NCT02700386

Hypofractionated, Comprehensive Radiation Therapy for Node-Positive Breast Cancer

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Document Date: October 8, 2019

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Protocol #: **15-1329**
Project Title: **Hypofractionated, Comprehensive Radiation Therapy for Node-Positive Breast Cancer**

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Version Date: **10/08/2019**

I. Hypotheses and Specific Aims:

Hypothesis:

1. Postoperative treatment with hypofractionated radiotherapy to the regionally draining lymphatics in addition to the breast or chest wall will be safe and well-tolerated.
2. Postoperative treatment with hypofractionated radiotherapy to the breast or chest wall in addition to the regionally draining lymphatics will result in acceptable rates of disease control.

Specific Aims:

1. To demonstrate the safety and tolerability of adjuvant hypofractionated radiotherapy to the breast (following lumpectomy) or chest wall (following mastectomy), and regionally draining lymphatics.
2. To determine the rates of axillary recurrence, Glocal-regional failure-free survival, distant metastasis-free survival, and overall survival at one and five years.
3. To evaluate the effects of hypofractionated radiotherapy on chest wall reconstruction.
4. To evaluate patient-reported quality of life.

II. **Background and Significance**:

Hypofractionation can be defined as delivery of radiotherapy in single daily doses greater than the 180-200cGy typically used in conventional fractionation. Hypofractionation, through use of larger doses per fraction and fewer total treatments, is a method of shortening overall treatment time in breast cancer therapy. There are many potential benefits of delivering postoperative radiation in a shorter period of time, including greater convenience for patients, broad applicability to nearly all breast cancer patients for whom adjuvant radiation is indicated, improved use of postoperative radiation when indicated, markedly decreased treatment costs at the system level, and increased utilization of existing radiation resources. Historically, conventional fraction sizes of 180 to 200 cGy of daily radiation were based primarily on studies examining squamous cell cancers from the cervix and head & neck disease sites. These small fraction sizes exploited a biological differential in squamous cell cancer fractionation sensitivity versus normal tissue fractionation sensitivity, allowing relative sparing of surrounding normal tissue. However, investigators from the United Kingdom and British Columbia hypothesized that the fractionation sensitivity for adenocarcinoma of the breast is close to that of the normal breast tissue and therefore with increasing fraction size a sufficiently large reduction of total dose could be implemented to keep late toxicity constant without losing tumor control. Ragaz and colleagues used hypofractionated radiotherapy (3500 cGy in 16 fractions) in the 1980s to treat the regionally draining lymphatics of an involved and dissected axilla. This trial reported no cases of brachial plexopathy, acceptable toxicity overall, and improved disease outcomes as compared to chemotherapy alone.[1] Four prospective randomized clinical trials have shown promising results with hypofractionated schedules for the intact breast alone (Yarnold 2005[2]; Owen 2006[3]; START A&B[4,5]; Whelan 2010[6]). In each of these studies, the goal was to deliver a hypofractionated dose that is biologically equivalent to the conventional regimen of 5000 cGy in 25 fractions. Long-term follow-up of these studies has demonstrated similar in-breast local control and normal tissue toxicity between the hypofractionated and conventionally fractionated arms. The publication of these trials, particularly the landmark START B and Whelan et al. trials, has led to increasing adoption of hypofractionation worldwide in the setting of breast conservation for early-stage, node-negative breast cancer.

These important trials, conducted in Canada and the United Kingdom, were primarily designed to address the safety and efficacy of hypofractionation in node-negative women with intact breasts after

lumpectomy alone. The START A&B trials did include a subgroup of 268 patients who received hypofractionated axillary radiotherapy (4005 cGy in 15 fractions), without any suggestion of excessive toxicity.[4] In the absence of more robust data and a designated trial, most radiation oncologists, especially in the United States, remain hesitant to prescribe hypofractionation to treat chest walls after mastectomy and/or a larger anatomical area to include the axilla, infraclavicular, and supraclavicular nodal basins, as well as the brachial plexus. Another important question is whether hypofractionation is a reasonable choice for women who have tissue expanders placed at the time of surgery in anticipation of eventual placement of synthetic implants. Many physicians worry that the theoretical risk of increasing late toxicity or tissue fibrosis with larger fraction sizes may lead to expander loss or other adverse functional outcomes. However, results from published landmark trials to the intact breast indicate no increased risk of increased fibrosis or adverse cosmetic outcome. In fact, START B indicated marginally superior tissue-toxicity outcomes with hypofractionated radiation as compared to conventional fractionation, with equivalent disease control.[4]

III. Preliminary Studies/Progress Report:

Within the University of Colorado Health System, we have particular expertise and experience in hypofractionation (4005cGy in 15 treatments and other similar schedules) in the treatment of breast cancer. Our institution began implementing hypofractionation as part of breast conservation shortly after the landmark publications on its safety[5,6], and in advance of subsequent national guidelines[7,8] which have now established this dose schedule as the standard of care for select patients in the intact-breast, node-negative setting. As a large National Comprehensive Cancer Center with a large geographical catchment area, our institution is well versed in treating this relatively common malignancy. We have treated over 600 patients with this or similar dosing schedules and our team has consistently demonstrated the technical expertise necessary to enroll patients on several large cooperative group trials pertaining to breast radiotherapy.

IV. Research Methods

A. Outcome Measure(s):

Primary Objective:

- Demonstrate the safety and tolerability of adjuvant hypofractionated radiotherapy to the breast (following lumpectomy) or chestwall (following mastectomy), and regionally draining lymphatics.

Secondary Objectives:

- Determine the rates of axillary recurrence, local-regional failure-free survival, distant metastasis-free survival, and overall survival at one and five years.
- Determine the rates of hypothyroidism and reconstruction expander loss/revision.
- Evaluate patient-reported quality of life and body image.

