per fraction of the remaining treatment fractions will be reduced to 2 Gy/fraction until completion. The clinical trial will be stopped early if regional nodal recurrence is greater than expected (5% of patients) as described in Section 14.

13.3 Data Management

Data will be entered into the Oracle Clinical database and maintained at NYUSOM under the direction of staff in the BDM core.

THE ORACLE SYSTEM PROVIDES AUDIT trails that track creation and modification of records that includes userID and time stamp. Once entered, the data are 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 are 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 are 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 userID 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.

13.4 Confidentiality

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

secure links to the BDM core at NYU School of Medicine. Patient records will be made available for inspection to auditing agencies to satisfy regulatory requirements.

14 STATISTICAL CONSIDERATIONS

14.1 Endpoints/Objectives:

The primary objectives of this study are to:

1. To evaluate feasibility of prone IMRT to breast, level I- III (includes Cohort A) and supraclavicular nodes (physics and dosimetry parameters).
2. To estimate acute toxicity of prone IMRT to breast, level I- III (includes Cohort A) and supraclavicular nodes

Secondary objectives are to:

1. estimate the incidence of re-simulation to improve dosimetry after initial prone set-up
2. evaluate changes in QOL of patients assessed at baseline and after treatment
3. estimate incidence of late radiation toxicity (e.g., lymphedema, fibrosis and telangiectasia) and to examine genetic determinants of breast fibrosis

Exploratory objectives include:

Estimation of local recurrence rates; estimation of median disease-free survival; estimation of median time to progression, and estimation of median overall survival time.

14.2 Statistical Considerations, Sample Size and Interim Analysis Plans

14.3 Statistical Analysis

Descriptive statistics will be provided for all demographic and disease characteristics of patients at baseline using frequency distributions for qualitative variables and summary statistics (e.g., median, mean, etc.) and graphical displays (e.g., boxplots) for quantitative variables.

14.3.1 Primary Endpoints

The primary outcome of this study is the proportion of patients with acute toxicity greater than grade 2 (Skin toxicities grade 3 and above) occurring within 60 days after first day of treatment. This rate will be estimated with an exact 95% confidence interval. Treatment feasibility will be evaluated for each patient by the ability to meet all physics dose constraints as outlined in section 7.5.6. The proportion of patients who meet the constraints will be estimated with an exact 95% confidence interval.

[redacted]

[redacted]

14.4 Accrual estimates

Estimated number of eligible patients for this trial is 4 - 6 patients per month. Since the recent publication of Giuliano AE (JAMA, 2011 Feb 9; 305(6):606-70), fewer axillary node dissection are being performed nationwide. Consequently, it is expected that the accrual to study NYU 09-0623 may slow down, because of fewer eligible patients. We expect to accrue 104 patients over 5 years.

14.5 Sample Size Considerations/Interim Analysis

The primary endpoint for the estimation of sample size is the proportion of patients with acute skin toxicity of greater than grade 2 occurring within 60 days after first day of treatment. Overall, the regimen will be considered to be unacceptable if more than 5% of patients have acute skin toxicity of greater than grade 2. With 104 patients enrolled in this study, we will have 80% power at a two-sided overall alpha level of 0.05 to test the null hypothesis that the proportion of patients with acute skin toxicity of greater than grade 2 is 0.05. With one interim analysis when 52 patients are evaluable for acute skin toxicity, Table 9 below provides the stopping boundaries for the alternative hypothesis that this proportion is greater than 0.10.

Table 9 - Stopping Boundaries for the Proportion of Patients with Acute Skin Toxicity > Grade 2 based on Pocock Boundaries, Overall 2-sided α = 0.05, Power =80%. H_0=0.05; H_1=0.10 [calculations from EAST 5.2, Cytel, 2008].

Analysis	Number of Patients	Reject H_0=0.05 Proportion observed	Reject H_0=0.05 z-statistic	Reject H_0=0.05 p-value
Interim	52	≥ 0.1153	≥ 2.57	≤ 0.031
Final	104	≥ 0.097	≥ 2.201	≤ 0.028

Additional monitoring will be carried out to estimate the proportion of patients with > grade 2 lymphedema. To test the null hypothesis that this proportion is 0.10 against the alternative that the proportion is 0.19, with 2-sided overall alpha level of 0.05 and power of 78%, at the time of the first interim analysis for skin toxicity, we can reject the null hypothesis if the observed proportion is ≥0.19; at the final analysis, we can reject the null hypothesis if the observed proportion is ≥0.165 based on Pocock boundaries. There is no adjustment for these two parallel analyses.

With 104 patients, we can estimate the exact 95% confidence interval for the proportion of patients for whom this procedure is feasible with a lower limit of 0.89 or greater if the observed proportion of patients is 0.95 or greater [calculations from PASS, NCSS, LLC (2008), J. Hintze, Kaysville, UT].

Safety Stopping Rule; In addition, regional nodal recurrence will be monitored as the study progresses. If we enroll 104 patients over a three year period with follow-up of one year after the last patient is entered, the regimen will be considered ineffective if the null hypothesis that the proportion of regional nodal recurrences is 5% is rejected at an interim review.

Regional nodal recurrence is defined as recurrence within the axilla, level III or supraclavicular nodes, documented by PET-CT imaging and/or biopsy.

With 5 interim looks (every 21 patients who are followed for at least 1 year), with Pocock stopping boundaries, the trial would be stopped if the observed numbers of regional nodal recurrences are greater than or equal to 1 of the first 21 patients, and greater than 2, 4, 6, and 8 respectively at the second – fifth looks with an overall 1-sided alpha level of 0.05 and power of 0.62 [Calculations from EAST 5.2, Cytel, Inc., 2008].

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APPENDICIES

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 – 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 ☐ 45-60 day F/U

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

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

☐ *Port Film or image review*

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

Progress note: _____

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

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

Attending Signature: _____ **Date:** _____

APPENDIX 3 – QUALITY OF LIFE QUESTIONNAIRES

NYU 09-0623 Phase I-II Study of Prone Accelerated Breast and Nodal IMRT
Quality of Life Questionnaire - Baseline

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

Patient Initials [ ] , [ ] [ ] (Last, First, Middle)

Patient Study ID [ ][ ][ ][ ][ ][ ][ ][ ][ ]

Participants should complete this questionnaire at baseline (after consent). 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 _____

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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)

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.

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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

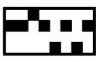
No pain — Pain as bad as you can imagine

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

Patient Study ID

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

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

Specify other problems:

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

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

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

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

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

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

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

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

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

Thank you for completing this questionnaire!

NYU 09-0623 Phase I-II Study of Prone Accelerated Breast and Nodal IMRT
Quality of Life Questionnaire - Follow-up

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

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

Patient Study ID ☐☐☐☐☐☐☐☐☐

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 End of RT O Day 45-60 O 2 years O

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 End of RT O Day 45-60 O 2 years O

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 End of RT O Day 45-60 O 2 years O

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 End of RT O Day 45-60 O 2 years O

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 End of RT O Day 45-60 O 2 years O

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 End of RT O Day 45-60 O 2 years O

RTOG PQ

NYU 09-0623 Phase I-II Study of Prone Accelerated Breast and Nodal IMRT

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 day of radiation therapy O
- O Form QLP: 45- 60 days after start of radiation therapy O
- O Form QLF: 2 years after radiation therapy O

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: → ●