Official Title:	Prone partial breast irradiation (PBI): prospective randomized controlled non-inferiority trial to compare radiation fibrosis with five versus three fractions
NCT Number:	NCT02276885
Study Number:	s14-01306
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	• October 12, 2018

NYU S14-01306

Prone partial breast irradiation (PBI): prospective randomized controlled non-inferiority trial to compare radiation fibrosis with five versus three fractions

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Funding Support
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Summary of changes :

Protocal version 3.3 dated 10/12/2018

- **Extending follow-up window frame from 60 to 90 days**
- **Adddition to Sectio 13: All analyses may be stratified by whether a patient started treatment within 60 days from surgery or within 90 days from surgery.**

Protocol version 3.2 dated 2/1/2018

Protocol version 3.1 dated 2/7/2017

- Revisions to Study Summary and sections 5.1, to change inclusion criteria to include patients *at least 50 years of age and older*, previously stated patients older than 50; new language offers clarity to desired subject population's age.
- Revisions to sections 6.8 Follow up, 8.5 Rationale for Study Design and 11.0 Study Calendar to eliminate the 60 day follow up time point. It is clinically not necessary to have such intense monitoring in the acute period, adds to burden imposed on the patient, and has demonstrated poor compliance. The acute side effects will still be captured in the 30d ($\pm$ 2 week) visit, which is standard of care for radiotherapy treatments.

  All subjects will be followed for 30 days ($\pm$ 2 weeks), at 90 days and 6 months ($\pm$ 6 weeks) , then yearly for 5 years ($\pm$8 weeks)
- Amendment to include in the main inclusion criteria patients with low-risk stage 0 disease that fit the criteria defined in the updated ASTRO evidence-based consensus statement for APBI. The recently updated consensus statement now includes low-risk pure DCIS as part of the "suitable" category for APBI outside of a clinical trial**.**

Protocol version 3.0 dated 9/14/2016

- Revisions to sections 6.8 Follow up, 8.5 Rationale for Study Design and 11.0 Study Calendar to change the duration of follow up from 10 years to 5 years (after the first year post-treatment). The follow up frequency remains unchanged, with language clarified to reflect 3 monthly visits during the first 90 days post-treatment, 3 months afterwards, and then yearly visits for the duration of follow up.

  After the end of radiation treatment, each subject will be followed monthly (+/- 2 weeks) for the first 90 days for serious adverse event reporting. Assessments will continue q6 for the first year, followed by yearly visits for the remaining 5 years.

- Deletion of sections describing the collection of blood samples from patients, as the exploratory endpoint of identifying germline polymorphisms in radiation-relevant pathways was described in older versions of this protocol but was ultimately not pursued and removed from the most current versions of the protocol.

  From section 2.7: *We will prospectively collect blood samples before and after treatment on these patients to determine whether we can identify germline polymorphisms in radiation-relevant pathways which may be able to predict which patients may be at risk for developing late radiation fibrosis. Since retraction/atrophy often reflect the extent of original surgery we will focus on measuring breast fibrosis to define the phenotype of late effects of radiation to the breast.*

  From section 6.0: *Research samples will be processed over at Dr. Robert Schneider's lab at NYU Alexandria Labs.*

- Revision of language in section 2 Background and Hypotheses to address typographical errors (removed reference to Fig. 1C, as no such figure exists, repeated word "protocol", and error in referenced appendix numbers). Additional revision of language in Table 5 Study Schema to address typographical error regarding number of eligible subjects (changed to 284 from 200).

- Removed Ms. Chandrashekhar and Dr. Yeh from protocol since they are no longer working with NYU.

Protocol version 2.2 dated 10/14/2015:

Changing the cover page to add Dr. Naamit Gerber as Co-Investigator. Removing the following personnel who are no longer at NYU: Maria Fenton-Kerimian, NP, Keith DeWyngaert Ph.D., Ravindran Kathirithamby- Research Director and Sharanya Chandrasekhar- Research Coordinator

Protocol version 2.1dated 04/10/2015:

Changing Principal Investigator to Dr. Carmen Perez.

Adding Dr. Silvia Formenti as Co-Investigator

Removing Research Blood component from the protocol and consent.

Informed Consent dated 03/25/2015:

Changing the Principal investigator in the informed consent to Dr. Carmen Perez.

Summary of changes : Amendment version 1.1 dated 10/14/2014.

Section 8.0 : Radiation Therapy

Revising the language in sections 8.3, 8.5, and 8.6.

8.3 Imaging: A treatment planning CT of the breast will be acquired with the patient in the treatment position (prone), utilizing the same immobilization devices as will be used for treatment. CT scan thickness should be ~~< 0.375~~ ≤ 0.375 cm through the tumor bed region. These images will be used in 3D treatment planning of the breast in accordance with the dose specification constraints.

8.5 Immobilization Techniques: Patients will be set-up for treatment and CT scanning utilizing ~~the NYU prone mattress~~ a dedicated table designed to accommodate prone positioning for breast treatment [15].

8.6 Target Positioning Verification: Digitally acquired radiographic images, acquired prior to each fraction, will be used to verify the position of the target with respect to the treatment machine's isocenter using digitally reconstructed radiographs (DRRs) as a reference image set. Both kV and MV images may be used to verify setup.

Amendment for NYU S14-01306: Prone partial breast irradiation (PBI): prospective randomized controlled non-inferiority trial to compare radiation fibrosis with five versus three fractions

We propose an amendment to study NYU S14-01306 ***to include in the subject eligibility criteria patients with pure DCIS (i.e., stage 0 breast cancer) that is classified as low risk as per RTOG 9804 criteria (1): screen-detected, low to intermediate nuclear grade, ≤ 2.5cm in size, resected with negative margins at ≥3mm)***. These patients would be included in the target accrual of 284 subjects. This proposed change is in response to the recently published update (i.e, September 2016) of an ASTRO evidence-based consensus statement regarding the use of accelerated partial breast irradiation (APBI) outside of a clinical trial (2). The new recommendations categorize the aforementioned low risk pure DCIS patients in the "suitable" group (Table 1 below). These clinical guidelines represent an executive summary in Radiation Oncology to guide the use of APBI, and as the low risk pure DCIS patients are now considered suitable candidates for this adjuvant breast radiotherapy strategy, it seems reasonable and safe to include this group in the study population of this clinical trial.

The recommendation to classify the low risk pure DCIS as "suitable" was done with 100% agreement of the panel members. Based on results from the randomized clinical trial RTOG 9804, with a median follow up of 7.2 years, the risk of ipsilateral breast tumor recurrence in this population was low at 6.7% in the observation arm compared to 0.9% in the whole breast adjuvant irradiation arm (1). Accordingly, patients in the ECOG 5194 prospective study meeting similar criteria to the patients in RTOG 9804 also experienced low rates of ipsilateral breast tumor recurrence (14.4% at a median follow up of 12 years), and these patients were observed but not treated with adjuvant breast radiotherapy (3). Therefore, observation is deemed to confer a low absolute risk of ipsilateral breast tumor recurrence in the subset of patients with low risk DCIS, for whom the addition of whole breast radiation confers a measurable but small absolute benefit in preventing a recurrence. The therapeutic index of adjuvant breast radiation in this low risk population may be improved with APBI, given the convenience and smaller volume of irradiated tissue using this strategy. Retrospective series support the efficacy of APBI in this setting, with 5 year risk estimates of ipsilateral breast tumor recurrence of 0% (4), 1.4% (5), and 2.6% (6).