B. Description of Population to be Enrolled (Eligibility):

Inclusion Criteria:

1. Adult women (≥18 years old) with breast cancer who have undergone surgery for their primary breast tumor (either lumpectomy or mastectomy +/- reconstruction) and are confirmed to have involved lymph nodes on surgical pathology.
2. Patient who have undergone either a total mastectomy or a lumpectomy are eligible. Acceptable procedures for assessment of axillary nodal status at the time of surgery include:
    - axillary node dissection;
    - sentinel node biopsy alone; or
    - sentinel node biopsy followed by axillary node dissection.
3. Eligible women include AJCC 7th ed. Stage cN0 or cN1 subsequently staged after surgery as Stage pIB (N1mic), pIIA, pIIB, pIIIA, pIIIB, or N3a (10 or more axillary nodes) only: note that ypN0 will also be eligible if pathologic confirmation of nodal involvement was documented prior to neoadjuvant chemotherapy and the patient was found to be node negative at the time of surgery. Note that women less than 50 years of age, women who received chemotherapy, patients staged as pN0 (i+ or mol+), and large-breasted women are eligible for enrollment.
4. The patient must have recovered from surgery with the incision completely healed and no signs of infection. If adjuvant chemotherapy was administered, chemotherapy-related toxicity that may interfere with delivery of radiation therapy should have resolved. The patient must have an ECOG performance status of 0 or 1 (KPS >70%).
5. The interval between the last surgery for breast cancer (including re-excision of margins) and randomization must be no more than 180 days if chemotherapy is not delivered adjuvantly. If adjuvant chemotherapy was administered, the interval between the last chemotherapy treatment and randomization must be no more than 180 days.
6. Before the patient is enrolled, the consent form, including any addenda, must be signed and dated by the patient and the person who explains the study to that patient.
7. Subjects will have the ability to understand, and the willingness to sign a written informed consent document.

Exclusion Criteria:

1. patients <18 years old
2. pregnant women
3. male patients
4. women with T4 disease, including inflammatory breast cancer
5. women who have declined or otherwise not received preceding surgery
6. women with positive margins after primary surgery
7. women with node negative disease

8. women without histologic confirmation of nodal involvement
9. women more than 180 days out from primary breast surgery or adjuvant chemotherapy
10. patients with clinically detected or suspicious lymph node involvement not readily amenable to surgical treatment (≥cN2 disease)
11. patients with synchronous bilateral breast cancers
12. patients with prior ipsilateral thoracic or breast radiation
13. patients with distant metastatic disease (cM1) or a life expectancy of less than 5 years
14. active collagen vascular disease, specifically dermatomyositis with a CPK level above normal or with an active skin rash, systemic lupus erythematosis, or scleroderma.
15. other non-malignant systemic disease that would preclude the patient from receiving study treatment or would prevent required follow-up.
16. patients with psychiatric or addictive disorders or other conditions that, in the opinion of the Investigator, would preclude the patient from meeting the study requirements.
17. patients with a separate non-cutaneous cancer diagnosis for which the patient has not been without evidence of disease for at least 5 years

Note: women <50 years of age, women who received chemotherapy, pN0 (i+ or mol+), and large-breasted women are eligible for enrollment.

These criteria were chosen to include most women with pathologic lymph-node positive disease who have undergone surgery for breast cancer. Women without node-positive disease were excluded as there is already Level I evidence supporting the use of hypofractionation for those women. Women with inflammatory breast cancer were excluded given the extreme biologic aggression of such malignancies and the general desire of the treatment team in general to maximize therapeutic intensity, at times including escalated radiation doses that may increase magnitude of expected toxicity.

C. Study Design and Research Methods

Schema: Single-arm Phase II

surgery for breast cancer (either lumpectomy or mastectomy) with involved regional lymph nodes by axillary dissection or sentinel lymph node biopsy
+/- neoadjuvant or adjuvant chemotherapy

REGISTER

adjuvant hypofractionated radiation (4005cGy in 15 fractions over three weeks) to the breast or chest wall **and** the undissected regional lymphatics

Routine follow-up visits will be performed in accordance with routine standard of care practice and as clinically indicated; however visits before radiation (baseline), and at 6, 12, 36, and 60 months will include a protocol mandated history and physical exam to include toxicity grading by the physician as well as quality of life questionnaires by the patient. Patients may see study or other oncologic clinicians in between these intervals for follow-up, though toxicity data collection will not be required at these visits. Mammography for any remaining intact breast should be performed annually or as clinically indicated. All protocol therapy and follow-up visits, are anticipated to be covered by the patient and/or their medical insurance provider.

D. Schedule of Study Assessments:

Study Visits	**Screening**	**Treatment-Phase**					**Follow Up**		
		Radiation On-Treatment Visits[6]				FU 6 Months	FU 12 Months	FU 36 Months	FU 60 Month
		Week 1	Week 2	Week 3	Week 4[5]				
Visit Window	*-28 days*					*± 30 days from RT end*	*± 30 days from RT end*	*± 60 days from RT end*	*± 60 days from RT end*
Procedures									
Informed consent	X								
Pregnancy Test (if premenopausal)	X								
Confirm eligibility (Inclusion/exclusion criteria)	X								
Medical history	X					X	X	X	X
Physical Exam (including weight)[1]	X					X	X	X	X
Height	X								
ECOG performance status	X	X	X	X	X	X	X	X	X
Vital Signs (blood pressure, pulse, respiratory rate, temp,)	X	X	X	X	X				
Lymphedema measurement	X					X	X	X	X
Shoulder mobility measurement[3]	X					X	X	X	X
Radiation		X	X	X	X				
Prior and concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
TSH	X						X	X	X
Mammogram[4]							X		
EORTC QLC-C30 questionnaire	X					X	X	X	X
BR.23 questionnaire	X					X	X	X	X

