Title: A Pilot Study of Hypofractionated Simultaneous Integrated Boost Radiotherapy in Stage 0-IIIBBreast Cancer Patients

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PI- Mylin A. Torres, M.D.
Co-investigators: Dr. Tian Liu, Dr. Andrew H. Miller

Study Centers: The Emory Clinic Clifton Campus, Emory Midtown Hospital, Emory St. Joseph's Hospital

Background:

For the majority of women with breast cancer (BrCA), radiation therapy (XRT) is critical for preventing local recurrence and improving breast preservation and survival.[1] XRT to the whole breast is a necessary component of breast conserving therapy and is standard of care following partial mastectomy; XRT has been shown to decrease locoregional recurrence by 2/3 and improve absolute survival by a minimum of 5% over lumpectomy alone.[1]

As the number of survivors has markedly increased, clinicians are now seeking to reduce treatment-related toxicities and inconveniences of treatment, namely the traditional 6 weeks of daily radiotherapy. Skin thickening, fibrosis, and edema are some of the most common acute and potentially long-term debilitating toxicities of BrCA XRT.[2, 3] During XRT, approximately 50% of patients develop significant cutaneous toxicity including moist skin desquamation, erythema, and hyperpigmentation.[2, 3]

Two recent studies have examined the role of hypofractionation (>2Gy per day with shorter overall treatment time) in the treatment of breast cancer.[4, 5] A recently published Phase III Canadian study randomized early stage BrCA patients to 42.5 Gy in 16 fractions (fxns) (2.66 Gy per day) or 50 Gy in 25 fxns (2 Gy per day) to the whole breast following lumpectomy and axillary lymph node dissection.[4] At 10 years, there was no difference in local control, survival, or cutaneous toxicity.[4] The UK START B study also randomized patients to 40 Gy in 15 fxns (2.66 Gy per day) or 50 Gy in 25 fractions (2 Gy per day) and found no difference in local control, survival, or cosmesis at 5 years.[5] Both studies successfully challenged the long held radiobiological belief that large daily fractions (>2 Gy per day) portends severe late normal tissue toxicity and unacceptable breast cosmesis following XRT. More recently, an updated analysis of the UK START trial was presented with 9.8 years of follow-up and there was still no difference in local control, survival or side effects between hypfractionated radiation and standard five weeks of XRT treatment.[6]

However, both the Canadian and UK studies included patient populations at relatively low risk of XRT-induced toxicity.[4, 5] Race, prior chemotherapy treatment, body habitus, and age have all been correlated with a patient's radiotherapy tolerance. More than 70% of participants in both hypofractionation studies were Caucasian and over the age of 50; fewer than 25% of patients received chemotherapy.[4, 5] It is known that African American women with BrCA experience more severe XRT-induced side effects than Caucasians, possibly contributing in part to poorer treatment adherence and worse outcome.[7-9] During and after XRT, African-Americans have worse cutaneous toxicity (edema, fibrosis, and pigmentation) than Caucasians (45% versus 10%, respectively). In addition, overall cosmesis, reflective of radiation-induced cutaneous toxicity, was good to excellent in 90% of Caucasians versus only 55% of African Americans following breast conserving treatment with XRT.[8] Negative perceptions of BrCA treatment including XRT may partially explain poor treatment

adherence rates in the African American community. Indeed, at our own institution, 26% of AAs with BrCA refused XRT in a recent study.[10] In addition to race, several studies have also found that patients heavily pre-treated with chemotherapy experience at least twice as much XRT induced skin desquamation and edema.[11-13] Moreover, women with larger breasts have higher rates of cutaneous toxicity due to the buildup of dose on the surface of the skin as the radiation beam tries to penetrate a large depth of tissue. For this reason, the Canadian study limited their enrollment to those women with less than 25cm of separation of the breast (the largest distance between the entry and exit point of the XRT beam on the breast). [4] Lastly, women less than age 50 have been found to have poorer cosmesis than older women following surgery and XRT.[7] Given the patient population treated in both the Canadian and UK studies, it is unclear if a shortened XRT regimen may be applied to a "high risk" patient (e.g. young patients previously treated with chemotherapy).