The benefits of the proposed amendment include improved accrual rate based on a broader eligibility criteria, as well as representation of a group of breast cancer patients (i.e., low risk pure DCIS /stage 0 breast cancer) in which the use of APBI is projected to increase in practice based on the updated ASTRO evidence-based consensus statement. If this group of patients is included in the trial, then the results from this study would be applicable to a broader representation of patients routinely treated with APBI. This amendment has been discussed with members of the Breast DMG, who are in agreement.

Table 1, from reference[2]:

Table 1 Comparison of patient groups in original and updated consensus statements

Patient group	Risk factor	Original	Update
Suitability	Age	≥60 y	≥50 y
	Margins	Negative by at least 2 mm	No change
	T stage	T1	Tis or T1
	DCIS	Not allowed	If all of the below: • Screen-detected • Low to intermediate nuclear grade • Size ≤2.5 cm • Resected with margins negative at ≥3 mm
Cautionary	Age	50-59 y	• 40-49 y if all other criteria for "suitable" are met • ≥50 y if patient has at least 1 of the pathologic factors below and does not have any "unsuitable" factors *Pathologic factors:* • Size 2.1-3.0 cm [a] • T2 • Close margins (<2 mm) • Limited/focal LVSI • ER(-) • Clinically unifocal with total size 2.1-3.0 cm [b] • Invasive lobular histology • Pure DCIS ≤3 cm if criteria for "suitable" not fully met • EIC ≤3 cm
	Margins	Close (<2 mm)	No change
	DCIS	≤3 cm	≤3 cm and does not meet criteria for "suitable"
Unsuitable	Age	<50 years	• <40 y • 40-49 y and do not meet the criteria for cautionary
	Margins	Positive	No change
	DCIS	>3 cm	No change

[a] The size of the invasive tumor component.
[b] Microscopic multifocality allowed, provided the lesion is clinically unifocal (a single discrete lesion by physical examination and ultrasonography/mammography) and the total lesion size (including foci of multifocality and intervening normal breast parenchyma) falls between 2.1 and 3.0 cm.

References for this amendment:

1. McCormick B, Winter K, Hudis C, et al: RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. J Clin Oncol 33:709-15, 2015
2. Correa C, Harris EE, Leonardi MC, et al: Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement. Pract Radiat Oncol, 2016
3. Solin LJ, Gray R, Hughes LL, et al: Surgical Excision Without Radiation for Ductal Carcinoma in Situ of the Breast: 12-Year Results From the ECOG-ACRIN E5194 Study. J Clin Oncol 33:3938-44, 2015
4. Goyal S, Vicini F, Beitsch PD, et al: Ductal carcinoma in situ treated with breast-conserving surgery and accelerated partial breast irradiation: comparison of the Mammosite registry trial with intergroup study E5194. Cancer 117:1149-55, 2011
5. Jeruss JS, Kuerer HM, Beitsch PD, et al: Update on DCIS outcomes from the American Society of Breast Surgeons accelerated partial breast irradiation registry trial. Ann Surg Oncol 18:65-71, 2011
6. Vicini F, Shah C, Ben Wilkinson J, et al: Should ductal carcinoma-in-situ (DCIS) be removed from the ASTRO consensus panel cautionary group for off-protocol use of accelerated partial breast irradiation (APBI)? A pooled analysis of outcomes for 300 patients with DCIS treated with APBI. Ann Surg Oncol 20:1275-81, 2013

Study Summary

Title	Prone partial breast irradiation (PBI): prospective randomized controlled non-inferiority trial to compare radiation fibrosis with five versus three fractions
Protocol Number	S14-01306
Study Duration	5 years
Study Center (s)	Perlmutter Cancer Center
Study Hypothesis	A regimen of 8 Gy X 3 over 5 days (every other day) is as safe (well tolerated) and effective as 6 Gy X 5 over five consecutive days.
Objectives	1. To prospectively randomize patients to one of two fractionation regimens of image –guided prone breast radiotherapy (PBI) as part of breast preservation in post-menopausal women with low risk-Tis or T1 breast cancers: 600cGy X 5 over five consecutive days (arm 1) versus 8 GyX3 given every other day (arm 2). 2. To test the hypothesis that rate of post-treatment radiation fibrosis (grades 2+3) on the 8 Gy x3 arm is not more than 10% worse than the rate on 6 Gy x5. 3. To estimate local control and evaluate cosmetic outcomes on the two arms.
Number of Subjects	Maximum number of patients to be enrolled 284.
Main Inclusion Criteria	• Post-menopausal women (50-90 years old) defined as either 1) at least 2 years without menstrual period or 2) patients at least 50 years or older with serological evidence of post-menopausal status or 3) hysterectomized patients of any age with FSH confirmation of post-menopausal status. • pT1 or low risk-pTis breast cancer, excised with negative margins. Criteria for low risk-pTis: - Screen-detected - Low to intermediate nuclear grade - ≤ 2.5cm in size - Resected with negative margins at ≥3mm) • Clinically N0 or pN0 including sentinel node negative
Study Product, Dose Route, Regimen	Prone partial breast irradiation (PBI)
Statistical Methodology	Approximately 1 out of 10 patients experience grade 2-3 fibrosis after lumpectomy and partial breast radiation. Based on our prior experience, we observed a 10% rate of grade 2-3 fibrosis in these patients. With 142 patients randomized to each of the two treatment arms, we can test the hypothesis that the rate of fibrosis with 8Gy x3 is not more than 10% worse than the expected rate on the 6 Gy x 5 arm with one sided alpha =0.025 and power =80%.

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SCHEMA

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation	Explanation
cGy	Centigray
CTV	Clinical target volume
CBCT	Cone-beam CT
CBF	Contralateral breast failure
CSS	Cancer-specific survival
DCIS	Ductal carcinoma in situ
DF	Distant failure
DFS	Disease-free survival
DVH	Dose-Volume Histogram
EB	External beam technique
FSH	Follicle stimulating hormone
Gy	Gray unit
IBF	Ipsilateral breast failure
IGRT	Image guided Radiotherapy
IMRT	Intensity Modulated Radiation Therapy
INF	Ipsilateral nodal failure
kV	Kilovoltage
MV	Megavoltage
OS	Overall survival
PBI	Partial breast irradiation
PBR	Prone breast radiotherapy
APBI	Accelerated partial breast irradiation
PTV	Planning target volume
s/p	status pos

1.0 Objectives

1.1 To prospectively randomize patients to one of two fractionation regimens of image –guided prone breast radiotherapy (PBI) as part of breast preservation in post-menopausal women with T1 or low risk-Tis breast cancers: 600cGy X 5 over five consecutive days (arm 1) versus 8 GyX3 given every other day (arm 2).

1.2 To test the hypothesis that rate of post-treatment radiation fibrosis (grades 2+3) on the 8 Gy x3 arm is not more than 10% worse than the rate on 6 Gy x5.