1. This encounter should include a focused physical exam to include, at minimum, a bilateral breast/chest wall, lymph node, and upper extremity exam, including weight.
2. All toxicity noted by the study clinicians should be documented at baseline, during weekly visits while receiving radiation, and at each per-protocol follow-up visit (6, 12, 36, and 60 months).
3. Clinicians should use a goniometer to measure *bilateral* shoulder mobility in four excursions: abduction, adduction, ante version, and retroversion.
4. Mammography for any remaining intact breast should be performed annually or as clinically indicated.
5. If applicable.
6. 15 treatments ± 4 additional fractions as a boost.

E. Description, Risks and Justification of Procedures and Data Collection Tools:

Adjuvant radiation will last 3-4 weeks (15 treatments +/- 4 additional fractions as a boost). Radiation should commence within 180 days of the date of primary surgery. Women will then be followed in accordance with the standard of care for node-positive breast cancer. Information pertaining to the primary and secondary endpoints will be collected at follow-up visits with study clinicians at 6, 12, 36, and 60 months.

Treatment of the internal mammary nodes will be left to the discretion of the treating physician based on clinical indication, practice pattern, and assessment of dose to the heart and underlying lung. Inclusion of internal mammary nodes is optional, though their inclusion or exclusion from the treatment field should be recorded.

Four additional fractions (a "boost" or "cone down") to areas deemed to be at particularly high risk of recurrence (generally the lumpectomy bed or chest wall scar) may be added at the end of the radiation course at the discretion of the treating physician. Fraction size for the boost treatment will continue at 267 cGy for an additional 1068cGy in four fractions. The exact site, dose, fractionation, and technique (i.e., IMRT, 3D, en face, etc.) should be recorded.

Routine follow-up visits will be performed in accordance with routine standard of care practice and as clinically indicated; however visits before radiation (baseline), and at 6, 12, 36, and 60 months will include a protocol-mandated history and physical exam to include toxicity grading by the physician as well as quality of life questionnaires by the patient. Patients may see study or other oncologic clinicians in between these intervals for follow-up, though toxicity data collection will not be required at these visits. Mammography for any remaining intact breast should be performed annually or as clinically indicated (at the University of Colorado Denver, this is typically six months post radiation then annually or as Bi-RADS indicated). Study clinicians will document data such as functional status (KPS/ECOG), evidence of, and CTCAE grading of any apparent treatment related toxicity. Lymphedema measurements will be performed at these visits. Shoulder mobility assessment will also be performed at these visits.

Radiation Details

Simulation and treatment may be performed with the patient in the supine or prone position post-lumpectomy. Patients should be optimally positioned with alpha cradle casts, Vac-Lok™ (or similar) fixation, breast boards, wing boards and/or other methods of immobilization at the discretion of the treating physician. Methods to minimize the cardiac exposure to radiation like heart block, gating, or breath hold are allowed at the discretion of the treating physician. Protection of the humeral head and the glenohumeral joint space with blocks is strongly encouraged. For all patients, the match slice will be delineated at CT simulation at the inferior edge of the clavicle, or as deemed appropriate by the treating physician.

For post-lumpectomy large-breasted patients, including those with a large inframammary skin fold, devices to improve positioning of the breast and prone positioning are permissible. A treatment planning CT scan in the treatment position will be required to define the clinical target volumes (CTV), planning target volumes (PTV), and Organs at Risk (OAR). The CT required for generation of a virtual plan with 3DCRT or IMRT must be post-final surgery, either lumpectomy or mastectomy and any re-excisions for margins.

For post-lumpectomy patients, radio-opaque markers are to be placed on the patient skin in the treatment position as external landmarks at the acquisition of the CT scan to facilitate contouring segmentation of the CT data-set. These markers should identify: 1) the lumpectomy incision, 2) the outline of the palpable breast tissue circumferentially. Note that the superior clinical extent of breast tissue may be at a different location than the match line between the breast and regional nodal irradiation fields.

For post-mastectomy patients, radio-opaque markers are to be placed on the patient skin in the treatment position as external landmarks at the acquisition of the CT scan to facilitate contouring segmentation of the CT data-set. These markers should identify the mastectomy scar with other landmarks (such as the estimate of the inframammary fold) optional at the discretion of the treating physician. Note that the position of the contralateral breast, if present, can be helpful.

All patients who will be receiving 3D treatment will have marking on the skin at the match plane between the breast/chest wall inferiorly and the undissected lymphatics superiorly. This will typically consist of a radio-opaque marker placed on the horizontal plane situated at the inferior aspect of the clavicular head.

The CT should extend cephalad to start at or above the mandible and extend caudally (or inferiorly) to at least 5 cm below the inframammary fold or marker thereof and encompass the entire lung volume. A CT scan image thickness of ≤ 0.5 cm should be employed. External skin localizing marks, which may include permanent tattoos, are recommended for radiation daily localization and set-up accuracy.

For patients that have an expander in place post-mastectomy for reconstruction, the amount of expansion during radiation is per the investigator's discretion. The degree of expansion on the treated side, ranging from collapsed to fully expanded, must remain stable from the time of CT simulation until completion of radiotherapy.

