Official Title:	Accelerated Radiation Therapy After Surgery in Treating Patients With Breast Cancer
NCT number:	01417286
Document Type:	Study Protocol and Statistical Analysis Plan- page 30, 31, 32, 33
Date of the Document:	02/15/2017

[redacted]

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Accelerated, Hypofractionated Post-Mastectomy Radiation Therapy in Women with Breast Cancer: A Phase II Trial

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Supported by: N/A

EXPIRES

OCT 17 2019

Approved by the Rutgers IRB

APPROVED

OCT 18 2018

Approved by the Rutgers IRB

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

2DXRT	Conventional External Beam Radiotherapy
3D-CRT	3-Dimensional Conformal Radiation Therapy
AE	Adverse Event
AJCC	American Joint Committee of Cancer
AP	Anterior-Posterior
APBI	Accelerated Partial Breast Irradiation
AWBI	Accelerated Whole Breast Irradiation
BCS	Breast Conservation Surgery
BCT	Breast Conserving Treatment
BCT+RT	Breast Conserving Therapy followed by Whole Breast Irradiation
BCTOS	Breast Caner Treatment Outcome Scale
BEV	Beam's Eye View
CBC	Complete Blood Count
CBCT	Cone-Beam Computed Tomography
CED	Cavity Evaluation Device
CINJ	Cancer Institute of New Jersey
CINJOG	CINJ Oncology Group
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
DCIS	Ductal Carcinoma In Situ
DSMP	Data Safety Monitoring Plan
DVHs	Dose Volume Histograms
E	Elsewhere Failure (local failure several cm from primary site)
EBRT	External Beam Radiation Therapy
EORTC	European Organization for Research Treatment in Cancer
FDA	Food and Drug Administration
fx	fraction
Gy	Gray
HDR	High Dose Rate
HCI	Huntsman Cancer Institute
HIPAA	Health Insurance Portability and Accountability Act
IBRT	Ipsilateral Breast Tumor Recurrence
IBTR	Ipsilateral Brest Tumor Recurrence
IRB	Institutional Review Board
IMRT	Intensity Modulated Radiation Therapy
LFS	Local Recurrence-Free Survival
LR	Loco-regional
MR	Marginal Recurrence
NCI	National Cancer Institute
NIH	National Institutes of Health
NSABP	National Surgical Adjuvant Breast and Bowel Project

OHRP	Office of Human Research Protection
OHRS	Office of Human Research Services
PBI	Partial Breast Irradiation
PD	Progressive disease
PHI	Protected Health Information
PI	Principal Investigator
PTV	Planning Target Volume
RL	Right-Left
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
RWJUH	Robert Wood Johnson University Hospital
SAE	Serious adverse event
TR	True Recurrence
TR/MM	True Recurrence/Marginal Miss
WBI	Whole Breast Irradiation

1. Purpose/Specific Objectives

1.1 Primary Endpoint:

The results from this novel fractionation scheme will be comparable to published locoregional control outcomes for conventionally fractionated chest wall irradiation.

1.1.1 Acute toxicity and late toxicity using previously published toxicity scales.

1.2 Secondary Endpoint(s)

1.2.1 Freedom from local failure and freedom from regional failure.

1.2.2 To identify co-variates responsible for poor cosmetic outcome in women with reconstructed chest walls when treated with accelerated, hypofractionated radiotherapy.

1.2.3 To correlate toxicity, local control and plastic surgical reconstruction failure with molecular markers

2. Background and Significance

2.1 Clinical Background

The treatment of breast cancer was dominated by radical mastectomy or modified radical mastectomy of the affected breast prior to the 1970's. This consists of an en bloc removal of the breast, muscles of the chest wall, and contents of the axilla and was advocated as the most appropriate local therapy for women with early stage breast cancers. However, the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 and other studies, found equivalent survival and local control rates among women treated with either mastectomy or lumpectomy followed by whole breast irradiation (WBI) [1, 2]. The NSABP B-06, which compared mastectomy to lumpectomy with and without radiotherapy in women with invasive carcinoma, found a 39% local recurrence rate at 20 years with lumpectomy alone, which was decreased to 14% with the addition of radiotherapy[1]. Several other randomized studies demonstrated equivalent long term survival and disease free survival rates in patients treated by breast conserving therapy (BCT) compared to mastectomy[2-5]. Additional randomized studies comparing lumpectomy alone to lumpectomy and radiation clearly demonstrate a 3-fold reduction in local relapse with the use of radiation following breast conserving surgery[6-10]. Nonetheless, many women are not candidates for breast conserving therapy due multicentric disease, inability to achieve adequate clear surgical margins, diffuse microcalcifications, or locally advanced/inflammatory disease. In these women, mastectomy remains the standard of care.

2.2 Rationale for Post-Mastectomy Radiation Therapy (PMRT)

The efficacy of irradiating the chest wall and draining lymph nodes after mastectomy in improving locoregional control has been firmly established by multiple older trials comparing mastectomy alone to mastectomy with postoperative radiation[11-17]. These trials typically used outdated radiation techniques and equipment that produced orthovoltage x-rays. Orthovoltage x-rays produce suboptimal dose distributions that would never be used for therapy in the modern context. Because of these reasons, the relevance of these older trials is limited in the context of modern radiation therapy, but they adequately demonstrated two important facts 1) that post-mastectomy RT can effectively reduce the burden of

residual locoregional disease, and that 2) in terms of treatment volume, radiation therapy is more comprehensive and more "radical" than even the most radical surgery. Notably, these trials did not demonstrate improvements in survival endpoints.

The locoregional effects of adjuvant systemic therapy alone (without radiation) can be studied through those trials of systemic therapy versus nil that have reported patterns of failure[18-32]. In summary, data demonstrating an improvement in locoregional control with systemic cytotoxic chemotherapy is somewhat inconsistent. However, the most recent EBCTCG meta-analysis of systemic therapy trials reported statistically fewer isolated local relapses in patients receiving polychemotherapy (recurrence rate ratio of 0.63 and 0.70 for women <50 and 50-69, respectively)[33]. However, it appears that increasing the intensity or agents of chemotherapy does not improve locoregional control over standard chemotherapy[34-39]. In contrast, adjuvant tamoxifen seems to improve locoregional control rather consistently, reducing the likelihood of recurrence on average by about one-half[18, 20-22, 31]. This was also demonstrated in the most recent EBCTCG meta-analysis cited above, which showed an isolated local recurrence rate ratio of 0.47 with tamoxifen versus without[33]. These observations, along with the demonstrable improvement in survival with systemic agents, call into question the relative benefit of PMRT in improving locoregional and survival endpoints in patients who have received or will receive systemic therapy.

Several trials have studied the efficacy and added benefit of post-mastectomy RT in the presence of systemic therapy[40-52]. The most definitive of these have come from the Danish Breast Cancer Cooperative Group[48, 49] and the British Columbia Cancer Agency[50]. In addition to these, the updated findings of the Early Breast Cancer Trialists Colloborative Group (EBCTCG) meta-analysis of postoperative radiation trials discussed later[53], have decisively altered practice and reaffirmed the role of post-mastectomy RT in modern breast oncology.

The Danish Breast Cancer Cooperative Group's protocol 82b randomized premenopausal women with high-risk breast cancer after modified radical mastectomy (total mastectomy and level 1 and 2 axillary dissection) to either 9 cycles of CMF chemotherapy or to 8 cycles of CMF chemotherapy and radiation therapy to the chest wall and regional nodes between the first and second cycles of chemotherapy[48]. High risk status was defined as positive lymph nodes, tumor size greater than 5 cm, or invasion of the skin or pectoralis fascia. Radiation therapy was delivered to a total dose of 50 Gy in 25 fractions or 48 Gy in 22 fractions using an anterior electron field to treat the chest wall and internal mammary nodes (IMs) and a matched anterior photon field to treat the supraclavicular, infraclavicular and axilla lymph nodes. A posterior axillary photon field was used in patients with a large anterior-posterior separation. Over 92% of all patients were treated with megavoltage equipment. The study enrolled 1,708 patients between 1982-1989. With a median follow-up of 114 months, the irradiated group demonstrated statistically significant improvements in locoregional recurrence (32 vs 9%), disease-free survival (35 vs 48% at 10 years), and overall survival (45 vs 54% at 10 years). Notably, over half of all locoregional recurrences were on the chest wall.

In the companion 82c protocol[49], postmenopausal women younger than 70 with high-risk breast cancer (defined as in 82b) were randomized after modified radical mastectomy to receive either 30 mg of tamoxifen daily for one year beginning 2-4 weeks after surgery alone or with concurrent radiation therapy delivered to the chest wall and draining lymph nodes. Radiotherapy details were identical to the 82b trial. Similar to the 82b trial, over 90% of women were treated with megavoltage equipment. Between 1982 and 1990 a total of 1375 patients were recruited and followed for a median time of 10 years.

As in the 82b study, the irradiated group demonstrated statistically significant improvements in locoregional recurrence (35 vs 8%), disease-free survival (24 vs 36%) and overall survival (36 vs 45%). Again, the majority of locoregional recurrences were on the chest wall, but the proportion of recurrences at all locoregional subsites was lower with PMRT than without. The Danish investigators deserve much praise for these well-designed efforts, which although not without flaw (as discussed below), clearly demonstrated that in certain patient subsets, aggressive locoregional control could translate into improved survival--independent of systemic therapy.