Furthermore, in the UK START study, post mastectomy patients were included as well as patients requiring regional nodal irradiation although only 15% of the enrolled patients were post-mastectomy patients and only 15% of the entire cohort needed regional nodal irradiation. Therefore, these patients at relatively higher risk for lymphedema/brachial plexopathy from XRT were under-represented in the UK START study. However, among the small number of patients treated with hypofractionated XRT to the regional lymph nodes (supraclavicular radiaton), there were no significant increases in lymphedema or brachial plexopathy compared to women treated with standard 5 weeks of XRT to the supraclavicular fossa.[6]

Additionally, a now standard boost dose to the lumpectomy cavity or chest wall, proven to significantly improve local control by 10% or greater in women less than 50 years of age [14-16], was not required in either arm of the Canadian or UK study. [4, 5] The boost dose has been shown to improve locoregional control in all patients by a minimum of 3% but appears to have the greatest impact in younger patients.[14-16] This boost dose has extended conventional XRT treatment from 5 (50 Gy in 25 fxns) to 6 weeks (60 Gy in 30 fxns) in the majority of patients treated within the United States.

At our institution, we have one of the largest experiences with simultaneous integrated boost (SIB) technique in patients with BrCA; we deliver 45 Gy in 25 fxns to the whole breast while treating the cavity simultaneously to a higher dose of 59.92 Gy in 25 fxns. Our published experience shows that at 3 years, our 5-week regimen is generally well tolerated with <1% of patients developing Grade 3 cutaneous toxicity and only 2.8% of patients recurring locally.[17] Our results are particularly important given that 39% of these patients were AA, 33% were premenopausal, 30% had breast separation >25cm, and 45% received chemotherapy, all factors associated with heightened skin toxicity from XRT. [17]

Seeking to shorten the treatment course further and improve convenience and treatment adherence, we propose to build upon our experience and the level I evidence advocating for hypofractionation in 15 days of treatment. Our proposed study will utilize the SIB technique with the whole breast treated to 40 Gy in 15 fractions and the cavity boosted simultaneously to 48 Gy in 15 fractions. Only one previous study has examined the feasibility of a similar fractionation with the whole breast treated to 40.5 Gy in 15 fractions, while the cavity is treated to 48 Gy.(20) At 1 year median follow-up time, 67% of patients had developed reversible grade 1-2 skin dermatitis and only 1 of 91 patients had recurred locoregionally.(20) However, only 1/3 of patients received chemotherapy and less than a quarter had large breast size. The majority of patients were over the age of 50 and 87% were Caucasian.(20) No study has examined the feasibility of a 15-day hypofractionated SIB XRT regimen in women at high risk for cutaneous toxicity (e.g. women below the age of 50, African American, and/or treated with chemotherapy). The unique patient population served by Emory will enable a study of SIB XRT given

over 15 treatments. Quality of life measures (e.g. Multidimensional Fatigue inventory (MFI)[18], the Pittsburgh Sleep Quality Index (PSQI) [19], the perceived stress scale (PSS)[20], the Inventory of Depressive Symptomalogy-Self Reported (IDS-SR)[21], the Short-Form Health Survey (SF-36)(25) and the Godin Leisure Time Questionnaire (GLTEQ)(26)) which have been validated in multiple populations, will also be assessed in these patients to determine if 15 days of treatment is feasible.