Target volumes and treatment planning

The definitions for the CTV, PTV, and normal structures used in this protocol generally conform to the RTOG-endorsed consensus guidelines for delineation of target and normal structures for breast cancer (http://www.rtog.org/corelab/contouringatlases/breastcanceratlas.aspx), thoracic cancer (http://www.ncbi.nlm.nih.gov/pubmed/20934273), and the 1993 International Commission on Radiation Units and Measurements (ICRU) Report #50: Prescribing, Recording And Reporting Photon Beam Therapy.

Normal structures (Organs at Risk – OAR):

- Ipsilateral lung: This may be contoured with auto-segmentation with manual verification.
- Contralateral lung: This may be contoured with auto-segmentation with manual verification.
- Brachial plexus: This is to be contoured on the ipsilateral side in all cases. The brachial plexus originates from the spinal nerves exiting the spinal canal through the neural foramina from the C4-C5 (C5 nerve roots) to the T1-T2 (T1 nerve roots) level as in the RTOG-endorsed thoracic (arms up) contouring atlas.[10]
- Heart: This is to be contoured on all cases, regardless of breast cancer laterality. The heart should be contoured beginning just inferior to the level in which the pulmonary trunk branches into the left and right pulmonary arteries (PA). Above the PA, none of the heart's four chambers

are present. The heart should be contoured on every contiguous slice thereafter to its inferior most extent near the diaphragm. The following structures, if identifiable, should be excluded from the heart contour: esophagus, great vessels (ascending and descending aorta, inferior vena cava). One need not include pericardial fat, if present. Contouring along the pericardium itself, when visible, is appropriate.

- Thyroid: The thyroid is easily visible on a non-contrast CT due to its preferential absorption of iodine, rendering it "brighter" or denser than the surrounding neck soft tissues. The left and right lobes of the thyroid are somewhat triangular in shape and often do not converge anteriorly at mid-line. All "bright" thyroid tissue should be contoured.
- Contralateral breast: The contralateral breast can be at risk for exposure to excess inadvertent dosing, particularly in cases of very medially located lumpectomy sites or optional inclusion of the IMN PTV. Therefore dose to the contralateral breast will be constrained in the treatment planning. This includes the apparent CT glandular breast tissue visualized by CT and consensus definitions regarding "breast" of anatomical borders from the RTOG Breast Atlas. The contralateral breast, or at least its medial circumferential outline, should be wired at CT simulation to help minimize dose to this structure during treatment planning.

Breast target volumes

Lumpectomy Bed volumes:

- *Gross Target Volume (GTV)*: While there is no true GTV following lumpectomy, identification of the lumpectomy cavity will serve as a GTV for definition purposes. The lumpectomy GTV will be contoured using all available clinical and radiographic information including, architectural distortion, seroma, air and/or extent of surgical clips (clips are strongly recommended).
- *Clinical Target Volume (CTV)*: Lumpectomy GTV + 1 cm 3D expansion. Limit the CTV posteriorly at anterior surface of the pectoralis major and anterolaterally 5 mm from skin and should not cross midline. In general, the pectoralis and/or serratus anterior muscles are excluded from the lumpectomy CTV unless clinically warranted by the patient's pathology.
- *Planning Target Volume (PTV)*: Lumpectomy CTV + 7 mm 3D expansion (excludes heart).
- *PTV Eval*: Since a substantial part of the Lumpectomy PTV often extends outside the patient (especially for superficial cavities), the Lumpectomy PTV is then copied to a Lumpectomy PTV Eval which is edited. This Lumpectomy PTV Eval is limited to exclude the part outside the ipsilateral breast and the first 5 mm of tissue under the skin and excluding the Lumpectomy PTV expansion beyond the posterior extent of breast tissue (chest wall, pectoralis muscles, and lung) when pertinent. The lumpectomy PTV Eval should not cross midline. This Lumpectomy PTV Eval is the structure used for analysis of DVH constraints, but should not be used for beam aperture generation.

Breast volumes:

- *Breast CTV*: Includes the palpable breast tissue demarcated with radio-opaque markers at CT simulation, the apparent CT glandular breast tissue visualized by CT, consensus definitions of anatomical borders from the RTOG Breast Cancer Atlas, and should include the Lumpectomy CTV. The Breast CTV is limited anteriorly within 5 mm from the skin and posteriorly to the anterior surface of the pectoralis, serratous anterior muscle excluding chest wall, boney thorax, and lung. In general, the pectoralis and/or serratous anterior muscles are excluded from the Breast CTV unless clinically warranted by the patient's pathology. RTOG anatomy consensus

guidelines are available at: http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx.

- *Breast PTV*: Breast CTV + 7 mm 3D expansion (excludes heart and does not cross midline).
- *Breast PTV Eval*: The Breast PTV Eval is intended to exclude the portion of the Breast PTV that extends outside the patient or into the boney thorax and lungs. The Breast PTV is copied to a Breast PTV Eval which is edited. This Breast PTV Eval is limited anteriorly to exclude the part outside the patient and the first 5 mm of tissue under the skin (in order to remove most of the build-up region for the DVH analysis) and posteriorly is limited to no deeper than the anterior surface of the ribs (excludes boney thorax and lung). This Breast PTV Eval is the structure used for DVH constraints and analysis.