The British Columbia trial enrolled 318 node-positive premenopausal breast cancer patients and randomized them after modified radical mastectomy to either radiation therapy or no additional locoregional therapy[50]. Both groups received adjuvant CMF chemotherapy for 12 (first 80 patients) or 6 months. Radiation therapy was delivered to the chest wall to a dose of 37.5 Gy in 16 daily fractions through opposed tangential photon fields. The supraclavicular and axilla nodes were treated with an AP field and a posterior axillary field, as is conventionally done, with a target midaxilla dose of 35 Gy. Bilateral IMNs were treated with an additional anterior field to a dose of 37.5 Gy in 16 fractions. All treatments were delivered with cobalt machines, between cycle 4 and 5 of chemotherapy. After a median follow-up of 20 years, the 20-year survival free of locoregional disease developing before systemic was 61% in the chemotherapy alone arm and 87% in the irradiated group. The irradiated group had significantly higher 20-year event-free survival (25 vs 38%), systemic disease-free survival (31 vs 48%), breast-cancer specific survival (38 vs 53%), and overall survival (37 vs 47%). There were slightly more non-breast cancer deaths in the irradiated group (9% vs 4%, p=0.11). There were 3 cardiac deaths (2%) in the irradiated group versus one (0.6%) in the control group (p=0.62), and 9% of patients in the irradiated group developed arm edema compared with 3% in the control group (p=0.035).

The Early Breast Cancer Trialists' Colloborative Group has collected primary data from every randomized trial of adjuvant radiotherapy in breast cancer, and periodically reports the ongoing analyses on the benefits and risks of radiation therapy in these patients. The most recent report from 2005 reviewed data on 9933 patients enrolled on 25 trials of PMRT, all of which were unconfounded by the use of systemic therapy[53]. Node-positive patients who had axillary clearance and received radiation therapy after mastectomy had a 5-year locoregional recurrence rate of 6%, compared to 23% for unirradiated controls (15-year rates were 8% vs 29%). In every large trial of PMRT in node-positive women, radiation therapy produced comparable proportional reductions in local recurrence in all women irrespective of age or tumor characteristics and regardless of time period--indeed a powerful demonstration of the efficacy of radiation therapy in reducing local recurrence.

Because the proportional reductions in local failures were similar across heterogeneous patient groups, the absolute reductions in local recurrence were variable and dependent on the *control risk*, ie larger reductions were seen in subsets with greater risk and smaller reductions were noted in women with lower risk. For patients with a control risk of local recurrence that exceeded 10%, the addition of RT improved local recurrence irrespective of systemic therapy (chemotherapy and/or hormonal therapy). Importantly, the overall 17% absolute improvement in *5-year* local control translated into a 5.4% absolute improvement in *15-year* breast cancer mortality (60.1% vs 54.7%, 2p=0.0002)[53]. In terms of absolute effects, a 4:1 ratio of benefit was seen, whereby a 20% absolute reduction in 5-year local recurrence resulted in a 5% absolute reduction in 15-year breast cancer mortality. Furthermore, women with node-positive disease who were irradiated after mastectomy and

axillary clearance experienced a 4.4% absolute improvement in all-cause mortality over controls (2p=0.0009), a difference not detected in the prior EBCTCG report published in 2000[54].

In their review of the EBCTCG data, Punglia et al note that treatments that had little or no effect on decreasing the 5-year local recurrence rate produced no benefit in 15-year breast cancer mortality[55]. They also draw attention to a subgroup analysis in the report which showed that the use of radiation therapy after mastectomy in node-positive patients improved 15-year survival only in patients who also received adjuvant systemic therapy and not in patients who were treated with mastectomy alone. This lends credence to the concept of an independent yet cooperative effect of adjuvant locoregional therapy and adjuvant systemic therapy.

Updated data from the EBCTCG was presented at the 2007 annual meeting of the American Society of Clinical Oncology[56]. In contrast to prior reports, the subgroup of patients with 1-3 positive lymph nodes demonstrated statistically significant improvements in 15-year breast cancer mortality (50.9% vs 43.3%, 2p=0.002) and all-cause mortality (56.1% vs 50.9%, 2p=0.05) with PMRT. In addition, a study of prognostic factors for 5-year local recurrence risks identified tumor grade as a highly significant factor, even when controlling for other known risk factors. These findings will undoubtedly be expounded upon in the next full report from the EBCTCG trialists.

The value of the EBCTCG overview cannot be overstated. However, the relevance of its findings may be limited by the inclusion of trials that used fractionation schemes, treatment machines, and treatment volumes that are antiquated by today's standards, as well as by the other limitations inherent to all meta-analyses. Attempts to correct for these limitations suggest that the EBCTCG results may actually *underestimate* the benefit of PMRT. For example, Van de Steene et al conducted a similar meta-analysis and demonstrated improved odds ratios for survival with PMRT by excluding trials that began before 1970, trials with small sample sizes (<600 patients), trials with poor survival rates (crude survival less than 80%), and trials that used outdated fractionation schemes[57]. Similary, Whelan et al performed a meta-analysis of PMRT trials that specifically included systemic therapy in both the control and experimental groups[58]. As with the EBCTCG study, the addition of RT led to reductions in the risk of any recurrence (odds ratio=0.69) and death (odds ratio=0.83). Finally, Gebski et al performed a meta-analysis in which they carefully attempted to control for the quality of radiation delivery in PMRT trials. The authors defined optimal dose as 40-60 Gy delivered in 2 Gy fractions (non-conventional fractionation schemes were converted to 2-Gy equivalents using bioeffective dose calculations) and appropriate treatment volumes as both chest wall and regional lymphatics (but not necessarily inclusive of the internal mammary nodes[IMNs])[59]. The data from the EBCTCG meta-analyses was then reanalyzed applying these criteria. Locoregional control was greater for trials with optimal dose and volume (80%), compared to those with suboptimal dose (70%) or volume (64%). An improvement in breast cancer mortality was limited to those trials that used appropriate doses and fields for irradiation (6.4% absolute increase in survival, p<0.001).

It is worth noting that the survival improvements demonstrated in the collective Danish and British Columbia experiments are among the most remarkable improvements in survival ever reported for any adjuvant therapy in a randomized trial. Taken together, these studies show that certain patient cohorts have a high risk for locoregional recurrence that cannot be addressed by systemic therapy alone. Reducing the rates of locoregional failure can result in improved survival, perhaps because persistent or recurrent locoregional disease

serves as a source of distant metastases and subsequent death. The collective PMRT data seems to indicate that adjuvant locoregional therapy and adjuvant systemic therapy independently benefit patients on the principle of spatial cooperation, with the former addressing microscopic locoregional residual disease and the latter addressing systemic micrometastases.

2.3 Altered Fractionation in Breast Cancer

In standard chest wall irradiation, daily fraction sizes of 180 cGy or 200 cGy are commonly used and are described as "conventional". The rationale for conventional fractionation and the relationship between fraction size and tissue response is well described by the α/β ratio in the linear quadratic model of fractionation sensitivity[60]. In this empiric model, "late-reacting" normal tissues such as fibroblasts and neurons have a low α/β ratio (2-5 Gy) and are very responsive to increases in fraction size, while "acutely-reacting" normal tissues such as intestinal epithelium have a high α/β ratio (>7 Gy) and are less responsive to changes in fraction size. The biological effect of a given fractionation scheme size is related to the α/β ratio by the equation:

Effect = E = n(ad + bd2) where

d = dose/fraction

n = # identical fractions

Estimates of the α/β ratio for squamous cell carcinomas of the head and neck and cervix uteri are > 7 Gy[61]. For this reason, the α/β ratio for tumor control probability is taken to be 10 Gy by convention, while the α/β ratio for normal tissue effects is taken to be 3 Gy. Different fractionation schemes can be equated using the relationship:

(nd/n1d1) = (a/b + d1)/(a/b + d) where

n = standard number of fractions

n1 = equivalent number of fractions in altered schedule

d = standard dose/fraction

d1 = desired dose/fraction

Although relatively high cumulative doses of radiation are needed for tumor control, the daily fraction size has to be respectful of the fraction sensitivity of normal tissues in the treated volume. Accounting for these assumptions, increases in fraction size have to be compensated for by reductions in cumulative radiation dose, which typically are insufficient for tumor control. As a result, daily fractions of 1.8 to 2 Gy are delivered over 4-8 weeks to reach a cumulative dose of 45-85 Gy.

The above discussion ignores the potential effect of cellular proliferation that may occur during a course of radiation therapy. Although commonly ignored because of the uncertainty of the relevant variables, a correction can be introduced into the above equation for this factor[62]:

BED = nd [1+d/α/β [(ln2)T / (α)Tpot]

BED = biological effective dose

d = dose/fraction

n = # of identical fractions.

T = overall treatment time after initial time lag to proliferation

Tpot = potential tumor doubling time.

Rosenstein et al in their publication comparing several PBI fractionation schemes used a Tpot value of 13 days, an initial time lag of 14 days, and an α value of 0.3[62].

In contrast to these assumptions for most epithelial tumors, the α/β ratio for breast tumors may be much lower than the conventional assumption of 10 Gy. In vitro experiments in human breast carcinoma cell lines have suggested an α/β ratio of about 4 Gy[63, 64]. An interesting set of clinical dose-response data for inoperable and locally recurrent breast cancer was published in 1952[65], and reanalyzed to fit the linear-quadratic model[60]. The point estimate for the α/β ratio from this data set was 4-5 Gy. Based on this information, the Royal Marsden Hospital and the Gloucestershire Oncology Centre collaborated in a randomized clinical trial to evaluate the relative toxicity and efficacy of different whole-breast fractionation schemes[66, 67]. A total of 1410 women were randomized to one of three arms between 1986 and 1999:

1. 50 Gy in 25 fractions over 5 weeks
2. 39 Gy in 13 fractions (3.0 Gy/fx) over 5 weeks
3. 42.9 Gy in 13 fractions (3.3 Gy/fx) over 5 weeks.

The overall treatment time was kept constant in all three arms. In the experimental arms, 5 fractions were delivered over 2 weeks. All patients were treated in the supine position. The primary endpoint was late breast change. Local control was a secondary endpoint. About 75% of patients were offered a conventionally fractionated electron boost to the lumpectomy cavity. The protocol did allow treatment of regional lymph nodes (supraclavicular and axillary) with additional radiation fields, and these were used in 20% of the patients. Fourteen percent of patients received CMF chemotherapy.