1.3 To estimate local control and evaluate cosmetic outcomes on the two arms.

2.0 Background and Hypotheses

Partial breast irradiation (PBI) is becoming a new paradigm for breast cancer radiation [1] No type I or II evidence is currently available to demonstrate equivalence to standard whole breast radiotherapy, and a prospective randomized trial jointly sponsored by NSABP and RTOG (NSABP B-39 and RTOG 0413) has completed accruing patients, comparing whole breast radiotherapy to PBI, either by brachytherapy or external beam techniques (EB): results of this trial are pending. Until results of this or similar trials are available, PBI remains a research domain, and it should be offered to patients only in the context of a clinical experimental protocol.

2.1 Advantages of PBI through external beam radiotherapy

Despite the fact that less extensive experience than that of brachytherapy is available, PBI delivery through an external-beam has many advantages. First of all, it is likely to be more acceptable to the patient since it is non-invasive and it does not require a surgical procedure or anesthesia. Moreover, since it is delivered after surgery, the pathological analysis of the segmental mastectomy specimen is available to inform the selection of the best candidates. In addition, EB-PBI is likely to become more widely reproducible, since it does not rely on the experience and skills of the radiation oncologist performing the brachytherapy implant. Besides, once the technique is established, it can be widely applied at any facility provided with a linear accelerator, without the risk presented by some brachytherapy approaches that cannot be completed because of the unfavorable interplay of patient's anatomy with the technical limitations of the applicator [2]. Finally, in terms of health care economics, an external beam approach spares the costs of an extra surgical procedure and several days as inpatient (in the case of LDR brachytherapy) [3].
EB-PBI was originally tested in a prospective randomized trial that compared it to whole breast and nodal radiation, at Christie Hospital, in Manchester, UK [4]. At a follow up of 65 months, while survival in the two arms was comparable, the PBI arm had twice the local recurrence rate than the whole breast arm (20 versus 11%). Noticeably, eligibility to the trial included tumors as large as 4 cm in diameter and EB-PBI was delivered by 8 or 14 MeV electrons, through a generally small field, without the imaging support available nowadays to target the tumor bed. Certain histological characteristic of the primary tumor, lobular type and/or presence of DCIS in the specimen, were more likely to be associated with recurrence. Conversely, in carriers of infiltrating ductal carcinomas treated by PBI, the failure rate outside the original quadrant was only 5.5 %.

This experience informed the more careful patient selection of the contemporary EB-PBI clinical trials, that limit eligibility to patients with smaller tumors with negative margins of resection and

without an extensive intraductal component.[5-8] The clinical target volume (CTV) usually consists of the tumor cavity visualized at CT planning, plus 1-1.5 cm of margin. An extra 1-2 cm is added to the CTV to create the planning target volume (PTV), taking into account some variability in the daily positioning.

2.2 The NYU experience of prone PBI

A prone approach for partial breast radiation has been tested at NYU in a clinical trial sponsored by an IDEA grant of the Department of Defense (NYU 00-23). Results of the first 47 patient accrued originally demonstrated feasibility [7]. Eligibility to this study was limited to post-menopausal women with non-palpable, mammographically detected tumors. In addition, the protocol required patients to have first refused to undergo standard six-week radiotherapy. Five fractions of 6 Gy were delivered to the PTV over ten days . The dose and fractionation was based on radiobiological modeling, aimed at determining a dose to deliver in five fractions that would achieve equivalence to the tumor control estimates of 50 Gy in 25 fractions, while maintaining a risk of fibrosis at the tumor bed comparable to that of a standard regimen of 60 Gy in 30 fractions [7] [9]. An $\alpha/\beta = 4$ for tumor control was used, and its validity has been recently confirmed by the results of a prospective randomized trial comparing accelerated to standard whole breast radiotherapy [10]. We recently reported the 5y results of this trial (see below, 2.3)

RTOG tested conformal EB-PBI in the supine position in a Phase I-II trial (RTOG 0319) which rapidly accrued its target population of 58 patients [8]. This important trial confirmed the feasibility of EB-PBI in a supine position, through multi-institutional accrual. Ten fractions of either 3.4 Gy or 3.85 Gy were delivered twice a day, separated by an interval of 6 hours, to a total dose of 34 Gy or 38.5 Gy. The dose/fractionations were chosen to mimic the extensive experience acquired by PBI through brachytherapy, based on the original assumption of $\alpha/\beta=10$ for tumor control.

At the early follow-up point of 2-3 years, it is encouraging to notice that either technique achieves excellent local control and cosmetic results. However, the results of prone EB-PBI are slightly superior in terms of normal tissue sparing, due to the fact that when prone, the treating beam can be directed to avoid exiting through the rest of the body [11].

Table 1. Series of Partial Breast Radiation Therapy

	Present series	Formenti *et al.* series*	Vicini *et al.* series†
Clinical characteristics			
Number of patients	61	47	31
Menopausal status	Premenopausal and postmenopausal	Postmenopausal	Postmenopausal
Median age	62 (38–91)	67.5 (51–88)	62 (47–88)
Maximum tumor size allowed	2 cm	2 cm	3 cm
Median tumor size (cm)	0.9 cm (0.1–2.0)	0.9 cm (0.13–1.9)	0.9 cm (0.1–2.7)
Negative margins	≥2 mm	≥5 mm	≥2 mm
Receptors	Negative or positive	Positive only	NA
Doses and fractionation			
Total dose	32 Gy	30 Gy	38.5 Gy
Dose per fraction	4 Gy	6 Gy	3.85 Gy
Number of fractions	8	5	10
Overall treatment time	4 days/b.i.d.	10 Days/q 2 days	5 days/b.i.d.
Technique	Minitangents + enface	Minitangents	3–5 noncoplanar
Position	Supine	Prone	Supine
Dosimetric characteristics			
Ipsilateral lung			
V20	0% (0–14%)	0% (0–4%)	4% (0–8%)
V10	2% (0–22%)	0% (0–6%)	9% (0–34%)
V5	6% (0–67%)	0% (0–10%)	16% (0–37%)
Heart (left side only)			
V20	0% (0–1%)	0% (0%)	0% (0–3%)
V10	0% (0–5%)	0% (0%)	0% (0–7%)
V5	0% (0–70%)	0% (0%)	NR

Table 1. reproduced from Taghian AG et al, IJROBP: 64(4):1092-99, 2006 [12]. The table depicts the similarities between the three published series of accelerated partial breast irradiation. The prone technique achieves better normal tissue sparing.

2.3 Results of NYU 00-23: five year local control

The 5-year results of the initial clinical trial of prone PBI mentioned in 2.2 were recently reported (Formenti et al. *Int J Radiat Oncol Biol Phys. 2012 November 1; 84(3): 606-611. doi:10.1016/j.ijrobp.2012.01.039).* Post-menopausal patients with Stage I breast cancer with non palpable <2 cm tumors, negative margins, and negative nodes, positive hormonal receptors, and no extensive intraductal component (EIC) were eligible to NU 00-23. The trial was offered only once eligible patients had refused to undergo standard whole-breast radiotherapy. Patients were simulated and treated on a dedicated table for prone set-up. Radiation was delivered conformally, and was 30 Gy in five 6 Gy/daily fractions over 10 days with port film verification at each treatment. Recurrence in the ipsilateral breast, ipsilateral nodal, contralateral breast, and distant failure (IBF, INF, CBF, DF) were estimated using the cumulative incidence method. Disease-free, overall, and cancer-specific survival (DFS, OS, CSS) were recorded.