Preliminary Data:
Recent work from our group indicates that ultrasound tissue characterization (UTC) may objectively and reliably measure XRT-induced cutaneous toxicity in BrCA patients. UTC is a non-invasive technique developed by Tian Liu, PH.D.(co-Investigator), to delineate sub-resolution tissue features that are not visible by standard B-mode ultrasonography.[22, 23] From the UTC analysis, we can obtain quantitative parameters (skin thickness, Pearson coefficient, and midband fit value) characterizing the dermal, hypodermal, and subcutaneous tissue. These spectral parameters are related to structural tissue properties including skin thickening, fibrosis, and edema. [22, 23] In published work, the clinical assessments of XRT-induced skin toxicity correlate strongly with UTC measurements and objectively validate this measurement of skin toxicity.[23] However, inter-observer subjective toxicity assessments have mild to moderate agreement. UTC would provide a reproducible way of characterizing toxicity. XRT-induced skin thickening increases with maximum thickness occurring at the completion of XRT. The thickening decreases significantly by 6 weeks post XRT in patients treated with a traditional 6 week course of XRT. We plan to use UTC to objectively quantify cutaneous toxicity during XRT in this study. Time points for analysis of cutaneous toxicity (baseline, fraction 15 of XRT and 2 - 5 weeks, 7 - 12 weeks, and 12 – 18 months post XRT) are based on these data.[23].

Study Design:

Eighty breast cancer patients with Stage 0-III BrCA treated with breast conserving surgery or mastectomy and clear margins will be recruited to the study. Patients must have **one or more** of the following characteristics and be eligible for breast or chest wall with or without regional nodal radiotherapy:

1. Prior Chemotherapy for Breast Cancer
2. >25 cm of breast separation (the largest distance on an axial slice of the planning CT simulation scan between the entry and exit points of the radiation beam on the body)
3. Non-Caucasian Race
4. $\leq$ 50 years of age
5. Requiring regional nodal irradiation without evidence of N3 disease

Because the above characteristics in isolation have been correlated with heightened levels of skin toxicity and/or were under-represented in previous trials of hypofractionated XRT, any patient fulfilling one of the above criteria, will be approached for enrollment in the study.

Males will be excluded.

To protect against possible side effects of radiation, women who are pregnant or nursing a child may not take part in this study.

Patients who have not received chemotherapy may start XRT up to 16 weeks after lumpectomy surgery. Patients who receive adjuvant chemotherapy after lumpectomy may start XRT up to 7 weeks after their last cycle of chemotherapy.

Dosimetry Guidelines for Hypofractionation SIB protocol for Breast Cancer

Please plan breast treatments according to ICRU Guidelines.(19)

Treatment plans must be generated with **heterogeneity corrections turned on.**

Eligible patients are those being treated after lumpectomy or mastectomy.

Whole Breast or chest wall Treatment:
The whole breast or chest wall will be treated with tangents (modulated with either wedges or field-n-field technique) to a dose of **2.66 Gy per day x 15 fractions**.

The whole breast or chest wall should receive at least 95% of the prescribed dose. The whole breast or chest wall should receive less than 115%. No more than 8% of the whole breast should receive <95% of the prescribed dose.

5mm bolus may be used on the chest wall in postmastectomy patients at the discretion of the treating physician.

Central lung distance <2.5cm from chest wall to posterior edge of tangents
Maximum heart distance <1.5cm from chest wall to posterior edge of tangents

Regional Nodal/ Supraclavicular Irradiation:
For patients requiring regional nodal irradiation, the physician will determine which lymph nodes are at risk and these targeted lymph nodes will be contoured (e.g. level I, II, III, and/or supraclavicular nodes and/or internal mammary lymph nodes).

The lymph nodes will be prescribed 2.66 Gy per day x 15 fractions and administered on the same day as the whole breast or chest wall treatment. The targeted regional lymph nodes should receive at least 90% of the prescribed dose. The targeted regional lymph nodes should receive less than 105% of the prescribed dose. If these dose constraints cannot be met, the treating physician has the option of decreasing the total dose to the targeted lymph nodes per day to 2.6 Gy per day x 15 fractions.

The supraclavicular nodes may be treated with an anterior oblique photon field or opposed oblique photon fields. The internal mammary nodes may be treated with deep tangents or an en face electron field.

Simultaneous Integrated Boost to the Cavity Treatment:

The boost treatment will be given on the same days as the whole breast treatment.

The lumpectomy cavity + scar (in lumpectomy patients) or chest wall scar (mastectomy patients) will receive **0.54 Gy per day x 15 fractions**.

95% of the tumor bed volume should receive at least 95% of the prescribed dose.