The 39 Gy arm was less likely to develop late radiation change compared to both 42.9 Gy and 50 Gy[67], but also had worse local control than the 42.9 Gy arm[66]. Interestingly, the 42.9 Gy arm, which had 3.3 Gy fractions, was not significantly different from the 50 Gy arm for both development of any late radiation change and local control. The α/β ratio for any late breast change was 3.6 Gy and the α/β ratio for tumor control was 4 Gy. The similarity of these two estimates is striking and serves to validate the hypofractionated regimens commonly being used for APBI. Finally, it must be noted that none of the 290 patients who were treated to the axilla and supraclavicular areas developed brachial plexopathy. A major limitation of the study is the use of a conventionally fractionated boost of 14 Gy in 7 fractions. How this boost interacted with the altered fractionation effects is unclear. It also unfavorably impacts the convenience of the experimental arms.

The Canadian NCI randomized 1234 patients (1993-1996) with T1 and T2 tumors with negative margins and pathologically negative nodes (on level 1 and 2 dissection) to:

1. 50 Gy in 25 fractions (2 Gy/fx) over 35 days or
2. 42.5 Gy in 16 fractions (2.66 Gy/fx) over 22 days[68].

Notably, women with breast separations greater than 25 cm were excluded. Dose was prescribed to the 1/3rd point, and homogeneity within 7% was required. Lumpectomy bed boosts and treatment to regional draining lymph nodes was not allowed. With a median follow-up of 69 months, local recurrence-free survival (LFS) was equal (97.2% vs 96.8%), and there was no difference in OS and DFS. Cosmesis was identical with excellent or good scores at 3 and 5 years in 77% of patients in both groups. Toxicities were also comparable. Grade 2 and 3 toxicities were negligible. At 5 years, 87% of women in the experimental arm had no skin toxicity, and 66% of women had no subcutaneous toxicity, compared with 82% and 60% in the control arm, respectively. A major limitation of the Canadian study is the lack of a lumpectomy boost, which significantly improves local control[69]. The patients eligible for the study had low risk for disease recurrence, limiting the general scope of the results. In addition, the regional nodes were untreated, making the safety of irradiating a larger volume unclear.

Other efforts at whole breast hypofractionation include the report from the Department of Radiation Therapy of the Necker Hospital in Paris, France[70]. These investigators randomized 230 women to 45 Gy in 25 fractions or 23 Gy in 4 fractions (5 Gy days 1 and 3, 6.5 Gy days 15 and 17). They included patients with intact breasts and postmastectomy chest walls. 79% had surgery (mastectomy or lumpectomy + Ir-192 implant (20 Gy)), while the rest had RT alone with chemotherapy (21%).

With a minimum follow-up of 4 years (patient enrolled 1982-1984), the local failures rates were 4/56 (7%) in the conventional arm vs 2/45 (4%) in the hypofractionation arm. They reported more fibrosis (18% vs 9%) and telangiectasia (14% vs 9%) in the hypofractionation arm, but no statistics were reported. Given the heterogeneity of the patient population, lack of formal statistics, and outdated radiation technique, the results of this report are not interpretable in the modern context.

Ortholan and colleagues conducted a prospective single arm study of whole breast hypofractionation in Nice, France[71]. The authors acknowledge the uncertainty of the α/β ratio, estimating a range of 4-10 Gy, they used 6.3 Gy for their calculations. Based on this, a single weekly fraction of 6.5 Gy was presumed to equal 5 fractions of 2 Gy. They delivered a total dose 32.5 Gy in 5 weekly fractions of 6.5 Gy delivered via cobalt unit or 6 MV photons. 71.5% of patients had an intact breast, 28.5% of patients had mastectomy. 31.8% of patients were treated to the internal mammary and supraclavicular areas. In 33% of patients with an intact breast, a boost of 6.5 Gy times 1 or 2 (weekly) by electrons or a brachytherapy boost (10-15 Gy) was delivered.

Acute toxicity in the form of grade 1 and 2 erythema was reported in only 26.5% of patients, and Grade 3 late effects/fibrosis in only 5.3%. With a median follow-up of greater than 5 years, only 3 local failures were reported (2.3%). The trial is limited by the mix of patients and the older techniques, but seems to indicate that hypofractionation is safe.

Rodger et al at the Western General Hospital, Edinburgh, UK published a retrospective review of late effects in post-mastectomy patients before and after a policy change in their

department, changing from 4.5 Gy times 10 fractions over 4 weeks to 2.25 Gy times 20 fractions, after a simple mastecomy. All patients were treated to the regional lymph nodes, and dose to supraclavicular and axillary areas was 4.25 Gy times 10 in the hypofractionation arm. 484 patients were treated with the 10 fraction regimen during 1/1979 and 3/1982, while 289 patients were treated with the 20 fraction regimen from 4/1982-12/1984. There were more late effects in the hypofractionation arm: grade 3-4 skin effects on the chest wall 29/79 (37% vs 0 (0/92)), subcutaneous effects 66% vs 10% on the chest wall and 29% vs 14% in the axilla. Grade 2-3 arm edema was also higher 29% vs 14%, as were rib fractures 52% vs 11%. Two plexopathies were seen in each group. The two regimens produced equal disease control.

Although not a randomized comparison, the outcomes reported in this study are instructional, especially in light of the linear-quadratic model, which was not available to the clinicians in Edinburgh. Assuming an α/β ratio of 4 Gy, the patients received a whole breast dose equal to 58 Gy in 2 Gy fractions, (Gy4=87.65, while 50 Gy in 2 Gy=75 Gy4). Assuming α/β ratio of 3, the patients received a whole breast dose of 62 Gy in 2 Gy fractions. Clearly the patients were overtreated. A simple correction of limiting the total fraction number to 8 fractions (instead of the 10 delivered) on the hypofractionation arm, would produce late effects comparable to 50 Gy in 2 Gy fractions[72].

Bates and colleagues at the St. Thomas' Hospital in London reported 10-year results of a prospective trial of post-mastectomy radiotherapy delivered in either 2 or 3 fractions per week[73]. This randomized trial was initiated in 1968 and compared two different fractionation schemes after a simple mastectomy (in most patients, although some had axillary dissection).

In one arm: the chest wall received 37 Gy in 12 fractions (3.08 Gy/fraction) over 28 days (with 70 kVp xrays) along with 45-51 Gy to the cervico-axillary areas (with Co-60) in 12 fractions and 42 Gy to internal mammary (IMs) nodes at a depth of 3 cm also over 12 fractions (with mixed beam (1:1) Co-60 and Cs-137 teletherapy). The other randomized arm treated the chest wall to 31.5 Gy in 6 fractions (5.25 Gy/fx) over 18 days, the cervico-axillary areas to 31-35 Gy, IMs to 28 Gy at depth of 3 cm with identical technique.

A total of 411 patients were randomized. Equal local control of 12.5% vs 12.8% was reported, and there were no significant differences in other disease control endpoints. Acute effects were equal in the two groups, including dysphagia and acute skin reactions.

Slightly worse late skin toxicity was reported in the 6 fraction group (average score 1.5 vs 1.3 (1=minimal, 2=moderate, 3=severe). However, the 12 fraction arm had higher late fibrosis (0.8 vs 1.2 average scores), higher shoulder restriction, and more lymphedema 29.5% vs 12%. No statistics were reported on the toxicity endpoints. Many factors could have contributed to the results, including the non-controlled use of axillary dissections. Nonetheless, similar to the lesson learned from the Edinburgh experience, a simple bioequivalent dose calculation shows that 45-51 Gy in 12 fractions of 3.08 Gy delivered to

the cervico-axillary areas was excessive, unlike the fractionation in the other arm which received higher doses per fraction but at a lower total dose.

This discussion makes it quite clear that hypofractionated, accelerated PMRT has been an area of active investigation, but remains relatively unexplored in current research efforts. Barriers to current research include the suboptimal results reported in poorly designed trials using outmoded equipment and no radiobiological rationale. The promise of short-course PMRT lies in the added convenience it may offer to patients who otherwise may not be able to receive PMRT, and it may also allow earlier sequencing of PMRT with systemic chemotherapy. Although sequencing seems to be unimportant in the context of breast preservation[74], it may be important in women at higher risk for locoregional recurrence. Given the excellent cure rates and low morbidity with current adjuvant radiation therapy technique and fractionation, it is only natural that subsequent improvements in the field take convenience and economic impact into account.

2.4 Rationale of proposed fractionation scheme

The primary rationale for accelerated PMRT is the enhanced convenience for patients which may result in increased access to PMRT. With data now available documenting the low α/β ratio for breast cancer, the fraction sensitivity of breast cancer can be exploited with higher fraction sizes, resulting in more compressed treatment times. However, care must be taken to not exceed the tolerance of normal tissues. We propose delivering a chest wall dose of 36.63 Gy in 11 fractions of 3.33 Gy delivered over 11 days, 1 fraction per day. This fractionation should produce late effects and tumor control comparable to a conventionally fractionated course of 45-46 Gy. Patients may also receive a chest wall "scar" boost of up to 4 fractions of 3.33 Gy delivered once daily at the discretion of the treating physician. This boost fractionation should produce tumor control comparable to a 16 Gy conventional boost. This fractionation scheme has the benefit of delivering the entire treatment over 11-15 treatment days (weekdays only). The proposed fractionation scheme is compared to a conventional fractionation scheme of 2 Gy times 30 in 39 days[75].

Tumor control	α/β ratio	Standard schedule (2 Gy x 30)	Proposed schedule (3.33 Gy x 15)	Proposed schedule in 2 Gy equivalents
	4	90 Gy_4	91.5 Gy_4	61 Gy
	4	86 Gy_4*	91.5 Gy_4	61 Gy
Normal tissue response**	α/β ratio	Standard schedule (2 Gy x 23)	Proposed schedule (3.33 Gy x 11)	Proposed schedule in 2 Gy equivalents
	3	77 Gy_3	77 Gy_3	46 Gy
	4	69 Gy_4	67 Gy_4	45 Gy

* Correcting for cell proliferation during the course of treatment

** These are for normal tissue effects within the whole breast volume of the standard schedule

3. Participating Institutions

[redacted]

4. Experimental Design and Methods

4.1 Duration of Study

Patients will be enrolled in this trial over the course of approximately 36 months. The duration of the protocol for each patient will be from the date of registration to the last day of radiation therapy. Patients will be followed regularly after treatment as per standard departmental policy (Section 9.2.1). The duration of the study is estimated to be 72 months, such that the minimum follow-up in the study cohort is 36 months.