One hundred patients accrued to this IRB-approved prospective trial, one with bilateral breast cancer. One patient withdrew consent after simulation and another elected to interrupt radiotherapy after receiving two treatments. Ninety-eight patients are evaluable for toxicity and, in one case, both breasts were treated with PBI. Median patient age was 68 years (range 53-88 years); in 55% the tumor size was <1 cm. All patients had hormonal receptor positive cancers: 87% underwent adjuvant anti-hormonal therapy.
At a median follow-up of 64 months (range, 2-125 months), there was one local recurrence (1% in breast failure, IBF) and one contralateral breast cancer (1% contralateral breast failure,CBF). There were no deaths due to breast cancer by 5 year. Grade 3 late toxicities occurred in 2 patients (1 breast edema, 1 transient breast pain). Cosmesis was rated good/excellent in 89% of patients

with at least 36 months follow-up. The encouraging results of this trial have generated interest to further reduce the number of radiotherapy sessions for partial breast radiation, and compare five to three fractions, the purpose of this protocol.

2.4 Inter-fraction reproducibility: the role of IGRT

A recognized challenge of partial breast irradiation is the daily identification of the correct target. Kader et al [13] have studied the evolution of the seroma with time (Fig 1A and 1B). When patients are treated in the supine position: both the volume of the cavity and the profile of the breast change over time (Fig 1A and 1B), a similar course is likely to occur during prone treatment. Clearly, an accelerated course, to complete within one week, has the advantage of treating a more stable volume. Ideally, daily target verification could both confirm the planning volume and enable correction of inter-fraction, setup-derived, changes of the target.

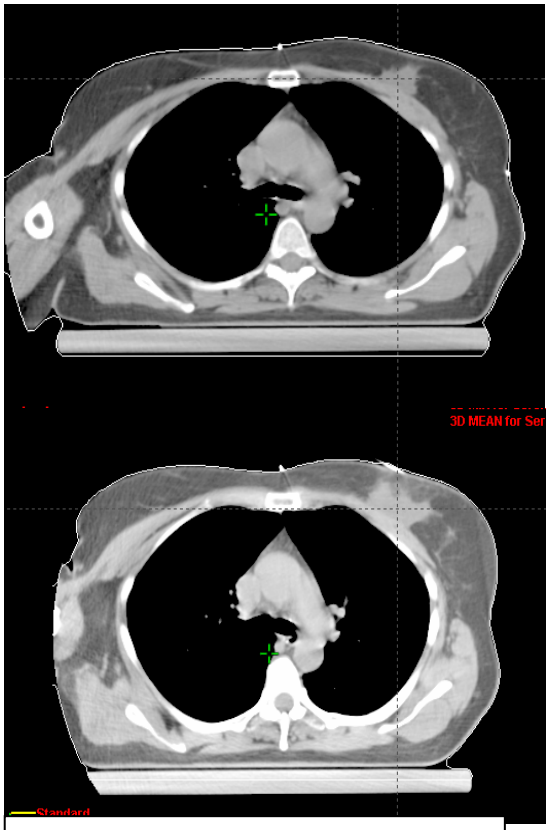

Figure 1A and B. Changes of the seroma over time, 2 and 6 weeks after surgery, respectively.

Published evidence suggests that image guided radiotherapy, IGRT can be utilized to reduce setup errors in partial breast radiation therapy delivery. The Princess Margaret Hospital reported on cone-beam CT (CBCT) guidance for setup error reduction and soft tissue visualization in accelerated partial breast irradiation (APBI)[14]. A total of 315 CBCT data sets revealed that systematic errors for the skin-mark setup were reduced from 2.7, 1.7, and 2.4 mm to 0.8, 0.7, and 0.8 mm in the right–left, anterior–posterior, and superior–inferior directions, respectively with CBCT guidance. The random errors were reduced from 2.4, 2.2, and 2.9 mm for skin-marks to 1.5, 1.5, and 1.6 mm for CBCT guidance in the right–left, anterior–posterior, and superior–inferior directions, respectively. Implementing CBCT guidance for APBI was shown to reduce the random and systematic setup error by almost half when compared with a skin-mark setup.

In our previous protocol of PBI, cone-beam CT (CBCT) was for the first and for the last radiation fraction in order (1) determine the errors for a conventional skin-mark setup, (2) measure the accuracy of a CBCT-guided setup and to compare with megavoltage portal images, and (3) determine the visibility of the post-lumpectomy seroma on the CBCT images. Results from this experience suggest high reliability of the prone setup, permitting to only obtain a CBCT, at baseline, before treatment starts.

2.5 Optimal accelerated fractionated regimen over a five days interval of time.

The optimal accelerated dose fraction for external beam partial breast irradiation remains to be established. One of the main objectives of this study will be to determine the acute effects using a regimen of 6 Gy x 5 daily fractions over five consecutive days. Our prior protocol evaluated the

feasibility of 6 Gy x 5 fractions over 10 days. In our preliminary experience there have been very minimal acute effects with this regimen.

The biologically equivalent doses of different fractionation schedules are the total doses for which the probabilities of a certain outcome/complication are the same. Certainly, they can be different for specific outcomes/complications.

The biologically equivalent doses in regard of several outcomes/complication to a treatment delivered in the standard 2 Gy fractions five times a week was estimated by the widely used formula[16, 17]:

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

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

$$Dnew = 5^*dref^* (\alpha / \beta + dref) / (\alpha / \beta + 2)$$

where α / β is a tissue dependent parameter, arising from the radiobiological linear - quadratic cell survival model. The resulting equivalent total doses are shown in Table 2.

TABLE 2. Equivalent total doses based on α / β Biologically Effective Doses (BED)

Dosexfractions	α / β (Gy)	BED Standard 2 Gy x 30 fx	BED Standard 2 Gy x 25fx	BED RTOG/NSABP 3.85 Gy x 10fx	BED NYU 6 Gy x 5fx	BED NYU 8 Gy x 3fx
Erythema	8	75 Gy_8	63 Gy_8	57 Gy_8	53 Gy_8	48 Gy_8
Desquamation	11	71 Gy_{11}	59 Gy_{11}	52 Gy_{11}	46 Gy_{11}	41 Gy_{11}
Telangiectasia	4	90 Gy_4	75 Gy_4	76 Gy_4	75 Gy_4	72 Gy_4
Fibrosis	2	120 Gy_2	100 Gy_2	113 Gy_2	120 Gy_2	120 Gy_2
Tumor	4	90 Gy_4	75 Gy_4	76 Gy_4	75 Gy_4	72 Gy_4

As shown in Table 2, the proposed hypo-fractionated schedule of 8Gy X 3 results in equivalent tumor control when compared with the standard regimen of six weeks of daily radiotherapy. In addition, as compared with the on-going NSABP trial (NSABP B-39 and RTOG 0413) and the NYU 6 Gy x 5 schedule, the proposed experimental schedule of 8 Gy x 3 fraction results in a lower calculated probability of acute effects and erythema, a similar probability for developing late radiation fibrosis as the NYU 6 Gy x 5 schedule and a slightly higher probability for developing late radiation fibrosis as compared to NSABP B-39/RTOG 0413. Specifically, we predict that the new 8 Gy X 3 schedule will result in comparable local control and toxicity of the previously tested 6GyX5 one, where the incidence of radiation fibrosis among 292 patients accrued ranged between 20-30%.