Effort should be made to reduce treatment volume receiving more than 115% of the boost dose to less than 1%.

Electrons **or** photons may be used for the boost fields. It is up to the clinician to decide and will often be decided based upon the depth of the cavity.

If using photons (mini-tangents), for deep cavities, **margin is 1.5cm on cavity + scar** to field edge

Suggested photon fields for the boost are to use the same gantry angles from the initial whole breast fields with the same couch kick as the whole breast tangents. If the cavity is laterally located, kick the couch on the lateral tangent for a 3rd field 10 to 20 degrees. Leave the medial tangent alone. If the cavity is medially located, kick the couch 10 to 20 degrees from the initial couch kick on the medial tangent for the 3rd field. Leave the lateral tangent alone.

If using en face electrons for shallow cavities or chest wall, margin is **2.0 cm on cavity + scar** to block edge in all dimensions but posterior to the cavity volume in the case of breast conserving surgery patients.

*****Please note that if using electrons to boost the cavity or chest wall, this must be done on a non-breathold scan even when using breathold for whole breast tangent treatment for left sided tumors.**

In addition to the port films, a cone beam CT scan will be done 1-2 times per week for localization of the tumor bed cavity. A cone beam CT scan is not necessary in post-mastectomy patients.

Dose Constraints to Normal Tissues:

Heart:
Maximum heart distance <1.5cm on tangents or mean dose < 6 Gyor the heart volume receiving 13 Gy must be less than or equal to 10%. ($V_{13Gy} \leq 10\%$)

Lung:
Central lung distance <2.5cm on tangents orthe ipsilateral lung volume receiving 18 Gy must be less than or equal to 15%. ($V_{18Gy} \leq 15\%$), the contralateral lung volume receiving 2.5 Gy must be less than or equal to 15%. ($V_{2.5Gy} \leq 15\%$), or Total Lung V20 <36%

Contralateral breast dose:

The contralateral mean breast dose must be < or equal to 3 Gy but aim should be less than 1 Gy

Data Collection:

Cutaneous toxicity will be assessed at baseline, fraction 15 of XRT and 2 - 5 weeks, 7 - 12 weeks, and 12 – 18 months post XRT by objective ultrasound measurements (UTC). Photographs of the treated breast or chest wall as well as the contralateral breast will also be taken. Documentation of the UTC and photographs will be kept in electronic format for reference. For each visit after the baseline (after treatment has begun), cutaneous toxicity will be assessed by a clinician. Participants will be seen by the investigator in follow up at the third and/or fourth visits and at the fifth visit and an investigator dictation will be performed.

Patients who have had a mastectomy and plan for permanent breast reconstructive surgery after radiation will be assessed within one month of their permanent reconstructive surgery and 5 – 7 months following their surgery using the same procedures as described above. It is highly variable as to when reconstruction will occur. If these time points do not fall within the time frame for the regular study visits, additional study visits will be added for these patients.

Participants will also be asked to complete the Multidimensional Fatigue inventory (MFI)[18], the Pittsburgh Sleep Quality Index (PSQI) [19], the perceived stress scale (PSS)[20], the Inventory of Depressive Symptomalogy-Self Reported (IDS-SR)[21], the PROMIS Fatigue Short form [28], the MOS-item Short-Form health survey (SF-36)(25) and the Godin Leisure-Time Exercise Questionnaire (GLTEQ)(26) to assess levels of fatigue, sleep, stress, and depression at the above time points. These surveys take approximately 15 minutes to complete. Patients who are simultaneously enrolled on the Fatigue in Breast Cancer Patients Undergoing Treatment (IRB00028295) may have survey visit assessments completed prior to baseline visit, as they are completing the same assessments for both studies. These surveys will be used for data purposes in lieu of having the patient complete the same paperwork twice. At each visit, patients will be asked to rate their fatigue level and breast pain on a scale of 0-10, 0 being none and 10 being extreme. They will be asked to rate how happy they are with the look of their breast on a scale of 0-10, 0 being not happy and 10 very happy. They will be asked to rate how different their radiated breast is from their non-radiated breast,on a scale of 0 – 10, 0 being no difference and 10 being completely different. The patient's self-report of fatigue at these visits will be used to assess the grade of their fatigue. In addition, patients will complete the LENT SOMA [27] scale patient questionnaire at all study timepoints to address pain within the breast. The objective LENT SOMA questionnaire Part 3 will be completed by a study clinician or trained nurse at each visit after baseline.