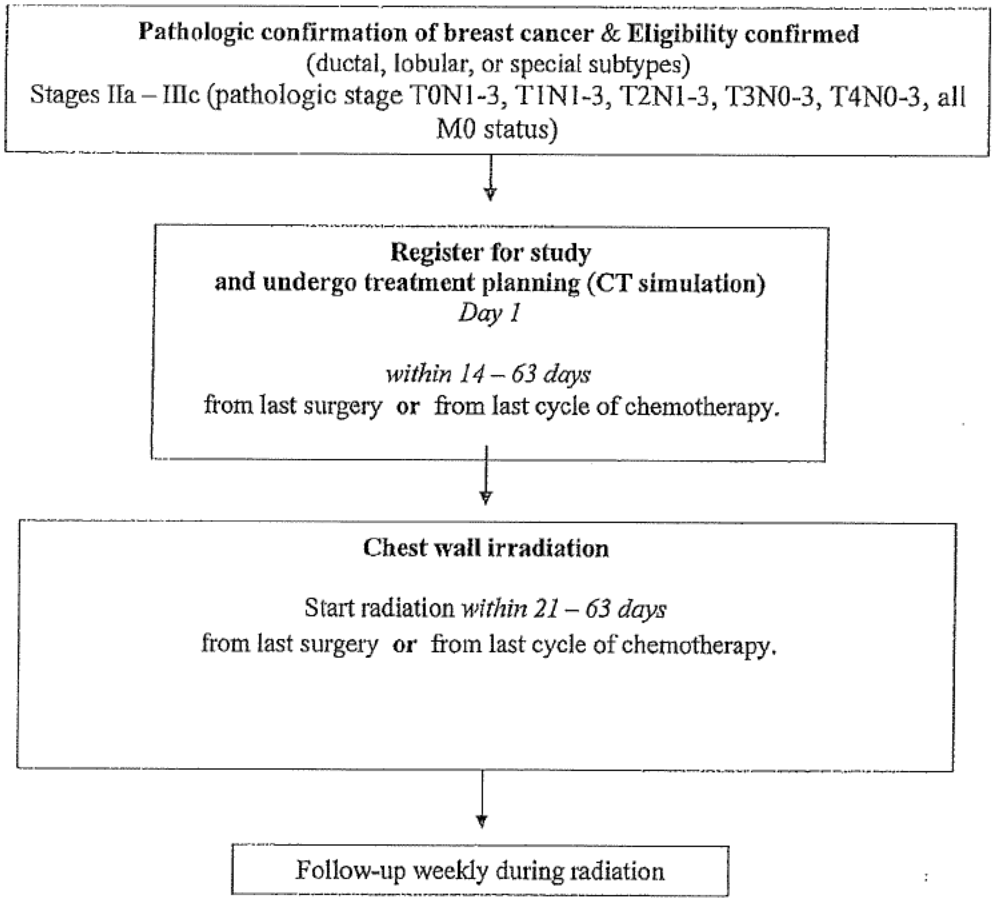
4.2 Study Design

This study is a non-randomized, single arm study of female patients with early stage or advanced invasive ductal, lobular, medullary, papillary, colloidal (mucinous), or tubular carcinoma receiving accelerated chest wall irradiation following mastectomy.

A patient who is diagnosed with breast cancer will be seen by their surgeon for evaluation of their cancer, discussion of surgical management, and possible enrollment onto clinical trials, including this trial.

- The patient has 14-63 days from the date of last surgery or date of last chemotherapy cycle to register and undergo CT simulation. Then the patient has 21-63 days after the last surgery/last chemotherapy cycle to start radiation therapy.
- PMRT may be delivered before cytotoxic chemotherapy.
- If chemotherapy is delivered after radiation therapy, it must begin no earlier than 21 days following completion of radiation therapy.
- All patients will meet with a medical oncologist or medical oncology nurse prior to beginning RT.
- All patients will receive radiotherapy based on CT treatment planning.
- If the patient underwent a mastectomy at an outside facility, she will still be eligible for the trial if all other eligibility criteria are met.
- Hormonal therapy, if indicated, can be initiated before, during or after radiation at the discretion of the treating physicians.

4.2.1 Study Schema – Postmastectomy radiation therapy



If chemotherapy is indicated and is delivered after RT, it must start ≥ 21 days after completion of RT.

RT time = 11 weekdays (once/day) chest wall irradiation = 11 RT days

Total Elapsed Time** = 11 total weekday RT = **15 elapsed days (mastectomy scar boost optional up to 4 fractions)

5. Study Enrollment Criteria

5.1 Inclusion Criteria

5.1.1 Invasive ductal, medullary, papillary, colloid (mucinous), or tubular histologies. Invasive lobular carcinomas are allowed.

5.1.2 AJCC Stage IIa – IIIc (pathologic stage T0N1-3, T1N1-3, T2N1-3, T3N0-3, T4N0-3, all M0 status) histologically confirmed invasive carcinoma of the breast treated with mastectomy and either sentinel node biopsy or axillary dissection. Inflammatory carcinoma (T4d) is allowed.

5.1.3 Patients with locally advanced breast cancer on clinical exam and diagnostics (> 3 cm and/or clinically node-positive) who have mastectomy after induction chemotherapy are allowed.

5.1.4 Multifocal/multicentric disease is allowed.

5.1.5 Negative inked histologic margins of mastectomy (no invasive cells at margin) or positive margin at pectoralis fascia or skin.

5.1.6 Tamoxifen, Arimidex or other hormonal therapy is allowed. It may begin any time relative to the radiation at the discretion of the treating physician.

5.1.7 Chemotherapy is allowed. If chemotherapy is indicated the chemotherapy can be delivered first, followed by radiation therapy beginning 21-63 days after the last cycle of chemotherapy or the radiation therapy can be delivered first and the chemotherapy can be delivered no earlier than 21 days post radiation therapy. Neoadjuvant chemotherapy is allowed; radiation therapy will be delivered after mastectomy or after any adjuvant chemotherapy as described above.

5.1.8 Chest wall reconstruction is allowed.

5.1.9 The patient must be enrolled and have treatment planning between 14 – 63 days from date of last surgery or last cycle of chemotherapy, and radiation must start within 21-63 days of date of last surgery or last cycle of chemotherapy.

5.1.10 Women must be $\geq$ 18 years of age.

5.1.11 Signed study-specific informed consent form prior to study entry.

5.1.12 ECOG performance status of 0 or 1.

5.2 Exclusion Criteria

5.2.1 Patient with distant metastases (M1).

5.2.2 Patients with ductal or lobular carcinoma in-situ alone (no invasive component) and patients with non-epithelial breast malignancies such as sarcoma or lymphoma.

5.2.3 Patient with T1N0 or T2N0 disease.

5.2.4 Prior radiation therapy to the chest.

5.2.5 Patients with collagen vascular diseases, specifically systemic lupus erythematosis, scleroderma, or dermatomyositis.

5.2.6 Patients with co-existing medical conditions with life expectancy < 2 years.

5.2.7 Patients with psychiatric (with the possible exception of incompetence as defined by [redacted] addictive disorders that would preclude obtaining informed consent.

5.2.8 Other malignancy, except non-melanomatous skin cancer, < 5 years prior to participation in this study; the disease-free interval from any prior carcinoma must be continuous.

5.2.9 Women who are pregnant or lactating due to potential exposure of the fetus to RT and unknown effects of RT to lactating females.

5.2.10 Women who are able to conceive and unwilling to practice an effective method of birth control. Women of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to treatment.

5.3 Inclusion of Women and Minorities

Women of all ethnic groups are eligible for this trial.

5.4 Participation of Children

Study participants must be over the age of 18 to be eligible for this trial.

5.5 Sources or Methods of Recruitment

Participants of this study will be recruited by the clinics of participating surgical, medical, and radiation oncologists in th[redacted]

5.6 Study Enrollment Procedures

[redacted]

6. Study Parameters

Evaluations	Prior to treatment	During Radiation (weekly)	FOLLOW-UP (after radiation therapy)			
			End of Radiation and 2 -8 weeks after RT	Then every 3-9 months (for 3 yrs)	Then every 6-15 months (out to 5 yrs)	
Signed informed consent	X					
History & Physical	X	X	X	X	X	
Pregnancy test (B-HCG)	X[1]					
Chest wall CT (Simulation)	X[2]					
Optional serum and tumor tissue samples	X[3]					

1 Within 7 days before starting treatment if of child bearing age. For menopausal status, see Appendix C.

2 After surgery/chemotherapy for treatment planning

3 For optional correlative studies, patients will be offered co-enrollment in CINJ Study # 040703 (IRB 0220070169). See Sections 9.4 and 11.

4. End of radiation = During the last 3 fractions of radiation

7. Treatment Plan

Postmastectomy RT consists of 3663 cGy in 11 fractions (333 cGy) over 11 weekdays (for 15 elapsed days); no boost is required, optional chest wall boost upto 4 fractions of 3.33 cGy is allowed (total 1332 cGy).

7.1 Equipment

◊ **External beam radiation therapy**

- Modality: Any combination of photon beams of energy 6 MV or higher, with or without the addition of electrons of any energy, may be used for treatment provided the dosimetric requirements of adequately treating the planning target volume and dose homogeneity are met. Proton therapy, IMRT, tomotherapy, and other highly conformal external beam techniques are allowed.
- Energy: Minimum of 6 mV photon or equivalent.

7.2 Imaging

◊ CT treatment planning is mandatory. Commercially available software for 3-D treatment planning should be used for treatment planning. The treatment planning CT scan should include the entire breast. A CT scan thickness of ≤ 3 mm is required. The patient's position should be reproducible and comfortable, and must be supine.