2.7 Risk of developing post-radiotherapy fibrosis: correlating a phenotype to a genotype – Genomic Analysis in order to determine genetic markers.

Exceeding a total dose of 60 Gy has shown to be associated with increased risk of fibrosis at the treated site. Even when the total dose is reduced, like in this trial (30 or 24Gy, respectively for arm 1 and 2), the use of fraction sizes in excess of the standard dose of 2 Gy may reflect in increased risk of fibrosis. This complication however occurs only in a minority of irradiated patients that currently cannot be identified in advance. While some induration at the original site is expected and it reflects the result of lumpectomy healing and seroma organization, fibrosis and retraction exceeding grade 1 (grade 2,3), is likely to represent a late effect of radiation.

Table 3 LENT SOMA DEFINITION OF FIBROSIS AND RETRACTION (appendix 2)

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%
Ulcer	Epidermal only, <1 cm^2	Dermal only, >1 cm^2	Subcutaneous

Not only does fibrosis compromise the cosmetic result but it also impairs the clinical exam of the breast. Post-radiation therapy fibrosis is characterized by mesenchymal cells replacing the normal tissue and overproducing extracellular matrix and it is clinically measured following the LENT/SOMA classification (Table 3 and appendix 2).

Table 4 summarizes the incidence of fibrosis and retraction (grade 1-3) among 276 patients treated in our current protocol of Image guided Radiotherapy for PBI, using five consecutive fractions of 6Gy. While the degree of this complication also reflects the different surgical techniques of segmental mastectomy, it appears that approximately 1/3 patients suffer some degree of breast distortion/fibrosis with the current hypo-fractionated regimen of 6GyX5. The current trial is designed as a non-inferiority study, powered to enable the detection of 10% or more difference in the incidence of fibrosis.

Table 4 INCIDENCE OF FIBROSIS AND RETRACTION
(276 women treated with prone partial breast radiotherapy 6 Gy x 5)

	Fibrosis		Retraction/ Atrophy	
Grade	**Number of patients**	**Percent**	**Number of patients**	**Percent**
1	68	24.64	63	22.83
2	18	6.52	21	7.61
3	3	1.09	4	1.45
Total Patients with Grades 1-3	89	32.25	88	31.89
Total Number of Patients in Study	276		276	

Recently, Quarmby et al. reported on TGFbeta1 gene polymorphisms on DNA obtained from 103 breast cancer patients who received radiotherapy. Patients who are carriers of specific polymorphisms of TGF-beta -509TT or +869CC alleles were between 7 and 15 times more likely to develop severe fibrosis. [18]

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2.8 Study Hypotheses

A regimen of 8 Gy X 3 over 5 days (every other day) is as safe (well tolerated) and effective as 6 Gy X 5 over five consecutive days.

3.0 RESEARCH RISK & BENEFITS

3.1 Risk of Study treatment

The risks involved in using the treatment machine or the CT scanning are described as possible fatigue, skin damage, swelling, muscle tightness, and position-induced muscle aches (back and shoulder).

3.2 Other Risks of Study Participation

Additional risks to study participation include breach of confidentiality. Privacy protection procedures are in place and good clinical practice guidelines are followed throughout the study to minimize the risks associated with breach of confidentiality.

3.3 Potential Benefits

The potential benefits to subjects with study participation are improved overall survival. The information obtained from this research may help others with this disease in the future.

3.4 Drug Information
NA

4.0 Staging Criteria
TNM Stage I, T1 N0 M0 breast cancer patients.
TNM Stage 0, TisNxM0 breast cancer patients.

5.0 RESEARCH POPULATION

Patient Eligibility
284 study subjects at least over the age of 50-90 female are to be entered into this study across all NYU School of Medicine and Bellevue Hospital (satellite campus). This study will be an out-patient study. We do not plan to enroll vulnerable population and there are no restrictions on race/ethnicity.

Inclusion criteria:

5.1 Post-menopausal women defined as either
1) at least 2 years without menstrual period or
2) patients at least 50 years or older with serological evidence of post-menopausal status or
3) hysterectomized patients of any age with FSH confirmation of post-menopausal status.

5.2 pT1 breast cancer, excised with negative margins.
Low risk-pTis breast cancer, excised with negative margins.
Criteria for low risk-pTis:
- Screen-detected
- Low to intermediate nuclear grade
- $\leq$ 2.5cm in size
- Resected with negative margins at $\geq$3mm)

5.3 clinically N0 or pN0 including sentinel node negative

Exclusion criteria:

5.4 Previous radiation therapy to the ipsilateral breast.

5.5 Presence of a proportion of DCIS in the core biopsy specimen which is compatible with extensive intraductal component (EIC).

5.6 Subject Recruitment, Registration and Screening
All efforts will be made to actively recruit and retain members of minority groups in this study. The inclusion and exclusion criteria in this study should not have a negative effect on the enrollment of these populations.

Target enrollment for this study is 284 patients. Each cohort will consist of 142 patients. Patients will be recruited from physicians at the NYU Perlmutter Cancer Center and Bellevue Hospital. Consenting, screening, and treatment takes place at the NYU PCC under the supervision of the Principal Investigator. Prospective subjects receive detailed information about this study its investigational nature, required study procedures, alternative treatments, risks and potential benefits of the study. They also receive the informed consent document to read. All questions are answered by the PI and qualified research personnel.

The Principal Investigator will:

1. Obtain signed and dated informed consent from the potential patient before ant study specific procedures are performed.
2. Determine patient eligibility See Sections 5.1 through 5.5.
3. Submit registration to NYU Perlmutter Cancer Center CTO
4. Receive registration confirmation from the Research Coordinator at NYU Perlmutter Cancer Center CTO, including a unique study identification number assigned to the patient by the research coordinator, which will be distributed to the study team upon registration.

Recruitment and consenting will take place in a private area such as an exam room to protect the patient's privacy. The informed consent process and documentation follows the established procedures of the NYU PCC CTO.

5.7 Informed Consent

Consent will be obtained only by a participating investigator who has completed requisite training for human subject research and has been instructed by the Principal Investigator about the patients and address any questions or concerns prior to obtaining written informed consent for participation and HIPAA authorization.

Patients will be given adequate time to read the consent form. They will be given time to ask questions about the study in private exam rooms. Questions will be answered by a participating physician, or qualified research study team member all of whom have completed requisite training for human subject research. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation. Investigators will stress that participation in the study is completely voluntary and will not affect the care patients receive or result in any loss of benefits to which patients are otherwise entitled.

For non-English speaking patients, institutional translation services will be utilized. For these patients the consent letter and all other information will be administered orally and a witness, not related to the research project, will be present while the oral presentation is given. A short form will be utilized for the subject to sign in his/her name and the translator and/or witness must sign the short form. The translator will also sign the main consent form.

For patients who cannot read. A witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The investigator will ask the patient questions to ensure s/he understands the study. If the

investigator determines the subject understands the study, the patient will mark an X where his/her name would go and the witness will sign the consent form.

5.8 Documentation of Consent

The Principal Investigator or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

6.0 REGISTRATION GUIDELINES

Patients will be registered with the Clinical Investigations Support Office of the department of Radiation Oncology and with the Clinical Research Office of the Cancer Center.