Blood will be drawn under fasting conditions at visits corresponding to cutaneous toxicity assessments. The blood will be analyzed for inflammatory markers (tumor necrosis factor (TNF)-alpha, soluble TNF receptor 2 (sTNFR2), interleukin (IL)-6, IL-1ra, and C - reactive protein (CRP) as well as genetic factors to determine if they are associated with development of cutaneous toxicity.

Information regarding disease characteristics (including stage, tumor size, grade), patient demographics (including age, race, co-morbidities, social history, body mass index), systemic treatment (including hormone therapy, systemic therapy), surgical treatment, radiation treatment, and clinical outcomes (local control, distant metastasis, survival, and treatment complications) will be collected and recorded.

Patients may also be asked to participate in a long term assessment between 1 and 10 years where they will complete the same study procedures as outlined above. Patients will be compensated $50.00 for completing this visit.

A follow up phone survey will be taken between 18 months and 10 years after treatment. Using the same scales as in the study visits, the patients will be asked to rate their fatigue level, breast pain, how happy they are with the look of their breast and how different their radiated breast is from their non-radiated breast. They will also be asked if they are on any hormonal treatment for breast cancer and if so, the date they started. We will obtain verbal consent for this survey from patients who completed this study before the follow up phone survey was originally approved on 9/24/2013.

Assuming 10% of patients dropout, 53 patients requiring breast only radiation will be enrolled (2-3 patients per month) to yield a total of 50 patients.

An additional 33 patients requiring regional nodal irradiation and breast or chest wall radiation will be enrolled. Assuming 10% of patients dropout, 33 patients of these patients will be enrolled (2-3 patients per month) to yield a total of 30 patients receiving regional nodal irradiation and breast or chest wall radiation.

In patients undergoing regional nodal irradiation, arm measurements will be taken of the ipsilateral and contralateral upper extremity at baseline, 7 - 12 weeks, and 12 – 18 months post XRT by a licensed lymphedema therapist or study staff trained by a licensed lymphedema therapist. These patients will also be assessed for brachial plexopathy using RTOG grading toxicity, LENT/SOMA grading toxicity, and a modified version of a validated questionnaire to assess symptoms of brachial plexopathy at baseline and 7 - 12 weeks, and 12 – 18 months post XRT.[24] If a patient develops RTOG or LENT/SOMA Grade 3 toxicity, an objective measurement (MRI and/or nerve conduction studies) of brachial plexopathy will be employed.

Objectives:

Primary objective: To assess the safety and feasibility of delivering 15 fractions of SIB radiotherapy to the breast in patients at risk for developing cutaneous toxicity.

Primary Outcome Measure:

1. Cutaneous Toxicity Rate
   Cutaneous toxicity rate will be assessed by the National Cancer Institute Common Toxicity Criteria (NCI-CTC) v 3. grading scale.
1. Rate of 20% or greater increase in arm lymphedema (compared to baseline arm measurements) will be assessed Among breast cancer patients receiving regional nodal irradiation
2. Rate of Grade 3 brachial plexopathy will be assessed among breast cancer patients receiving regional nodal irradiation by RTOG and LENT/SOMA scales

Secondary Outcome Measures:

1. Rate of cutaneous toxicity, as measured by changes in cutaneous measurements , acquired vis ultrasound tissue characterizations (UTC)
2. Local control will also be assessed through routine physical examination, annual screening mammograms, ultrasound, and biopsy to confirm local recurrence.
3. Blood will be analyzed for biomarkers and inflammatory markers including(tumor necrosis factor (TNF)-alpha, soluble TNF receptor 2 (sTNFR2), interleukin (IL)-6, IL-1ra, and C - reactive protein (CRP) as well as genetic factors to determine if they are associated with development of cutaneous toxicity.