7.3 Planning Target Volume

7.3.1 PTV for the chest wall RT will include all tissue within the boundaries of standard chest wall tangential fields, excluding lung, heart and any non-chest wall structures within the volume (e.g. rib, liver). A formal PTV contour is not mandatory but is encouraged. Standard tangential fields will be set as is routine practice for the treating radiation oncologist, using medial and lateral skin wires for the tangent borders. However, no greater than 3 cm of lung should be visible at any level of the tangent beam. Collimation is not allowed if a third or fourth field (supraclavicular field/PAB) is matched to the tangents. In this case, the tangents must be designed with a nondivergent cranial edge perfectly matched to the third/fourth fields. The determination for adding a third or fourth field is left to the discretion of the treating radiation oncologist, but is typically used for the majority of patients with indications for PMRT.

7.4 Dose limitations for normal tissues

- ◊ The perpendicular distance from the chest wall to the posterior field edge can include at maximum 3 cm of lung tissue at any point along the length of the tangent.
- ◊ For left-sided cancers, the heart should be blocked from the primary beams as long as the 90% isodose line is covering the intended target volume.
- ◊ Dose to the brachial plexus should not exceed 107% of prescription dose.

7.5 Treatment Dose

Postmastectomy chest wall will get 3663 cGy in 11 fractions; a scar boost is optional at the discretion of the treating physician, upto 1332 cGy in 4 fractions. Treatment may be started on any weekday, and will not be given over holidays or weekends.

- ◊ **Prescription Point**

7.5.1 Dose from the chest wall fields can be prescribed at a point 1.5 cm anterior to the posterior edge of the fields at mid-separation, or to a point 1/3rd the distance from this point to the skin, or to an isodose line encompassing the PTV. IMRT technique and other highly conformal techniques are allowed.

7.6 Time-Dose Considerations

- ◊ Dose per Fraction: 3.33 Gy to the prescription point
- ◊ Deliver one fraction per day.
- ◊ Total Elapsed Time is 15-19 days.

NOTE: Patients may have missed treatment days due to acts of nature or personal/medical emergencies. Typically 1-2 missed days are simply added to the end of the treatment course for the same total dose. Greater than 2 skipped days or greater than 3 consecutive days without treatment (one missed day plus weekend) will be discussed by study investigators and decision to retain patient on treatment or remove patient from study will be made by consensus decision of [redacted]

7.7 Homogeneity and Reference Points

- ◊ The dose within the PTV for chest wall RT must be within 90-115% of the prescribed dose for the chest wall. Wedges, field in field, and electronic compensation can be used to achieve this endpoint, although a medial wedge greater than 15 degrees in not allowed. A contour for PTV on the chest wall is not required. The treating physician should judge coverage of treatment volume by the 90 percent isodose line on each slice of the axial treatment plan. The point-dose hotspot in this volume should not exceed 115%.
- ◊ The change in dose from minimum to maximum within the treatment volume will be < 25% for the external beam plan.

◊ If electrons are used on the chest wall, maximum doses of 120% are allowed but should not exceed 2cc of volume.

7.8 Treatment Technique

◊ Treatment planning may be performed at any time after consent and registration.

◊ Treatment must be performed using CT-Guided planning with the capability of performing true 3-dimensional reconstruction.

7.8.1 Use of a matched 3rd field to treat the supraclavicular lymph nodes at the discretion of the treating radiation oncologist is allowed. It is anticipated that the majority of women receiving postmastectomy RT will have matched fields for regional lymphatic irradiation. Dose will be prescribed to a depth of 3 cm, or to the deepest point of a contour representing the supraclavicular lymph nodes, using a single AP field as is done routinely.

7.8.2 Use of a matched 4th field as a posterior axillary boost (PAB) to treat the axilla at mid-depth is allowed at the discretion of the treating radiation oncologist. As is routinely done, a single PA field will be used to supplement the dose contribution from the AP supraclavicular field to the midplane at the level of the axilla to bring it to the prescription dose.

7.8.3 Wedges are allowed although a medial wedge greater than 15 degrees in not allowed.

7.8.4 Use of bolus is allowed on the chest wall fields at the discretion of the treating physician.

7.8.5 A block should be drawn on the BEVs for all chest wall fields when necessary to completely exclude the heart from the primary beam if this can be achieved without compromising target coverage.

7.8.6 The position of the brachial plexus will be contoured using the brachial/axillary vessels as a surrogate anatomical landmark. Dose to this volume should be constrained to 100% of the prescription dose; however a maximum dose of 107% is considered an acceptable.

7.9 Quality Assurance of Dose Distribution

Each treatment plan shall be judged as:

- **Acceptable:**
  - Dose volume histogram analysis of the target volume confirms 90% of the prescribed dose covers ≥ 90% of the PTV.
  - Dose delivered once a day for 11 daily treatments for PMRT on consecutive weekdays.
  - No greater than 3 cm of lung should be visible at any level of the tangent beam on beam's eye view.

- Heart excluded from primary beam on chest wall fields. If the heart is included in the field, no greater than 1cc of a heart is allowed to receive a fraction dose exceeding 2 Gy.
- Minimum and maximum doses within 90-115% of prescription dose.
- Electron plans (typically for the scar boost) allow 120% of prescription dose as maximum dose provided the volume receiving 120% does not exceed 2 cc.

- **Unacceptable:**
  - Dose volume histogram analysis of the target volume shows < 90% of the prescribed dose covers < 100% of the PTV.
  - Maximum dose on the whole chest wall exceeds 115% (or 120% if electrons are used).
  - Greater than 1 cc of the heart receives a fraction dose exceeding 2 Gy.
  - Dose delivered over a period of time extending greater than the limits defined above.
  - Brachial plexus dose in excess of 107% of the prescription dose.
  - [redacted]

7.10 Dose Adjustments/Delays/Modifications/Removal from study

7.10.1 Treatment Breaks/Interruptions: Radiotherapy is given in continuous course. It is not anticipated that treatment breaks should be needed. If a break seems necessary or must be given due to unavoidable medical necessity (i.e., intercurrent illness), [redacted]

7.10.2 Removal From Study: Dr. Haffty should be notified within 48 hours by telephone or e-mail and within 7 working days by writing of the removal of a patient from protocol.

7.10.3 Inability to Adequately Perform Treatment Planning: If the radiation oncologist is unable to devise a dosimetrically-satisfactory treatment plan, then the patient will be removed from study.

7.10.4 Recurrence During Treatment: Any evidence of local, regional or distant recurrence during the period of therapy will result in removal from study. Further, local-regional and systemic therapy will be at the discretion of the attending physicians. Patients who develop recurrence subsequent to the completion of the treatment program will be managed as deemed appropriate by the attending physicians.

7.10.5 Undue Toxicity: Treatment may terminate prior to its planned completion should the attending physicians feel that the patient is suffering undue toxicity. Such situations should be discussed with [redacted] from study.

7.10.6 **Patient Refusal to Continue Treatment**: A patient may withdraw her consent to participate at any time. In this case, alternative therapy, or no further therapy, may be given at the discretion of the attending physician.

7.11 Anticipated Toxicity

Erythema and desquamation in the vicinity of the treated volume are anticipated to occur. Some patients may develop a moist desquamation, which usually heals within a few weeks. Cellulitis is rare, however. Fatigue is also to be expected. Toxicities will be recorded using CTCAE v 4.0 and attribution of AEs will be recorded.

7.11.1 **Toxicity Management**: Appropriate medical & skin care should be given according to standard practices per departmental guidelines.

7.12 Concomitant Medications

Patients are allowed to continue all prescription medications as they had previously been prescribed. Patients are discouraged to use herbal remedies during the course of radiation therapy, as their interaction with radiation are not very well understood. For patients receiving chemotherapy, chemotherapy may start either before or after radiation treatments, however, there must be a minimum of 3 weeks between chemotherapy and radiation treatments.

7.13 Supportive Care Guidelines

Patients are allowed to receive full supportive care therapies concomitantly during the study such as anti-emetics, skin care, and antibiotics. No other chemotherapy, immunotherapy, or experimental medications will be permitted while the patients are receiving radiation therapy. The use of hormonal cancer therapy during radiation therapy is allowed. Patients may be enrolled on other clinical trials if they do not conflict with the use of radiation therapy as described above.

8. Toxicity Monitoring and Adverse Event Reporting

All patients who receive one dose of protocol therapy will be evaluable for assessment of toxicity. Prior to each cycle the treating physician or their designee will fully assess the patient's condition with respect to possible treatment related toxicities. All adverse events Grade 2 or greater related to radiation therapy, whether observed by the physician or reported by the patient, occurring during the active portion of therapy, or up to 30 days after the last dose of treatment will be graded by a numerical score according to the National Cancer Institutes' (NCIs') Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (http://ctep.cancer.gov/reporting/ctc.html) and recorded in the patient's medical record. Toxicities (including laboratory abnormalities) will be reported as outlined in the data capture plan.

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

The Investigator will follow all patients who experienced an AE until there is a return to the patient's baseline condition or until a clinically satisfactory resolution is achieved.

8.1 Adverse Events.

8.1.1 Reporting Requirements

◊ An adverse experience is defined as any unintended or abnormal clinical observation that is not of benefit to the patient. Either the condition was not present prior to exposure to the study therapy, or it has worsened in intensity or frequency following exposure to the study therapy.

◊ All "unexpected" (defined below) and/or "serious" (defined below) adverse events occurring during the active portion of therapy, or up to 30 days after the [redacted]

8.2 Definition of Serious Adverse Events (SAEs)

A serious adverse event (experience) is one occurring at any dose level that results in any of the following outcomes:

- Death
- Life-threatening- immediate risk of death from the reaction.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Requires intervention to prevent one of the outcomes listed in this definition.

The definition of serious adverse event (experience) also includes important medical events. Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events will usually be considered serious.

8.3 Definition of Related Adverse Events

8.3.1 There is a reasonable possibility that the drug caused the adverse experience. That is, the event is judged by the investigator to be possibly, probably or definitely related to the treatment.

8.4 Definition of Unexpected Adverse Events

8.4.1 Any adverse drug experience and/or specificity, that is not included in the current investigator's brochure and/or package insert.