Chest wall target volumes post-mastectomy

- *Mastectomy Scar:* Around the mastectomy scar is a common location for chest wall recurrences post-mastectomy. To help reproducibility in the design and evaluation of post-mastectomy radiotherapy treatment plans, an initial clinical target volume for the mastectomy scar will be created. The Mastectomy Scar will first be contoured by delineating the radiopaque wire placed over the scar at CT simulation as a surrogate of the scar and including any visible postoperative changes on CT in the subcutaneous tissue deep to the wire per the investigator's discretion.
- *Mastectomy Scar CTV:* Mastectomy Scar and associated surgical change + 1 cm 3D expansion. Limit the CTV expansion posteriorly at anterior surface of the ribs or expander/implant (if present) and anterolaterally at skin. This structure should not cross midline.
- *Mastectomy Scar PTV:* Mastectomy Scar CTV + 7 mm 3D expansion (excludes heart).
- *Mastectomy Scar PTV Eval:* Since a substantial part of the Mastectomy Scar PTV extends outside the patient – a Mastectomy Scar PTV Eval is created. This Mastectomy Scar PTV Eval is limited to exclude the part that extends outside the ipsilateral body/chest wall and the first 3 mm of tissue under the skin (in order to remove some of the buildup region for the DVH analysis) and posteriorly is limited to exclude lung and heart. The Mastectomy Scar PTV Eval should not cross midline and should be contained within the borders of the Chest wall PTV Eval. This is the structure used for DVH constraints, analysis, and compliance. *(**NOTE:** Occasionally, the Mastectomy Scar location will lead to a CTV and PTV Eval that does cross midline. The investigator will have to assess clinically whether adequate radiation can be delivered if the Mastectomy Scar CTV and PTV Eval is truncated at midline. If it is felt that the Mastectomy Scar CTV and PTV Eval must cross midline – this case may have significant challenges in meeting Compliance Criteria for this protocol and might not be suitable for enrollment.)*
- *Chest wall CTV:* Includes the Mastectomy Scar CTV, and takes into account the radiopaque markers placed at CT identifying clinical extent of chest wall, surgical changes visualized by CT, and consensus definitions of anatomical borders of chest wall from the RTOG Breast Cancer Atlas http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx. The Chest wall CTV will encompass the any reconstruction (expander/implant/flap) if present, and is limited by the skin anteriorly and should not extend deeper than the ribs so that it excludes the lung and heart. Depending on the location of the Mastectomy Scar CTV, it should exclude the sternum medially and the axilla deep to anterior surface of the pectoralis major muscle laterally. In general, the chest wall CTV should not cross midline.
- Expanders, implants or autologous tissue present for reconstruction will be included in the Chest wall CTV. The degree of expander expansion present is per the treating physician's discretion. The expander should remain at the same expansion through the course of treatment that is present for the CT simulation.

- *Chest wall PTV:* Chest wall CTV + 7 mm 3D expansion (excludes heart and does not cross midline).
- *Chest wall PTV Eval:* As a part of the Chest wall PTV often extends outside the patient, the Chest wall PTV is then copied to a Chest wall PTV Eval which is edited. This Chest wall PTV Eval is limited anteriorly to exclude the part outside the patient and the first 3 mm of tissue under the skin (in order to remove some of the buildup region for the DVH analysis) and posteriorly is limited to no deeper than the posterior rib surface and excludes lung and heart. In general, the Chest wall CTV should not cross midline. This Chest wall PTV Eval is the structure used for DVH constraints and analysis and not for beam aperture generation.

Regional nodal target volumes

- *Supraclavicular CTV:* Based on consensus definitions from RTOG Breast Cancer Atlas. Superior extent typically is immediately below the caudal edge of the cricoid; medially excludes thyroid, trachea, and esophagus. The lateral border extends to the lateral edge of the sternocleidomastoid muscle superiorly and the clavicle at its more inferior extent, and the inferior border extends to the caudal aspect of the clavicular head.
- *Supraclavicular PTV*: Supraclavicular CTV + 5 mm margin in all directions. The following structures should be excluded from the Supraclavicular PTV to minimize excess dose to normal tissues: ipsilateral thyroid, trachea, esophagus, and ipsilateral lung. This means that some or all of the medial border of the Supraclavicular CTV and PTV will be similar. The Supraclavicular PTV should exclude the vertebral body.
- *Axillary CTV:* The extent of axilla to be targeted for regional nodal irradiation will depend on the extent of axillary surgery performed. The axillary CTV consists of the portion of the axilla that remains "undissected." If an axillary node dissection has been done prior to radiotherapy, the inferior border of the axillary CTV will generally be the most superior (or cephalic) extent of the dissection (i.e., radiation need only be delivered to the undissected axilla). In rare cases, such as a high proportion of nodes involved, treatment will be directed at the dissected axilla and included in this volume at the discretion of the treating physician. Review of the operative report, postoperative changes on the planning CT, and discussion with the patient's surgeon can be used for determining the most cephalic extent of the dissection and inferior border of the Axillary CTV. Axillary dissection typically removes level 1–2 axillary nodes, so that the Axillary CTV in these cases is expected to include level 3. When a sentinel node biopsy alone is done without completion axillary dissection, the axillary CTV will then include all 3 levels of the axilla as all three levels are "undissected." The consensus definitions for anatomical borders of the axillary levels are from the RTOG Breast Cancer Atlas: http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx
- A*xillary PTV:* Axillary CTV + 5 mm. The ipsilateral lung should be excluded from the Axillary PTV. This means that some or all of the medial border of the Axillary PTV can be similar to the Axillary CTV.
- *Internal mammary node (IMN) CTV:* Includes the internal mammary/thoracic vessels extending from the first to third intercostal spaces on the ipsilateral side regardless of whether or not they will be targeted.
- *Internal mammary node (IMN) PTV:* The IMN CTV + 5 mm medially, laterally, superiorly, and inferiorly. In order to minimize excess normal tissue irradiation, no additional expansion of the IMN CTV into the lung or heart should be done for the IMN PTV. The deep edge for the IMN PTV will be similar to the IMN CTV. No anterior expansion of the CTV into the chest wall or breast

volumes will be done. Treatment of this structure is optional and will be included at the discretion of the treating physician.