4. Change in Multidimensional Fatigue Inventory (MFI) Score

   [Time Frame: Baseline, End of Follow Up (Up to 18 months)] [Safety Issue: No]

   The Multidimensional Fatigue Inventory (MFI) is a 20-item self-report instrument designed to measure fatigue. Scores range from 20 to 100.The higher the score, the more fatigued.

5. Change in Pittsburgh Sleep Quality Index (PSQI) Score

   [Time Frame: Baseline, End of Follow Up (Up to 18 months)] [Safety Issue: No]

   The PSQI is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval. Scores range from 0 to 21. A score of less than or equal to 5 is associated with good sleep quality. A score greater than 5 is associated with poor sleep quality.

6. Change in Perceived Stress Scale (PSS) Score

   [Time Frame: Baseline, End of Follow Up (Up to 18 months)] [Safety Issue: No]

   The PSS is a self-reported instrument used to measure the perception of stress. Scores range from 0 to 40. Score of 20 or higher are considered high stress.

7. Change in Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form Score

   [Time Frame: Baseline, End of Follow Up (Up to 18 months)] [Safety Issue: No]

   The PROMIS Fatigue questionnaire is a self-report tool used to evaluate frequency, duration, and intensity of fatigue over the past seven days. Scores range from 7 to 35. The higher the score, the more fatigue.

8. Change in an Inventory of Depressive Symptomatology-Self Reported (IDS-SR) score

   [Time Frame: Baseline, End of Follow Up (Up to 18 months)] [Safety Issue: No]

   The IDS-SR is a self-reported measure in which participants rate the frequency of depression symptoms within the past seven days. Scores range from 0 to 84, with higher score reflecting greater severity of depressive symptoms.

9. Change in Short Form-36 (SF-36) Health Survey Score

   [Time Frame: Baseline, End of Follow Up (Up to 18 months)] [Safety Issue: No]

   The SF-36 is a self-reported survey of health status. Scores range from 0 to 100. Lower scores indicate disability. The higher the score, the less disability.

10. Change in Godin Leisure-Time Exercise Questionnaire (GLTEQ) Score

    [Time Frame: Baseline, End of Follow Up (Up to 18 months)] [Safety Issue: No]

    The GLTEQ is a self-reported questionnaire used to measure usual leisure-time exercise habits during a typical seven day period. A score of 24 or more indicates active and substantial exercise benefits. A score of 23 units or less indicates insufficiently active and less substantial exercise benefits.

11. Change in Lent Soma Scale Patient Questionnaire Score

    [Time Frame: Baseline, End of Follow Up (Up to 18 months)] [Safety Issue: No]

    The Lent Soma questionnaire is a self-reported measure of pain. Scores range from 0 to 9. The higher the score, the more pain reported.

12. Change in Fatigue Level

    [Time Frame: Baseline, End of Follow Up (Up to 18 months)] [Safety Issue: No]

    Participants will be asked to rate their fatigue level on a study specific scale from 0 to 10 where 0 represents no fatigue, and 10 represents the most extreme fatigue.

13. Change in Breast Pain Level

    [Time Frame: Baseline, End of Follow Up (Up to 18 months)] [Safety Issue: No]

    Participants will be asked to rate their breast pain level on a study specific scale from 0 to 10 where 0 represents no pain, and 10 represents the most extreme pain.

14. Change in Breast Appearance Satisfaction Score

    [Time Frame: Baseline, End of Follow Up (Up to 18 months)] [Safety Issue: No]

    Participants will be asked to rate the look of their breast on a study specific scale from 0 to 10 where 0 represents not happy, and 10 represents very happy.

15. Difference in Radiated Breast Appearance Score

    [Time Frame: Baseline, End of Follow Up (Up to 18 months)] [Safety Issue: No]

    Participants will be asked to rate how different the look of their radiated breast is compared to their non-radiated breast on a study specific scale from 0 to 10 where 0 represents no difference, and 10 represents completely different.