9. Treatment Evaluation/Criteria for Response

◊ Loco-regional (LR) control will be assessed by physical examination and other relevant imaging per the discretion of the patients treating physicians. All LR failures have to be confirmed by biopsy, and should be coded as either chest wall recurrence, axilla, supraclavicular, or internal mammary.

9.1 Toxicity

9.1.1 The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE) (http://ctep.cancer.gov/forms/CTCAEv4.pdf) for acute toxicity of the skin will be used to score and report acute toxicity.

◊ Patients will be seen in follow-up weekly during treatment, at the end of radiation, then 2-8 weeks after RT, 3-6 months for 3 years, then every 6-12 months out to 5 years.

9.1.2 Additional toxicity end points:

◊ **Brachial plexopathy**: Investigators should record information relevant to brachial plexopathy at each follow-up visit, and include 1) method of detection, 2) signs & symptoms, and 3) method of treatment (see CRF in Appendix D).

◊ **Pain**: Information about pain should be recorded at each visit as documented in the CRF in Appendix D.

◊ **Pigmentation and Telangiectasia**: Information regarding skin pigmentation and telangiectasia will be recorded at each follow-up visit and graded I-IV (refer to CRF in Appendix D).

9.2 Cosmesis

9.2.1 Patients who have breast mound reconstructions will have the type and timing of the reconstruction recorded. Need for reconstruction revisions will be recorded.

9.3 Collection and analysis of tumor and serum samples

Several candidate predictors of radiosensitivity or radioresistance have been explored, both at the molecular and genetic level, and our group is actively participating in these research efforts[61].

[redacted]

predictors of host sensitivity and tumor sensitivity to radiation therapy.

◊ [redacted]om study IRB 0220070169 will be [redacted]elative science/translational studies.

[redacted]

10. Removal of Patients from Study/Off Study Criteria

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

a) Disease progression/relapse during active treatment,
b) Intercurrent illness that prevents further administration of treatment,
c) Unacceptable adverse event(s),
d) In the event of any drug-related life-threatening toxicity or laboratory abnormality the patient will be withdrawn from further treatment,
e) Patient decides to withdraw from the study,
f) Noncompliance with treatment plan,
g) General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator, or
h) Protocol violation - any patient found to have entered this study in violation of the protocol might be discontinued from the study at the discretion of the Principal Investigator.

11. Laboratory Evaluation – Optional Correlative Studies and Future Use

[redacted]

12. Pharmaceutical / Devices Information

This is a radiation therapy study and no pharmaceutical agents or devices will be used.

13. Data Collection and Records to be Kept

13.1 Case Report Forms (CRFs)

The Principal Investigator will be responsible for assuring that all data specified in the study-specific data capture plan is collected and entered onto the electronic case report forms (eCRFs).

[redacted]

13.2 Research Charts

[redacted]

13.3 Reports

Publications and annual reports for submission to the [redacted] PI using the data captured on the CRFs.

14. Data and Safety Monitoring

[redacted]

15. Multi-Institutional Guidelines (e.g., CINJ Oncology Group trials)

15.1 IRB Approvals

[redacted]

15.2 Other Pre-Study Documents

Each participating center is required to have the following documents on file at CINJ OHRS:

- Curricula Vitae of all Physician Investigators
- [redacted]
- [redacted]
- Signed investigator agreement from the Principal Investigator at each participating center
- Medical license from each Investigator

15.3 Initiation Meetings

A study initiation meeting will be conducted with each participating institution prior to enrollment of patients from the institution. OHRS staff will conduct the study initiation meeting in close proximity to IRB approval of the study at the participating center. In most situations the study initiation meeting will be conducted via teleconference. Web-based training regarding e-CRF completion will be utilized as appropriate.

15.4 IRB Continuing Approvals

[redacted]

15.5 Amendments and Consents

[redacted]

15.6 Patient Registration

All patients from participating institutions must register patients with the OHRS central registration desk, as described in Section 5.7 of this protocol.

15.7 Data Collection and Toxicity Reporting

The PI at each institution will be responsible for assuring that all the required data is collected and entered onto the eCRFs accurately and completed eCRFs submitted as described in Section 13.

15.8 Data Monitoring and Source Document Verification

[redacted]

15.9 Data and Center Audits

[redacted]

16. Statistical Considerations

16.1 Primary and Secondary Hypotheses

The primary hypothesis of this study is that the delivery of hypofractionated, accelerated chest wall radiotherapy will result in toxicities will be similar to those reported for this patient population using standard of care postmastectomy radiation therapy.

The secondary endpoint is that locoregional control that is equal (non-inferior) to that reported for a conventional fractionation course of postmastectomy radiotherapy.

16.2 Sample Size Justification

The primary aim of this study is to ensure that the toxicity rate (defined as chest wall pain greater than or equal to grade 3, or painful/symptomatic brachial plexopathy and acute symptomatic pneumonitis greather than or equal to grade 3) from hypofractionated post-mastectomy radiation is controlled at an acceptable level. The current toxicity rate from standard regimens is approximately 3%. We need to ensure that the rate from the hypofractionated scheme is as low as possible, and specifically that it is below 9% with 80% power, using a 10% level one-sided test of proportions. To meet this requirement, we will need to accrue 67 patients. If there are 5 or more toxicity events among 67 patients, we reject the hypothesis that the rate is 3%. The exact significance level of this discrete variable test is 0.0508, and the exact power is 0.732.

Early stopping: The study will be stopped early if, at any time, we are more than 80% sure that the toxicity rate exceeds 9%. For example, if we have 4 patients experiencing a toxicity event out of the first 33 patients enrolled, we will stop the trial. But if there are only 3 patients with toxicity, the trial would continue. As mentioned above, if five patients show unacceptable toxicities, the trial will end, even if this happens before the full 67 patients have been accrued. This stopping rule table consists of posterior probabilities that the true toxicity level exceeds 9%, assuming a uniform prior on a binomial distribution.

k: Number of unacceptable toxicities

	0	1	2	3	4
1	0.8281	0.9919			
2	0.753571	0.977158	0.999271		
3	0.68575	0.957035	0.997281	0.999934	
4	0.624032	0.932619	0.993659	0.999696	0.999994
5	0.567869	0.904847	0.988165	0.999152	0.999967
6	0.516761	0.874519	0.980667	0.998163	0.999894
7	0.470253	0.84232	0.971113	0.996589	0.999738
8	0.42793	0.808834	0.959522	0.994296	0.999455
9	0.389416	0.774553	0.94596	0.991166	0.99899
10	0.354369	0.739891	0.930533	0.987098	0.998286
11	0.322475	0.705194	0.913376	0.982007	0.997279
12	0.293453	0.670749	0.894639	0.97583	0.995905
13	0.267042	0.636792	0.874489	0.968523	0.994098
14	0.243008	0.603515	0.853096	0.96006	0.991796
15	0.221137	0.571069	0.830634	0.950433	0.98894
16	0.201235	0.539575	0.807273	0.939651	0.985474
17	0.183124	0.509125	0.78318	0.927737	0.98135
18	0.166643	0.479785	0.758515	0.914727	0.976525
19	0.151645	0.451602	0.73343	0.900668	0.970963
20	0.137997	0.424606	0.708065	0.885617	0.964637
21	0.125577	0.398811	0.682554	0.869637	0.957525
22	0.114275	0.37422	0.657017	0.852799	0.949615
23	0.10399	0.350825	0.631565	0.835179	0.940902
24	0.094631	0.32861	0.606299	0.816854	0.931387
25	0.086114	0.307552	0.581307	0.797904	0.921079
26	0.078364	0.287622	0.556669	0.77841	0.909993
27	0.071311	0.268789	0.532454	0.758453	0.89815
28	0.064893	0.251016	0.508725	0.738113	0.885578
29	0.059053	0.234265	0.485531	0.717468	0.872306
30	0.053738	0.218496	0.462917	0.696594	0.858371
31	0.048902	0.203668	0.440919	0.675563	0.843811
32	0.044501	0.189739	0.419566	0.654445	0.828668
33	0.040496	0.176667	0.398882	0.633306	0.812988
34	0.036851	0.164412	0.378883	0.612208	0.796817
35	0.033534	0.152931	0.35958	0.591209	0.780202

We will use a fixed sample size of 67 patients, with locoregional recurrence rate as the secondary outcome of interest. For up to 5 recurrences out of 67 patients, we can say with 90% confidence that the true recurrence rate would be between 3.7% and 14.5%. We feel this is an acceptable level, and would be deemed non-inferior to previously reported recurrence rates.

16.3 Methods for Randomization and Stratification

This study is a non-randomized, single arm study of female patients with invasive ductal carcinoma receiving accelerated chest wall irradiation following mastectomy. Thus, there is no randomization or stratification.

16.4 Outcome Measures

Time to local, regional, and/or distant failure will be recorded for primary endpoint analysis. Secondary endpoints will be measured by the data collected for toxicity as dichotomous variables; need for cosmetic reconstruction revision will also be collected and analyzed as a dichotomous variable.

16.5 Statistical Analysis

All time intervals will be calculated from the date of diagnosis. Fisher's exact test will be performed to correlate clinicopathological covariates with toxicity and with plastic surgical revision.. The association of variables with LR failure times will be investigated by fitting a parametric model and examining the significance of the parameter estimates. Nonparametric estimates of the survival or recurrence-free distributions or recurrence (failure) distribution will be obtained by life table methods. Tests will be declared statistically significant if the calculated P-value was ≤ 0.05. All tests appear as 2-sided P-values.

16.6 Compliance and Missing Data

Compliance will be defined as patients who complete the course of radiotherapy in a time frame as described above. If a patient is unable to do so, they will be removed from the study. Data will be accumulated on a daily basis for each patient. If by chance there is missing data, it will be imputed based on the population as a whole.

17. Human Subjects

17.1 Patient Population

Female patients ages 18 or greater with Stages I-IIIc invasive carcinoma of the breast who receive mastectomy are eligible for this trial.