Treatment planning

CT-based planning with tissue inhomogeneity correction is required. *IMRT or 3D-CRT planning techniques are permitted.*

The following definitions and conditions are applied concerning IMRT in this protocol:

1. The treatment plan will be considered IMRT for the purposes of this protocol if an inverse planned optimization is used to determine the beam weights to meet the target and critical structure dose-volume constraints.
2. The plan generated by direct aperture optimization that employs an inverse planning algorithm is considered as IMRT when the target and critical structure dose-volume constraints are met and at least 3 apertures for each beam direction are used.
3. If IMRT is combined with the standard open medial and lateral tangential fields for whole breast irradiation, the IMRT beam should deliver > 50% of the total number of monitor units for the beam orientation.
4. If an IMRT plan is used with another IMRT plan, forward-planning photon beams, and/or electron beam, the 3D composition dose distribution and DVHs should be generated.
5. All standard IMRT planning and delivery systems using MLC (step-and-shoot, dynamic MLC, slide-and-shoot, VMAT, tomotherapy) are allowed and classified as IMRT as long as target and critical structure dose-volume constraints are met.
6. IMRT planning and delivery systems using physical beam-intensity compensators designed by an inverse algorithm to modulate beam intensity so that the required dose constraints are met are also accepted as IMRT.
7. The patient-specific pre-treatment QA measurement is required prior to the first treatment for an IMRT plan.

All plans that do not fit into the above definitions and conditions are classified as 3DCRT plans. Specifically, the plans generated using forward-planning methods or segmental techniques such as "field-in-field" to meet dose-volume constraints are considered as 3DCRT plans. These forward-planned or segmental treatment techniques are those intended to mainly improve the uniformity of the dose distribution but not to produce steep dose gradients to protect critical structures (e.g., heart or lung).

The plans with the number of apertures < 3 for each beam direction are considered 3DCRT plans even if they were generated with inverse planning algorithms

Whole breast plus boost radiation therapy

The Breast PTV is used to generate the beam apertures with an additional margin to take into account penumbra. Fields should include all of the Breast PTV and boost PTV. The aperture margin generally needed beyond the PTV is 5 mm. The goals of treatment planning are to encompass the breast PTV and minimize inclusion of the heart and lung. Field arrangements for 3DCRT and IMRT of the Breast PTV are at the discretion of the treating physician. Multiple beam arrangements are to be designed during the treatment planning process to produce an optimal plan that meets the dose-volume constraints on the Breast PTV and normal tissues outlined below.

The optional lumpectomy boost may be given by either electron beam or photon beams using either 3DCRT or IMRT. A composite dose distribution and DVHs that include whole breast irradiation using either IMRT or 3DCRT and lumpectomy cavity boost using electron beams, IMRT or 3DCRT must be completed. Simultaneous integrated boost using IMRT is not allowed. Brachytherapy boost is not allowed.

Boost radiation, if administered, must be planned from the initial CT for radiation planning. Changes in patient positioning for the boost are not allowed. If electron boost is used, there must be adequate dosimetric coverage of the Lumpectomy PTV Eval. Bolus may not be used at any time for patients treated with breast conserving surgery.

Chest wall with or without reconstruction radiation therapy
The goals of treatment planning are to encompass the Chest wall PTV (and regional node targets) and minimize inclusion of the heart and lung. Field arrangements for 3DCRT and IMRT are at the discretion of the treating physician. Multiple beam arrangements that use photons alone of various or mixed energies or in combination with electrons are to be designed during the treatment planning process to produce an optimal plan that meets the dose-volume constraints on the Chest wall PTV and normal tissues outlined below.

In those cases where an expander is in place for purposes of breast reconstruction, there can be a metal port that will need to be taken into account in the radiation treatment planning. Every attempt should be made to acquire the correct density of the expander port so correct modeling can be accomplished. Beam arrangements are to be designed in these cases so that the dose to the chest wall is considered "Per Protocol" or "Variation Acceptable" on DVH analysis.

The treating physician may optionally elect to deliver a chest wall boost. Boost radiation must be planned from the initial CT for radiation planning. A composite dose distribution and DVHs that include chest wall irradiation using either IMRT or 3DCRT and chest wall boost using electron beams, IMRT or 3DCRT must be completed. Simultaneous integrated boost using IMRT is not allowed. Brachytherapy boost is not allowed. If a mastectomy scar boost is used, the dose will be 1068cGy in 4 fractions of 267cGy. There must be adequate dosimetric coverage of the Mastectomy Scar PTV Eval on the plan composite dose volume analysis.

Regional nodal radiation therapy

The goals of treatment planning are to encompass the supraclavicular, undissected axillary and internal mammary node (optional) targets with the Breast PTV or Chest wall PTV, depending upon the type of surgery performed, and minimize inclusion of the heart and lung. Field arrangements for 3D conformal and IMRT are at the discretion of the treating physician. Multiple beam arrangements are to be designed during the treatment planning process to produce an optimal plan that meets the dose-volume constraints on the supraclavicular, axillary, and internal mammary node targets with the Breast or Chest wall PTV and normal tissues outlined below. In particular, for inclusion of the internal mammary nodes with either the chest wall or breast, there are multiple known field arrangement methods, (e.g., partially wide tangents, combined photon and electron fields, "Danish Technique," etc.) These or any other treatment approach is permissible. Inclusion of the internal mammary nodes will be optional and left to the discretion of the treating physician.

Treatment plans must meet Dose Volume Constraints for the contoured targets and normal structures. Various treatment approaches may be used to develop treatment plans and a composite plan including boost plans must be generated.

Required dose-volume histogram (DVH) analysis
The composite treatment plan for the whole breast with boost and regional nodal irradiation or chest wall and regional nodal irradiation must be done prior to the start of irradiation. All maximum doses should be defined in one dose calculation voxel, e.g., 3x3x3 mm or 3 mm^3.