6.1 At the time of registration, one signed and dated informed consent will be obtained, along with three copies for patient, medical record, Clinical Investigations Support Office of the department of Radiation Oncology and with the Clinical Research Office of the Cancer Center.

6.2 At the time of registration, the eligibility registration worksheet will be completed.

6.3 A flow sheet to record baseline characteristics including demographic and disease characteristics will be used to collect data as well as detailing clinical parameters and toxicity. The flow sheets will be maintained during therapy and the entire duration of the study (5 years).

6.4 Confidentiality

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

All patients will be required to sign a written informed consent prior to being registered on this study. Every effort will be made to answer questions raised by patients and their families or advocates regarding the protocol and alternative therapies prior to asking a patient to sign the consent form.

Once eligibility is verified, a unique patient study number will be issued within 24 hours of receiving all required registration material. The patient will not be identified by name. This is the point, at which, the patient is considered on study. Subjects must <u>not</u> start any protocol procedures prior to registration.

6.5 Screening Process

During the screening visit, the following will happen:

1. The study doctor will ask the subject questions about their medical history, including information about other medical problems.

2. You will be asked what prescription medications, over-the-counter (OTC) supplements, herbal products, vitamins, and any other OTC products you are taking.

3. The study doctor will perform a physical examination and collect your vital signs (heart rate, breathing rate, blood pressure and temperature).

6.6 Selection Process

If subject is eligible to participate in this study, the subject is randomly assigned to one of two radiation treatment groups:

Group 1 (Arm 1): will receive a radiation dose of 6Gy each day for 5 consecutive days.

Group 2 (Arm 2): will receive a radiation dose of 8Gy every other day over a period of 5 days.

Before starting radiotherapy, you will be required to undergo a radiation therapy planning session/simulation session to enable your radiation doctor to carefully design the radiation treatment so that only the area that is affected by tumor is radiated while trying to avoid surrounding normal tissue. A simulation session is required to obtain images of your chest to tailor the radiation treatment to your body shape. During this simulation session, you will lie prone (on your belly) so that we can best cover the radiation target region (the tumor bed) while avoiding heart and lung tissue as much as possible. The tumor bed is where your tumor was before you had it surgically removed.

6.7 Early Withdrawal of Subjects

A subject has the right to voluntarily discontinue treatment or withdraw from the study at any time, for any reason, and without repercussion. The investigator has the right to discontinue a subject from the study or withdraw a subject at any time.

Reasons for subject withdrawal from the study may include:

- Subject withdrawal of consent at any time
- Any medical condition that the investigator determines my jeopardize the patient's safety if she continues in the study or continues treatment.
- The investigator determines it is in the best interest of the patient
- Failure of subjects to adhere to protocol requirements

Every effort will be made to obtain information on subjects who withdraw from the study, including the reason for taking a participant off the study. The date the participant was removed, must be documented.

6.8 Follow-up

After the end of radiation treatment, each subject will be followed for 30 days (± 2 weeks), at 90 days and 6 months (± 6 weeks) for serious adverse event reporting. Assessments will continue with yearly (± 8 weeks) visits for the remaining 5 years.

7.0 METHODS & PROCEDURES

7.1 Descriptive Factors/Stratification/Randomization Scheme

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

7.2 Randomization Scheme

Research Coordinators will randomize patients to one of the 2 arm of the study, as soon as they have provided informed consent and eligibility packet to participate in the research study. The randomization list will be done via REDCap, a browser-based, metadata-driven EDC software solution for research databases and will be maintained in the department of Radiation Oncology.

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Table 5 Study Schema

Eligibility	**284 stage I or low risk-stage 0 breast cancer in post-menopausal women, s/p segmental mastectomy** **Low risk-stage 0 criteria:** • Screen-detected • Low to intermediate nuclear grade • ≤ 2.5cm in size • Resected with negative margins at ≥3mm	
Day 0	**Informed consent and randomization** **CT planning for determination of tumor bed on the prone position**	
Day 1-5 **(start within 90 days from last breast surgery)**	**Daily IGRT, IMRT or Conformal Partial breast irradiation, randomly assigned to:**	

	600 cGy X 5 fractions, over 5 consecutive days (arm 1) **or** **800 cGy X 3 fractions, every other day, over 5 days (arm 2)**	

8.0 RATIONALE FOR STUDY DESIGN

8.1 The women in this study will receive either 5 or 3 radiation fractions to the tumor bed. We have chosen to study T1 or low risk-Tis post menopausal women because in this subset: 1) the tumor is small enough to be treated by partial breast radiation 2) the odds of having multicentric disease are low, making it ethical to avoid whole breast irradiation, 3) the most benefit from reducing the radiation schedule from 5 to 3 could be expected.

8.2 The Principal Investigator explains all elements of the protocol to the patients and answers any and all questions. Clinical procedures are performed by the principal investigator. The consent process takes place in the Department of Radiation Oncology at NYU Medical Center.

8.3 Once the process of eligibility has been determined, patients will be randomly assigned to one of the 2 arms:
Arm 1: 6 GyX5 over 5 days, on five consecutive days
Arm 2: 8 GyX3 over 5 days, every other day

8.4 Simulation and treatment will be started within 90 days from surgery, in order to maximize the chances of optimal lumpectomy cavity visualization on the planning and cone beam CT scans. Start of treatment within 60 days from surgery is encouraged, but the treating physician is allowed a window up to 90 days from last breast surgery to start the radiation treatment, as long as clinical judgment supports accurate visualization of the target lumpectomy cavity at that timepoint.

8.5 All subjects will be followed for 30 days ($\pm$ 2 weeks), at 90 days and 6 months ($\pm$ 6 weeks) , then yearly for 5 years ($\pm$ 8 weeks) (see 11.0 Study calendar).

9.0 RADIATION THERAPY/TREATMENT PLAN

9.1 Radiation Dose Specification: The prescription dose is the dose delivered to a reference point within the clinical target volume. The prescription dose should cover at least ninety- five percent of the planning target volume.

9.2 Target Volumes:

9.2.1 The resection cavity should be discernible based upon architectural changes in the breast tissue by the CT images and is defined as the clinical target volume (CTV).

9.2.2 The planning target volume (PTV) = CTV + 1.5 cm margin.

9.2.3 PTV eval = PTV limited to be within the defined ipsilateral breast tissue, specifically excluding the 1st 5 mm of tissue under the skin and tissue beyond the chest wall, pectoralis muscles and lung.

9.2.4 Whole breast reference volume: all tissue encompassed within traditional tangent field borders, excluding tissue deep to the chest wall interface and using the skin surface as the superficial border.

9.3 Imaging: A treatment planning CT of the breast will be acquired with the patient in the treatment position (prone), utilizing the same immobilization devices as will be used for treatment. CT scan thickness should be ≤ 0.375 cm through the tumor bed region. These images will be used in 3D treatment planning of the breast in accordance with the dose specification constraints.

9.4 Treatment Machine: A linear accelerator with > 4 MV x-rays is required.

9.5 Immobilization Techniques: Patients will be set-up for treatment and CT scanning utilizing a dedicated table designed to accommodate prone positioning for breast treatment [15].

9.6 Target Positioning Verification: Digitally acquired radiographic images, acquired prior to each fraction, will be used to verify the position of the target with respect to the treatment machine's isocenter using digitally reconstructed radiographs (DRRs) as a reference image set. Both kV and MV images may be used to verify setup.