Monitoring Plan for Severe Adverse Events:

We hypothesize that a maximum of 20% of patients might experience severe acute skin side effects defined as NCI-CTC Grade 3. This corresponds to symptoms interfering with activities of daily life. A Data Safety and Monitoring Board (DSMB) will monitor patient outcomes and suspend the protocol in the event that more than 16 of 80 patients demonstrate severe acute skin toxicity. During the study, the patients will be monitored continuously throughout the study such that if at any time during the study the upper limit of the number of patients developing Grade 3 toxicity exceed what is listed in the table below, the trial will be discontinued. With a 10% dropout rate, a total sample size of 83 patients was calculated to effectively test our hypothesis. For patients not requiring regional nodal irradiation, we will only collect adverse events related to skin toxicity, lung toxicity and heart toxicity. We will not report grade 1-2 radiation dermatitis as adverse events because most patients will at least have gr 1 dermatitis. We will keep a record of toxicity at each visit by collecting the Lent Soma evaluation of

the clinician at each visit after treatment starts. Patient reported fatigue rate will not be collected on the adverse event report, but will also be recorded at each visit

Total Patients	Upper limit of number of patients with toxicity for the trial to continue	Proportion of patients with toxicity if exceed the upper limit	Lower limit of 95% CI	Upper Limit of 95% CI
3	<3	100%	29%	100%
4	<4	100%	40%	100%
5	<4	80%	28%	99%
6	<4	67%	22%	96%
7	<5	71%	29%	96%
8	<5	63%	24%	91%
9	<5	56%	21%	86%
10	<6	60%	26%	88%
11	<6	55%	23%	93%
12	<6	50%	21%	79%
13-50	<7	>20%	NA	

Patients Requiring Regional Nodal Irradiation

Among patients requiring regional nodal irradiation, we hypothesize that <3.0% of patients will develop severe brachial plexopathy following radiation to the regional nodes defined as LENT/SOMA or RTOG Grade 3 or higher (Continuous paresthesias with incomplete motor paresis; pain medication is generally required or objective neurologic findings with paresthesia or paresis) As this toxicity occurs after radiation treatment is complete, patients will be formally assessed for brachial plexopathy at baseline and at 7-12 weeks and 12-18 months post radiation for comparison with baseline assessments. However, patients will be asked to contact Dr. Torres if symptoms of brachial plexopathy develop in between or after study visits. We also hypothesize that less than 15% of patients receiving regional nodal irradiation will develop 20% or greater increase in arm lymphedema (compared to baseline measurements) assessed at 7-12 weeks and 12-18 months post radiation. Of note, lymphedema that develops in the context of weight gain (>/=15% increase in weight) or trauma to the arm will not be attributed to the radiation treatment itself and will not be considered an event to due to the treatment. If this side effect is secondary to radiation rather than surgery, it generally occurs after radiation is complete. Lymphedema that takes place during the 3 weeks of radiation or before radiation begins will be attributed to surgery. During the study, the patients

will be monitored throughout the study such that if at any time during the study the upper limit of the number of patients receiving regional nodal irradiation developing Grade 3 brachial plexopathy or 20% or greater increase in arm lymphedema exceed the number just described or more than 20% develop grade 3 skin toxicity within the breast or chest wall, the trial will be discontinued to the patients requiring regional nodal irradiation but may remain open to patients who do not require regional nodal irradiation. For patients requiring regional nodal irradiation, we will only collect adverse events related to brachial plexopathy, lymphedema, skin toxicity, lung toxicity, heart toxicity. We will not report grade 1-2 radiation dermatitis as adverse events because most patients will at least have gr 1 dermatitis. We will keep a record of toxicity at each visit by collecting the Lent Soma evaluation of the clinician at each visit after treatment starts. Patient reported fatigue rate will not be collected on the adverse event report, but will also be recorded at each visit.

Stopping rule for monitoring 3 types of toxicities in patients Receiving Regional Nodal Irradiation.

(If any one of the 3 stopping rules is met, the trial stops for excessive toxicity.)