Chest wall or breast:

- ≥ 95% of the Chest wall or Breast PTV Eval will receive ≥ 95% (38 Gy) of the chest wall or breast prescribed dose of 4005 cGy.
- ≤ 50% of the volume of Chest wall or Breast PTV Eval will receive ≥ 44 Gy when a boost is included in the composite plan DVH
- Maximal point dose (defined as dose to >0.1cc) within irradiated tissue:
    - when *photons only* are used for a composite plan that includes the Chest wall or Breast PTV Eval +/- IMN PTV: ≤ 115% of the prescription chest wall or whole breast dose to >0.1cc of tissue.
    - when *electron and photons* are mixed for a composite plan that includes the Chest wall or Breast PTV Eval +/- IMN PTV: ≤ 130% of the prescription Chest wall or whole breast dose to >0.1cc of tissue

The Compliance Criteria for Chest wall **boost** are:

- ***Per Protocol:*** ≥ 95% of the Mastectomy Scar PTV Eval will receive ≥ 4819 cGy which is 95% of the cumulative boost prescribed dose of 5073 cGy
    - ***Variation Acceptable:*** ≥ 90% of the Mastectomy Scar PTV Eval will receive 4565 cGy which is 90% of the cumulative boost prescribed dose of 5073 cGy
- ***Per Protocol:*** ≤ 5% of the Mastectomy Scar PTV Eval will receive ≥ 5580 cGy which is 110% of the boost prescribed dose of 5073 cGy
    - ***Variation Acceptable:*** ≤ 10% of the Mastectomy Scar PTV Eval will receive ≥ 5580 cGy which is 110% of the boost prescribed dose of 5073 cGy
- ***Per Protocol:*** Maximal point dose will be ≤ 534 cGy which is 115% of the boost prescribed dose of 5073 cGy
    - ***Variation Acceptable:*** Maximal dose point is ≤ 6088 cGy which is 120% of the boost prescribed dose of 5073 cGy

Lumpectomy PTV Eval:

- ≥ 95% of the Lumpectomy PTV Eval will receive ≥ 4819 cGy which is 95% of the cumulative boost prescribed dose of 5073 cGy
- ≤ 5% of the Lumpectomy PTV Eval will receive ≥ 5580 cGy which is 110% of the boost prescribed dose of 5073 cGy
- Maximal point dose will be ≤ 5834 cGy which is 115% of the boost prescribed dose of 5073 cGy

Supraclavicular (SCV):

- ≥ 95% of the SCV PTV will receive ≥ 95% of the prescribed dose of 4005 cGy
- Maximal point dose (to >0.1cc) will be ≤ 4606 cGy which is 115% of the SCV prescribed dose of 4005 cGy

Axillary volume (undissected):

- ≥ 95% of the Axillary PTV will receive ≥ 95% of the prescribed dose of 4005 cGy
- Maximal point dose will be ≤ 4406 cGy which is 110% of the Axillary prescribed dose of 4005 cGy

Internal mammary nodal (IMN) volumes (optional):

- ≥ 90% of the IMN PTV will receive ≥ 90% of the prescribed dose of 4005 cGy
- Maximal point dose will be ≤ 4406 cGy which is 110% of the IMN prescribed dose of 4005 cGy

Normal Tissue Constraints

Contralateral breast:

- *Per Protocol:* < 5% receives 300 cGy
- *Variation Acceptable:* < 5% receives 410 cGy

Ipsilateral lung:

- *Per Protocol:* ≤ 30% of the ipsilateral lung should receive ≥ 20 Gy
  - *Variation Acceptable:* ≤ 35 % of the ipsilateral lung should receive ≥ 20 Gy
- *Per Protocol:* ≤ 50% of the ipsilateral lung should receive ≥ 10 Gy
  - *Variation Acceptable:* ≤ 60% of the ipsilateral lung receives ≥ 10 Gy
- *Per Protocol:* ≤ 65% of the ipsilateral lung should receive ≥ 5 Gy
  - *Variation Acceptable:* ≤ 70% of the ipsilateral lung receives ≥ 5 Gy

Contralateral lung:

- *Per Protocol:* ≤ 10% of the contralateral lung should receive ≥ 5 Gy
  - *Variation Acceptable:* ≤ 15% of the contralateral lung should receive ≥ 5 Gy

Heart:

- *Per Protocol:* ≤ 5% of the whole heart should receive ≥ 25 Gy for left-sided breast cancers, and 0% of the heart should receive ≥ 25 Gy for right-sided breast cancers
  - *Variation Acceptable:* ≤ 5% of the whole heart should receive ≥ 30 Gy for left-sided breast cancers, and 0% of the heart should receive ≥ 30 Gy for right-sided breast cancers
- *Per Protocol:* ≤ 30% of the whole heart should receive ≥ 15 Gy for left-sided breast cancers, and ≤ 10% of the heart should receive ≥ 15 Gy for right-sided breast cancers
  - *Variation Acceptable:* ≤ 35% of the whole heart receives ≥ 15 Gy for left-sided breast cancers, and ≤ 15% of the heart receives ≥ 15 Gy for right-sided breast cancers
- *Per Protocol*: Mean heart dose should be ≤ 4 Gy
  - *Variation Acceptable*: ≤ 5 Gy. Every attempt should be made to make the cardiac exposure to radiation as low as possible.

Skin bolus

Skin bolus is not allowed for the treatment of intact breast patients post lumpectomy. The use of skin bolus for post-mastectomy irradiation is per the treating physician's discretion. If using bolus, the skin dose should follow the same constraints as the Chest wall PTV Eval. Verification of clinical skin dose is with nanoDot™ dosimeter (or similar) is encouraged.