9.7 IGRT Target Localization: Cone-beam CT (CBCT) images will be acquired prior to the first radiation treatment. By using IGRT to image the post-operative tumor bed of the breast in "real-time", the operator may automatically align the tumor bed with the treatment machine on the day of treatment. If shifts are made based upon the CBCT images, they will be recorded and the following day's portal images will be taken. If the resection cavity is not visualized then cone-beam CT images will be used to ensure optimal positioning of the breast tissue.

9.8 Treatment Planning: 3D-Conformal or Intensity Modulated Radiation Therapy (IMRT) treatment planning is allowed. This includes "field-in-field" beams as well as the use of dynamic multi-leaf collimator (MLC) derived using inverse planning or electronic compensator techniques. Field arrangements and technique should be chosen that satisfy the PTV_eval and normal tissue dose constraints using Dose-Volume Histogram (DVH) analysis. By carefully selecting the gantry and table angle combinations that do not enter or exit through other organs of the body, the dose can be confined to the traditional breast treatment volumes treated using a pair of tangent photon beams. No plan will be deemed acceptable if fields are directed towards the contralateral breast, heart or lung. Non-coplanar beam arrangements are encouraged, but not required. Dose calculations with tissue inhomogeneity correction must be used.

9.9 Normal Tissue Dose Constraints:

9.9.1 Uninvolved by tumor breast: Less than 60% of the whole ipsilateral breast should receive >50% of the prescription dose and less than 35% of the whole breast should receive the prescription dose.

9.9.2 Ipsilateral lung: Less than 15% of the lung can receive 30% of the prescribed dose.

9.9.3 Contralateral lung: Less than 15% of the lung can receive 5% of the prescribed dose.

9.9.4 Heart: Less than 5% of the heart can receive > 5% of the prescription dose.

10.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

10.1 Expected toxicities include fatigue and skin reactions within the radiation field. Erythema, dry and wet desquamation of the skin will be recorded weekly.

10.2 In the previous study of 45 patients there were no grade 2-3 skin toxicities[19]. Additional experience with the same regimen in 292 patients, demonstrated no grade 2-3 acute toxicity.

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

10.4 The risks associated with venipuncture may occasionally include pain, bruising, fainting or a small infection at the puncture site.

11.0 STUDY CALENDAR

All subjects will be followed the first 30 days (± 2 weeks), at 90 days and 6 months (± 6 weeks) for serious adverse event reporting. Assessments will continue with yearly (± 8 weeks) visits for the remaining 5 years. Acute and late effects will be recorded following the criteria described in Appendix 1 and 2. At each post treatment follow-up visit, a physical exam to detect clinical recurrence will be performed. Mammographic studies and/or MRI will be performed and reviewed on an annual basis. The degree of fibrosis assessed by palpation will be measured as per Appendix 2, late effects.

Table 6 Flow Chart/Time and Events Schedule for Treatment and Follow up

Procedure Summary	Pre treatment	Day 1	Day 2	Day 3	Day 4	Day 5	30 days post treatment	Follow Up - 90 day post treatment	Follow Up 6 months post treatment	Follow up - Every year for 5 years
Informed Consent	X									
MD/NP visit: physical and vital signs/cosmesis assessment (you will be examined for any skin changes at the radiation site)§	X	X§*		X§*		X§*	X	X	X	X
Medical History	X						X*	X*	X*	X*
Mammogram	X								X**	X**
Lumpectomy Pathology Report	X									
Randomization (Treatment assignment)	X									
Treatment simulation***	X									
Baseline CBCT, first RT		X								
Port films/ each RT dose after the first one[a,b]			X	X	X	X				
Radiation Therapy		X[a,b]	X[a]	X[a,b]	X[a]	X[a,b]				
AEs		X	X	X	X	X	X	X	X	X

§MD evaluation will occur at least once during treatment visits.
§* MD evaluation will occur at least once if randomized to Arm 2
* first 30 days (± 2 weeks) post-treatment, then 90 days and 6 months (± 6 weeks) , and then yearly for the next 5 years (± 8 weeks).
** Standard annual mammogram (or MRI) for both breasts.
*** May occur before Informed Consent, as this is part of standard of care
[a]Arm1 6Gy X 5 fractions (5 days)

[b]Arm2 8Gy X 3 fractions (3 days)

12.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

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

12.2 Local recurrence will be classified as it follows:

12.2.1. Local recurrence within the field of conformal radiation is defined as TRUE LOCAL RECURRENCE.

12.2.2 In breast recurrence outside the treatment volume will be defined as LOCAL RECURRENCE OUTSIDE THE FIELD, SAME BREAST

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

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

Local/regional recurrences will be further grouped as:

12.3.1 ISOLATED LOCAL/REGIONAL RECURRENCES

12.3.2. CONCOMITANT LOCAL/REGIONAL AND DISTANT RECURRENCES

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

12.3.3. METACRONOUS LOCAL/REGIONAL RECURRENCES.

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

13.0 STATISTICAL AND DATA MANAGEMENT CONSIDERATIONS

Study Design: This study is a prospective randomized controlled trial to test the hypothesis that 8 Gy x 3 fractions is not worse that 6 Gy X 5 fractions, with respect to the development of breast fibrosis.

The current 6X5 schedule results in 1% 5 year recurrence rate and 10% of grade 2 or 3 fibrosis and approximately 32% of any induration or retraction, measured at after a minimum of 6 months from treatment. In other words approximately one out of 10 patients experience grade 2-3 fibrosis after lumpectomy and partial breast radiation.

Based on our prior experience, we observed a 10% rate of grade 2-3 fibrosis in these patients. With 142 patients randomized to each of the two treatment arms, we can test the hypothesis that the rate of fibrosis with 8Gy x3 is not more than 10% worse than the expected rate on the 6 Gy x 5 arm with one sided alpha =0.025 and power =80% .
The trial will have a planned interim analysis when 142 patients across both arms are evaluable for fibrosis assessment at 2 years from accrual. Table 7 below provides the stopping boundaries for the interim and final analyses. The trial will not stop while waiting for the results from the interim analysis.

All analyses may be stratified by whether a ppatient started treatment within 60 days from surgery or within 90 days from surgery.

Table 7 Stopping Boundaries for Non-inferiority with Respect to Proportion of Patients with Fibrosis Treated with 8Gy x3 Compared with Control of 6GY x5 Overall 1-sided alpha = 0.025, power =80%, O'Brien-Fleming Boundaries Calculations from EAST V 6.2, Cytel Inc.

		To Reject Ho of Non-inferiority		
Analysis	Number of Patients Randomized and Evaluable for Fibrosis	Critical Value of z-statistic	Alpha level	Difference in Proportion of Patients with Fibrosis (8Gy x3 -6Gyx5)
Interim	142	≤-2.96	≤0.0015	≤-0.0493
Final	284	≤-1.97	≤0.0245	≤0.0299

Data management will be carried out by staff of the Department of Radiation Oncology and the NYUCI under the direction of Drs. Perez and Goldberg. Randomization will occur via REDCap (Research Electronic Data Capture), after consent is acquired, by the PI, research nurse, in the department of Radiation oncology. Data will be entered into Velos, a database management system maintained by the NYULMC PCC CTO according to the procedures of the NYULMC PCC CTO. Patients will be followed every 12 months to evaluate their status with respect to recurrence. Recurrences will be evaluated using standard criteria in the Dept. of Radiation Oncology that are provided in the protocol. Data will be transferred from the Velos database to the Division of Biostatistics for analysis. The Principal Investigator, Research Nurse, and Research Coordinators have access to data collected.