17.2 Potential Risks

Postmastectomy RT is routinely delivered to high risk subsets of women, including those with greater than 4 positive nodes, and those with 1-3 positive nodes and other adverse clinicopathological features. The side effects and risks of radiation therapy include fatigue, skin reaction/fibrosis, pain, lung inflammation/fibrosis, and secondary malignancy. With patients coming to treatment daily, we have adequate resources and support to assist patients in any manner, if required. The physician will evaluate the patient at least weekly to determine any routine or adverse side effects of the treatment. If adverse affects are seen, appropriate medical action will be taken.

17.3 Consent Procedures

Informed consent must be obtained prior to commencing any research procedures. The PI shall seek such consent only under such circumstances that provide the prospective patient opportunity to consider whether or not to participate and that minimizes the possibility of coercion or undue influence. The information given to the patient, or the representative, shall be in a language understandable to the subject or representative. The informed consent document may not include any exculpatory language through which the subject or representative is made to waive any of the subject's legal rights or

releases, or appears to release the investigator, the sponsor or the institution from liability for negligence.

17.4 Potential Benefits

The benefit of accelerated irradiation over conventional irradiation is the improved convenience of accelerated irradiation. More specifically, a conventional course of adjuvant post-mastectomy radiotherapy to 60 Gy would be delivered over 30 treatment days and over 42 calendar days (6 weeks). In contrast, a course of accelerated post-mastectomy radiation therapy as defined in this study would be delivered in 11-15 fractions over 15-19 days.

17.5 Risk-Benefit Ratio

The benefit of postmastectomy RT in improving overall survival, disease-free survival, and locoregional control rates is well documented. Multiple, large-scale prospective trials have demonstrated that the risks of radiation are modest, as described above, and do not outweigh the benefits of treatment. The goal of this study is to reproduce the excellent results of conventional post-mastectomy irradiation both in terms of efficacy (disease control) and toxicity (side-effects) using a more convenient, abbreviated course of post-mastectomy irradiation. As discussed above, the feasibility of this approach has been demonstrated by Yarnold[50], Formenti[57], and Whelan[51] in their reports. Alternative treatments can include conventional chest wall irradiation, hormonal therapy alone, or no therapy. As already noted, the goal of the trial is to improve the convenience of radiation therapy using a shortened course of treatment, which may benefit women by improving quality of life. The accelerated fractionation scheme is expressly calculated to be biologically comparable to conventional irradiation in terms of efficacy and toxicity.

17.6 Gender and Minorities

Women of all races and ethnicities are eligible for this trial.

18. Economic/Financial Considerations

This study does not require financing from outside resources. Radiation therapy delivered to the patient is covered by insurance.

19. Publication of Research Findings

[redacted]

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Appendix A

Information Template for Trial Submission to NJCTC

Protocol Title: Accelerated, Hypofractionated Post-Mastectomy Radiation Therapy in Women with Breast Cancer: A Phase II Trial

Brief Trial Description/Rationale:

This study is a non-randomized, single arm study of female patients with invasive carcinoma of the breast who have had (or will have) a mastectomy followed by radiation therapy. The term "accelerated" means that a higher radiation dose per treatment will be delivered over a shorter period of time (compared to the standard). Prior studies suggest that the accelerated radiation scheme used in this study is comparable to the standard or conventional whole breast radiation. That is, the evidence points to accelerated treatments may work at least as well as the longer, standard treatments. Along with measuring the treatment toxicity and recurrence outcomes, we will be recording the need for plastic reconstruction revisions (how well the study treatment plan preserves the appearance of your surgically reconstructed breast).

How long do you anticipate the protocol to be open?

Patients will be enrolled in this trial over the course of approximately 36 months. The duration of the protocol for each patient will be from the date of registration to the last day of radiation therapy. Patients will be followed regularly after treatment as per standard departmental policy. The duration of the study is estimated to be completed in 72 months.

Inclusion Criteria (main):

- Invasive ductal, medullary, papillary, colloid (mucinous), or tubular histologies. Invasive lobular carcinomas are allowed.
- AJCC Stage I – IIIc (pathologic stage T1-T4d, N0-N3, M0) histologically confirmed invasive carcinoma of the breast treated with mastectomy and either sentinel node biopsy or axillary dissection. Inflammatory carcinoma (T4d) is allowed.
- Multifocal/multicentric disease is allowed.
- Negative inked histologic margins of mastectomy (no invasive cells at margin) or positive margin at pectoralis fascia.
- Tamoxifen, Arimidex or other hormonal therapy is allowed. It may begin any time relative to the radiation at the discretion of the treating physician.
- Chemotherapy is allowed. If chemotherapy is indicated the chemotherapy can be delivered first, followed by radiation therapy beginning 21-63 days after the last cycle of chemotherapy or the radiation therapy can be delivered first and the chemotherapy can be delivered no earlier than 21 days post radiation therapy. Neoadjuvant chemotherapy is allowed; radiation therapy will be delivered after mastectomy or after any adjuvant chemotherapy as described above.

- Chest wall reconstruction is allowed.
- The patient must be enrolled and have treatment planning between 14 – 63 days from date of last surgery or last cycle of chemotherapy, and radiation must start within 21-63 days of date of last surgery or last cycle of chemotherapy.
- Women must be ≥ 18 years of age.
- Signed study-specific informed consent form prior to study entry.

Exclusion Criteria (main):

- Patient with distant metastases (M1).
- Patients with ductal or lobular carcinoma in-situ alone (no invasive component) and patients with non-epithelial breast malignancies such as sarcoma or lymphoma.
- Palpable or radiographically suspicious contralateral axillary, supraclavicular, infraclavicular or internal mammary nodes, unless there is histologic confirmation that these nodes are negative for tumor.
- Prior radiation therapy to the chest.
- Patients with collagen vascular diseases, specifically systemic lupus erythematosis, scleroderma, or dermatomyositis.
- Patients with co-existing medical conditions with life expectancy < 2 years.
- Patients with psychiatric or addictive disorders that would preclude obtaining informed consent.
- Other malignancy, except non-melanomatous skin cancer, < 5 years prior to participation in this study; the disease-free interval from any prior carcinoma must be continuous.
- Women who are pregnant or lactating due to potential exposure of the fetus to RT and unknown effects of RT to lactating females.
- Women who are able to conceive and unwilling to practice and effective method of birth control. Women of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to treatment.

[redacted]

Appendix B

Performance Status Criteria

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix C

DETERMINATION OF MENOPAUSAL STATUS

Menopausal Status Determination

The following criteria will be used to define *postmenopausal*:

- A prior documented bilateral oophorectomy, **or**
- A history of at least 12 months without spontaneous menstrual bleeding, **or**
- Age 55 or older with a prior hysterectomy, **or**
- Age 54 or younger with a prior hysterectomy without oophorectomy (or in whom the status of the ovaries is unknown), with a documented FSH level demonstrating confirmatory levation in the lab's postmenopausal range.

Women failing to meet one of these criteria will be classified as pre-menopausal

Appendix D

Case Report Forms

CASE REPORT FORM #1 – PATIENT ENROLLMENT

Patient Identification: ☐☐-☐☐☐☐ (Site / Sequential)					
1. Enrollment Date: ☐☐/☐☐/☐☐ (M M / D D / Y Y)		2 Date of Birth: ☐☐/☐☐/☐☐ (M M / D D / Y Y)			
3 Age at Diagnosis: ☐☐		4 Menopausal Status:	☐ Pre	☐ Peri	☐ Post
5 Race:	☐ Black	☐ Caucasian	☐ Hispanic	☐ Asian	☐ Other
6 Histology:					
☐ Invasive ductal	☐ Pure DCIS	☐ Invasive lobular	☐ Other		
7 Grade:	☐ I	☐ II	☐ III		
8 AJC Classification:		Tis:	☐ T1	☐ T2	
		If T2, ≤ 3 cm	☐ Yes	☐ No	
9 Largest Tumor size: ☐☐ mm					
10 Surgical Margins:					
☐ Negative (no tumor on ink)		☐ Close (< 2 mm)	☐ ≥ 2 mm		
11 Nodes:	Negative	☐ Yes	☐ No	Numbered Excised: ☐	Number positive: ☐
12 Sentinel node biopsied:		☐ Yes	☐ No	Axillary Dissection: ☐ Yes	☐ No
13 Estrogen receptors – Positive: Value = _____				☐ Yes ☐ No	☐ Unknown
14 Progesterone receptors – Positive: Value = _____				☐ Yes ☐ No	☐ Unknown
15 Her2Neu – Positive:				☐ Yes ☐ No	☐ Unknown
16 Adjuvant therapy for this cancer episode:					
☐ None			☐ Hormonal therapy type _____		
☐ Chemotherapy type _____			☐ Other _____		
17 Mastectomy Date (Last Surgery Date): ☐☐/☐☐/☐☐ (M M / D D / Y Y)					
18 Lesion location:	☐ Left	☐ Right			
☐ UIQ	☐ LIQ	☐ Central	☐ UOQ	☐ LOQ	
19 Plastic reconstruction of treated side	☐ Yes	☐ No	If yes, before RT initiation?	☐ Yes or ☐ No	
20. Type of reconstruction (if applicable, select all that apply):					
☐ Temporary Expander	☐ Prosthesis/Implant	☐ TRAM	☐ LAT	☐ DIEP	☐ SGAP/IGAP

CASE REPORT FORM #2 – FOLLOW-UP VISITS

Patient Identification: ☐☐ - ☐☐☐☐ (Site – Sequential)

Date of Visit ☐☐/☐☐/☐☐ (M M / D D / Y Y) Scorer Name:

1. Complication Assessment (Must be evaluated at each visit)

A	Acute skin toxicity	☐ Not evident	☐ If Yes, complete CRF #3;
B	Brachial plexopathy	☐ Not evident	☐ If Yes, complete CRF #4; Section I
C	Acute lung toxicity	☐ Not evident	☐ If Yes, complete CRF #3;
D	Pain	☐ Not evident	☐ If Yes, complete CRF #3&CRF #4; Section II
E	Revision of plastic reconstruction	☐ Not evident	☐ If Yes, complete CRF #4; Section IV
F	Fibrosis	☐ Not evident	☐ If Yes, complete CRF #3
G	Other (Fatigue, Lung, Heart)	☐ Not evident	☐ If Yes, complete CRF #3&/or CRF#4,5 or 6