Total Patients	Upper limit of number of patients with Grade 3 brachial plexopathy (<3%)	Upper limit of number of patients with 20% or greater increase in arm lymphedema (<15%)	Upper limit of number of patients with grade 3 skin toxicity within the breast or chest wall (<20%)
3	<2	<3	<3
4	<2	<3	<4
5	<2	<4	<4
6	<2	<4	<4
7	<2	<4	<5
8	<2	<4	<5
9	<2	<5	<5
10	<2	<5	<6
11	<2	<5	<6
12	<2	<5	<6
13-30	<2	<5	<7

Correlative Studies: Blood will be analyzed for inflammatory markers (TNF-alpha, soluble sTNFR2, IL-6, IL-1ra, and CRP) to determine if they are associated with development of cutaneous toxicity. By acquiring the objective UTC measurements at 5 time points, the development and resolution of cutaneous toxicity as it relates to time may be further understood.

A description of the Feasibility:

There is no drug in the proposed study. Our department has 7 linear accelerators all capable of delivering hypofractionated external beam radiotherapy. We also have extensive experience treating patients with simultaneous integrated boost radiotherapy. As determined by 2000 census, the majority of minorities in our community are African American, and African Americans make up 61.4% of the population of metropolitan Atlanta. A study including this population would be feasible. At the three Emory radiation centers, there are approximately 350 patients seen annually with 200 patients having early stage breast cancer. With approximately 80 African American breast cancer with Stage 0-II patients treated annually at Emory Clifton Campus, Emory Midtown, and Grady Memorial Hospital. In a recent study, over 60% of our patients had breast separation >25cm. [17] This trial should be able to accrue 33 high risk patients (2 to 3 patients per month, and assuming a 10% dropout rate) needed to assess the feasibility of this novel hypofractionated simultaneous integrated boost (SIB) regimen.

Dr. Tian Liu (co-PI) is an NIH funded physicist with expertise in ultrasound tissue characterization (UTC) of radiation induced cutaneous toxicity. Dr. Liu's Ultrasonic Imaging Laboratory is fully equipped with three clinical ultrasound machines including a state-of-the art Sonix RP scanner with raw radiofrequency echo signals and advanced research interface. The laboratory is located on the tunnel level within the Department of Radiation Oncology. It comprises 500 sq. ft. and is equipped with ultrasound data acquisition system and calibration targets. UTC measurements will be easily performed in patients using Dr. Liu's equipment and software. Measurements of breast tissue take about 10 minutes to complete.

The MFI, PSS, PSQI, IDS-SR, SF-36 and GLTEQ, and LENT SOMA are surveys which have been validated in various populations and take 15 minutes to complete in total.

Blood for inflammatory markers is routinely processed within the laboratory of my research mentor, Dr. Andrew Miller, Professor of Psychiatry and an international expert on inflammatory induced behavioral changes. He has agreed to help process the blood from this study.

Potential risks:

The risk to patients is minimal. Blood draws will be performed at a maximum of eight different time points during the course of their treatment and follow-up.

You may feel slight discomfort from the blood draws at the site of the needle stick. Slight swelling and bruising are fairly common but usually go away soon. Rarely, people may have a vasovagal syncope.

Vasovagal syncope (vay-zoh-VAY-gul SING-kuh-pee) occurs when you faint because your body overreacts to certain triggers, such as the sight of blood or extreme emotional distress. It may also be called neurocardiogenic syncope.

The vasovagal syncope trigger causes your heart rate and blood pressure to drop suddenly. That leads to reduced blood flow to your brain, causing you to briefly lose consciousness.

Vasovagal syncope is usually harmless and requires no treatment. But it's possible you may injure yourself during a vasovagal syncope episode. Your doctor may recommend tests to rule out more serious causes of fainting, such as heart disorders.

All patients will be assigned a study number, and this number will be used in place of patient's names or identification numbers so there should be minimal risk of loss of patient confidentiality. The master sheet containing the patient number and study ID will be kept in a password protected database.

Compensation:

Women who complete the long term assessment will be compensated $50.00 for that study visit.

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