Analysis: Patient characteristics at randomization will be summarized by treatment group using descriptive statistics and graphical displays. For the primary endpoint of fibrosis, the proportions of patients by grade of fibrosis will be compared in the two treatment arms using contingency table methods and chi square tests. The primary analysis will be the difference in proportions of patients with grade 2 or 3 fibrosis between the two treatment groups compared using a non inferiority z- test. Secondary endpoints including rates of recurrence at 1, 2, and 3 years post randomization will be estimated with 95% confidence limits within treatment groups along with plots of Kaplan-Meier time to recurrence curves.
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14.0 ADVERSE EVENT REPORTING AND DSMC

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

Definitions of adverse events

Adverse event (AE)

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

Serious adverse event (SAE)

An adverse event occurring at any dose that results in any of the following outcomes:

-death

-a life-threatening adverse drug experience

-inpatient hospitalization or prolongation of existing hospitalization excluding those for administration, transfusional support, disease staging/re-staging procedures, concomitant radiotherapy, thoracentesis/paracentesis, or placement of an indwelling catheter, unless associated with other serious events.

-persistent or significant disability/incapacity,

or

-congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug experiences when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Death, regardless of cause, which occurs within 30 days of the last dose of or after 30 days and is a result of delayed toxicity due to administration of the , should be reported as a serious adverse event.

Unexpected adverse event

An adverse event that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the Investigator's brochure or package insert.

Life-threatening

Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

Reporting adverse events

Adverse events

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

The investigator must determine the toxicity of adverse events according to the CTC version 2.0 (Appendix 1) and their causal relationship.

Serious adverse events

Adverse events classified as serious require expeditious handling and reporting to comply with regulatory requirements.

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

SAE contact information for NYULMC PCC Clinical Trials Office;
Please email all SAEs to NYUPCCsafety@nyumc.org, Dr. Carmen Perez, and the NYULMC PCC regulatory specialist within 24 hours of learning of the SAE.

Serious adverse events will be reported to:

Name Carmen Perez, M.D. *Address* 160 East 34th Street NY, NY10016
Phone number: (212) 731-5003 Fax number: (212) 731-5513

The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

The Principal Investigator is responsible for reporting all unexpected problems involving risk to participants or others to NYU Perlmutter Cancer Center CTO.

Federal regulations require timely reporting by investigators to the NYULMCIRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

This section also specifies the NYULMC IRB requirements for investigator reporting of unanticipated problems posing risk to subjects or others, including adverse events. The IRB requirements reflect the current guidance documents released by the Office of Human Research Protections (OHRP), and the Food and Drug Administration (FDA) and are respectively entitled "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – improving Human Subject Protection".

The NYU IRB address is:
NYU School of Medicine IRB
1 Park Avenue, 6th Floor
New York, NY 10016

14.1 MEDICAL MONITORING It is the responsibility of the Principal Investigator to oversee the safety of the study at these sites. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. The Data Safety and Monitoring Committee (DSMC) will review the study at least annually. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

14.1.2 DATA AND SAFETY MONITORING PLAN
This study will be monitored by the Data Safety Monitoring Committee (DSMC) of the New York University (NYU) Perlmutter Cancer Center (PCC). The DSMC operates based on the 2011 National Cancer Institute approved Charter. It is an existing and multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for clinical trials conducted in the NYULMC Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the Director of the NYULMC PCC.

Per the NYU PCC Institutional Data Safety and Monitoring Plan, this study will be monitored by DSMC at least annually (from the date the first patient is enrolled), and at the completion of the study prior to study closure. This review includes accrual data, subject demographics and adverse events. The Principal Investigator is required to attend the review of their study. Additional reviews can be scheduled based on SAE reports, investigator identified issues, and external information, etc. The DSMC will review safety data every 6-8 weeks.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

At the NYU Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review and DSMC review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

(1) Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research nurses, data manager and research team.

(2) DSMC, at least annually

(3) Institutional Review Board (IRB): An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.

(4) In addition, the quality assurance unit will monitor this trial every 6-8 weeks, to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines.

14.2 DATA AND SOURCE DOCUMENTATION

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into Velos. Relevant source documentation to be reviewed by the DSMC throughout the study includes:

1. Baseline measures to assess eligibility and disease status
2. Subject demographics
3. Treatment records
4. Adverse events

Velos, an electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned research coordinator, and CTO quality assurance specialists will have access to the database. Velos is the primary data collection instrument for the study. All data requested in Velos must be reported. All missing data must be explained. The quality assurance specialists will monitor this trial 6-8 weeks for data entry accuracy.

15.0 STUDY FINANCES

15.1 RESEARCH CONFLICT OF INTEREST

There are no conflicts of interest to report.

15.2 COST TO SUBJECTS

Each subject or their insurance company will be charged and held responsible for the costs of care provided as part of this study. Radiotherapy is a standard treatment for breast cancer and will be billed to subjects and their insurance companies.

There will be no monetary compensation for participating in this study.

16.0 REFERENCES

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APPENDIX 1

Common Toxicity Criteria: Acute reactions

	0	-1	-2	-3	-4
HAND-FOOT SKIN REACTION	**No change**	**Skin changes or dermatitis without pain (e.g., erythema, peeling)**	**Skin changes with pain not interfering with function**	**Skin changes with pain interfering with function**	
RADIATION DERMITITIS	**No change**	**Faint erythema or dry desquamation**	**Moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema**	**Confluent moist desquamation ≥1.5 cm diameter and not confined to skin folds; pitting edema**	**Skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion**
PNEUMONITIS	**No change**	**Radiographic changes but asymptomatic or symptoms not requiring steroids**	**Radiographic changes and requiring steroids or diuretics**	**Radiographic changes and requiring oxygen**	**Radiographic changes and requiring assisted ventilation**
FATIGUE	**No change**	**increased fatigue over baseline, not altering normal activities**	**Moderate causing difficulty in performing some activities**	**Severe causing difficulty in performing some activities**	**Bedridden or disabling**
ALOPECIA	**No change**	**Mild hair loss**	**Pronounced hair loss**		
ANOREXIA	**No change**	**Loss of appetite**	**Oral intake decreased**	**Requires IV fluid**	**Requires feeding tube**
DYSPHAGIA	**No change**	**can eat regular diet**	**Eats pureed liquids**	**Requires IV fluid**	**Requires feeding tube**
GASTRITIS	**No change**		**Needs medication**	**Uncontrolled by meds requires hospitalization or surgery**	**Life threatening bleeding needing emergent surgery**
NAUSEA	**No change**	**able to eat**	**Oral intake decreased**	**Requires IV fluid**	
STOMATIITS	**No change**	**painless ulcers or mild soreness without lesions**	**Painful but can eat and swallow**	**Requires IV fluid**	**Requires feeding tube or parenteral nutrition**

APPENDIX 2

LENT/SOMA Criteria: Late Reactions

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

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

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