2 Local failure:

☐ Scar ☐ Chest wall ☐ Inflammatory ☐ Biopsied ☐ Invasive ☐ Non-invasive ☐ Grade _____ ☐ Receptor status _____

3 Regional failure:

☐ Axilla ☐ Supraclavicular fossa ☐ Internal mammary nodes ☐ Skin ☐ Other

4 Distant Failure

☐ Lung ☐ Bone ☐ Other

CASE REPORT FORM #3 –ACUTE TOXICITIES (CTCAE V.3)

Patient Identification: ☐☐ - ☐☐☐☐ (Site - Sequential)

Date of Visit ☐☐/☐☐/☐☐ (M M / D D / Y Y) Scorer Name:

RESPIRATORY ALTERATIONS

	1	2	3	4	COMMENTS
BRONCHOSPASM/ WHEEZING	ASYMPTOMATIC	SYMPTOMATIC NOT INTERFERING WITH FUNCTION	SYMPTOMATIC INTERFERING WITH FUNCTION	LIFE-THREATENING	
COUGH (DRY,WET, BLOOD)	SYMPTOMATIC, NONNARCOTIC MEDICATION ONLY INDICATED	SYMPTOMATIC AND NARCOTIC MEDICATION INDICATED	SYMPTOMATIC AND SIGNIFICANTLY INTERFERING WITH SLEEP OR ADL		
DYSPENIA	DYSPNEA ON EXERTION, BUT CAN WALK 1 FLIGHT OF STAIRS WITHOUT STOPPING	DYSPNEA ON EXERTION BUT UNABLE TO WALK 1 FLIGHT OF STAIRS OR 1 CITY BLOCK (0.1KM) WITHOUT STOPPING	DYSPNEA WITH ADL	DYSPNEA AT REST; INTUBATION/VENTILATOR INDICATED	
VOICE CHANGES	MILD OR INTERMITTENT HOARSENESS OR VOICE CHANGE, BUT FULLY UNDERSTANDABLE	MODERATE OR PERSISTENT VOICE CHANGES, MAY REQUIRE OCCASIONAL REPETITION BUT UNDERSTANDABLE ON TELEPHONE	SEVERE VOICE CHANGES INCLUDING PREDOMINANTLY WHISPERED SPEECH; MAY REQUIRE FREQUENT REPETITION OR FACE-TO-FACE CONTACT FOR UNDERSTANDABILITY; REQUIRES VOICE AID (E.G., ELECTROLARYNX) FOR ≤50% OF COMMUNICATION	DISABLING; NON-UNDERSTANDABLE VOICE OR APHONIC; REQUIRES VOICE AID (E.G., ELECTROLARYNX)FOR >50% OF COMMUNICATION OR REQUIRES >50% WRITTEN COMMUNICATION	

SKIN ALTERATIONS

	1	2	3	4	COMMENTS
DERMATITIS	FAINT ERYTHEMA OR DRY DESQUAMATION	MODERATE TO BRISK ERYTHEMA; PATCHY MOIST DESQUAMATION, MOSTLY CONFINED TO SKIN FOLDS AND CREASES; MODERATE EDEMA MOIST DESQUAMATION OTHER	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	
INDURATION/FIBROSIS	INCREASED DENSITY ON PALPATION	MODERATE IMPAIRMENT OF FUNCTION NOT INTERFERING WITH ADL; MARKED INCREASE IN DENSITY AND FIRMNESS ON PALPATION WITH OR WITHOUT MINIMAL RETRACTION	DYSFUNCTION INTERFERING WITH ADL; VERY MARKED DENSITY, RETRACTION OR FIXATION		
ATROPHY,SKIN	DETECTABLE	MARKED	--	--	--
ATROPHY, SUBCUTANEOUS FAT	DETECTABLE	MARKED	--	--	--
HYPERPIGMENTATION	SLIGHT OR LOCALIZED	MARKED OR GENERALIZED	--	--	--
HYPOPIGMENTATION	SLIGHT OR LOCALIZED	MARKED OR GENERALIZED	--	--	--
TELANGIECTASIA	FEW	MODERATE NUMBER	MANY AND CONFULENT	--	--
ULCERATION		SUPERFICIAL ULCERATION <2 CM SIZE; LOCAL WOUND CARE; MEDICAL INTERVENTION INDICATED	ULCERATION >2 CM SIZE; OPERATIVE DEBRIDEMENT, PRIMARY CLOSURE OR OTHER INVASIVE INTERVENTION INDICATED (E.G. HYPERBARIC OXYGEN)	LIFE THREATENING CONSEQUENCES; MAJOR INVASIVE INTERVENTION INDICATED (E.G., COMPLETE RESECTION, TISSUE RESONSTRUCTION, FLAP OR GRAFTING)	---

ENERGY

	1	2	3	4	COMMENTS
FATIGUE	MILD FATIGUE OVER BASELINE	MODERATE OR CAUSING DIFFICULTY PERFORMING SOME ADL	SEVERE FATIGUE INTERFERING WITH ADL	DISABLING	

PAIN

	1	2	3	4	COMMENTS
PAIN	MILD PAIN NO INTERFERING WITH FUNCTION	MODERATE POINA; PAIN OR ANALGESICS INTERFERING WITH FUNCTION, BUT INOT INTERFEARING WITH ADL	SEVERE PAIN; PAIN OR ANALGESICS SEVERLY INTERFERING WITH ADL	DISABLING	

CASE REPORT FORM #4 – TOXICITIES

Patient Identification: ☐☐ - ☐☐☐☐ (Site - Sequential)

Date of Visit: ☐☐/☐☐/☐☐ (M M / D D / Y Y)

I BRACHIAL PLEXOPATHY

☐ NOT APPLICABLE

1 Date of Onset: _____ Date of Resolution: _____

2 Method of detection (List all that apply):

☐ Clinical ☐ Physician ☐ Patient ☐ Imaging ☐ Other

3 Symptomatic (List all that apply):

☐ Pain ☐ Requiring non-narcotic analgesics ☐ Requiring narcotic analgesics ☐ Motor impairment ☐ Sensory impairment

4 Method of treatment (List all that apply):

☐ Observation ☐ Medication ☐ Physical therapy ☐ Surgical exploration ☐ Other

II PAIN

☐ NOT APPLICABLE

1 Date of Onset: _____ Date of Resolution: _____

2 Location of pain (List all that apply):

☐ Breast ☐ Axilla ☐ Chest wall ☐ Arm ☐ Other

3 Degree of extent of pain (List all that apply):

a Intensity: _____ (1-10; 1 = Least, 10 = greatest) b Duration: _____ (1-10; 1 = Infrequent, 10 = constant)

c ☐ Requiring only non-narcotic analgesics d ☐ Requiring narcotic analgesics

III TELANGIECTASIA

☐ NOT APPLICABLE

1 Date of Onset: _____ Date of Resolution: _____

2 Degree:

☐ Grade 1 (< 9 cm^2) ☐ Grade 2 ($9 - 36$ cm^2) ☐ Grade 3 (> 36 cm^2) ☐ Grade 4 (Whole Field)

IV REVISION OF PLASTIC RECONSTRUCTION ☐ NOT APPLICABLE

1 Date of Onset: _____ Date of Resolution: _____

2 Degree:

☐ G_1 (localized) ☐ G_2 (Generalized)

[redacted]

CASE REPORT FORM #5 – CHEST WALL LATE TOXICITIES

Patient Identification: ☐☐ - ☐☐☐☐ (Site - Sequential)

Date of Visit: ☐☐/☐☐/☐☐ (M M / D D / Y Y)

I LATE TOXICITY – SKIN (RTOG/EORTC) ☐ Not done

☐ Grade 0	None
☐ Grade 1	Slight atrophy; pigmentation change; some hair loss
☐ Grade 2	Patch atrophy; moderate telangiectasia; total hair loss
☐ Grade 3	Marked atrophy; gross telangiectasia
☐ Grade 4	Ulceration
☐ Grade 5	Death

II LATE TOXICITY – SUBCUTANEOUS (RTOG/EORTC) ☐ Not done

☐ Grade 0	None
☐ Grade 1	Slight induration (fibrosis) and loss of subcutaneous fat
☐ Grade 2	Moderate fibrosis but asymptomatic; slight field contracture < 10% linear reduction
☐ Grade 3	Severe induration and loss of subcutaneous tissue Field contracture > 10% linear measurement
☐ Grade 4	Necrosis
☐ Grade 5	Death

CASE REPORT FORM #6 – HEART/LUNG LATE TOXICITIES

Patient Identification: ☐☐ - ☐☐☐☐ (Site - Sequential)

Date of Visit ☐☐/☐☐/☐☐ (M M / D D / Y Y)

I LATE TOXICITY – LUNG (RTOG/EORTC)

☐ Not done

☐ Grade 0	None
☐ Grade 1	Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances
☐ Grade 2	Moderate symptomatic fibrosis or pneumonitis (severe cough); low grade fever Patchy radiographic appearances
☐ Grade 3	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes
☐ Grade 4	Severe respiratory insufficiency/continuous O_2/assisted ventilation
☐ Grade 5	Death

II LATE TOXICITY – HEART (RTOG/EORTC)

☐ Not done

☐ Grade 0	None
☐ Grade 1	Asymptomatic or mild symptoms Transient T wave inversion & ST changes
☐ Grade 2	Sinus tachycardia>110 (at rest) Moderate angina on effort Mild pericarditis; normal heart size; persistent abnormal T wave and ST changes
☐ Grade 3	Low QRS Severe angina Pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement
☐ Grade 4	EKG abnormalities Tamponade; severe heart failure Severe constrictive pericarditis
☐ Grade 5	Death

EXPIRES [redacted] APPROVED

OCT 17 [redacted]

Approved by [redacted]