Treatment verification

Before first treatment
Imaging of each 3DCRT beam must be obtained and approved by a physician prior to initiation of treatment. Standard QA and pretreatment IGRT or patient positioning is similarly required for all IMRT cases.

Subsequent images or films
Subsequent treatment verification will be as per departmental standards, but minimally every 5 fractions. The imaging modality and process should be performed based on the institutional guidelines.

Documentation requirements
All films or images are to be maintained at the local facility.

Baseline and Follow-Up Procedures

Patients will be seen in follow up as clinically recommended; evaluation for protocol specified data points will at baseline prior to radiation initiation and during specified follow up visits at 6, 12, 36, and 60 months from completion of radiotherapy, to monitor for disease recurrence and treatment-related toxicity. The following should be completed prior to RT (baseline) and at the 6, 12, 36, and 60 month visits. Note that a study calendar can be found at the end of this protocol (Appendix A). In accordance with NCCN guidelines mammography of any remaining intact breast will be performed once every 12 months, though in the absence of clinical signs and symptoms suggestive of recurrent disease, there is no indication for laboratory or imaging studies for metastases screening.

- History and Physical Exam
    - Each per-protocol follow-up encounter will include an interview with a study clinician to elicit signs and symptoms of disease recurrence or treatment-related toxicity. This encounter should include a focused physical exam to include, at minimum, a bilateral breast/chest wall, lymph node, and upper extremity exam, including weight. Height captured at screening only.
- Grading of toxicity
    - All toxicity noted by the study clinicians should be documented at baseline, during weekly visits while receiving radiation, and at each per-protocol follow-up visit (6, 12, 36, and 60 months). Toxicity should be described and graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Study clinicians should also comment on the persistence or resolution of toxicity documented at the previous encounter.
- Lymphedema
    - An increase in inter limb arm circumference of at least 10% in the lower arm or the upper arm, or both, compared with the contralateral arm at the same time point, will be judged to be clinically significant lymphedema[11] and recorded as one of the composite adverse events per the primary endpoint of this study. Arm circumference 15 cm above the medial epicondyle (upper arms) and 15 cm below the medial epicondyle (lower arms) will be measured prior to radiotherapy (baseline) and at 6, 12, 36, and 60 months by clinicians.
    - Lymphedema, if present, should also be graded according to CTCAE v4.03 though this grade will not be scored as per the primary endpoint.

- Shoulder mobility
    - Patients will take quality of life questionnaire EORTC QLQ-C3014 and breast-cancer module (BR23) prior to radiotherapy (baseline) and at 6, 12, 36, and 60 months. This questionnaire includes specific items relating to shoulder mobility, particularly item #49 – "During the past week, was it difficult to raise your arm or to move it sideways?". Responses to all items are on a four-point scale with 1-'Not at All', 2-'A Little', 3-'Quite a Bit', 4-'Very Much'. Responses to item #49 of 3 or 4 will be scored as decreased shoulder mobility as was done in the START trials.[4,12]
    - Clinicians should also use a goniometer to measure *bilateral* shoulder mobility in four excursions: abduction, adduction, anteversion, and retroversion. These goniometric measurements will be recorded prospectively prior to radiotherapy (baseline) and at 6, 12, 36, and 60 months, but will not factor into the primary composite endpoint.
- Thyroid function – Thyroid stimulating hormone levels will be required to be drawn prior to radiotherapy (baseline) and at 12, 36, and 60 months. Of course, TSH may also be monitored by other members of the patient's care team (outside of study clinicians), though this is not a requirement of the study. The proportion of patients with increased TSH levels or requiring a new start of thyroid replacement medication will be reported as a percent
- Radiation effects on reconstructed breast tissue – In patients for whom a tissue-expander is placed at the time of mastectomy to facilitate eventual breast implantation, the rate of expander compromise requiring revision or removal will be prospectively recorded. This rate will be expressed as a percent.
- Quality of Life and Body Image
    - Patients will take quality of life questionnaire EORTC QLQ-C3014 and breast-cancer module (BR23) prior to radiotherapy (baseline) and at 6, 12, 36, and 60 months. This questionnaire was developed by the European Organization for Research and Treatment of Cancer to assess quality of life in cancer patients. This validated, patient-reported measure[13-15] has been used in multiple prospective breast cancer studies.[11,12]

Monitoring and Oversight

Oversight.

The Lead Principal Investigator (Lead PI) will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial, executing the DSM plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and patient safety for all clinical studies at the CU Cancer Center. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs, UAPs and reportable AEs are reported to the DSMC, IRB and the sponsor per study protocol. All SAEs, UAPs and reportable AEs are to be reported to the DSMC within 5 business days of receiving notification of the occurrence.
Each subject's treatment outcomes will be discussed by the Investigators and Clinical Research Coordinators (CRCs) at regularly scheduled disease-oriented working group meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.
The Lead PI will provide a DSM report to the CU Cancer Center DSMC on a six month basis. The DSM report will include a protocol summary; current enrollment numbers; summary of toxicity data to include specific SAEs, UAPs and AEs; any dose modifications; all protocol deviations; and protocol amendments. The DSM report to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted, as well as any internal DSMB reports. Results and recommendations from the review of this six month report by the DSMC will then need to be submitted by the site to the IRB of record at the time of continuing review.

As the Lead PI in this multi-site trial, the Lead PI is responsible for organizing and conducting monthly teleconferences with all participating sites. The Lead PI will also be responsible for including data from all of the participating sites within the overall trial's six month DSM report to the DSMC to include minutes from monthly PI teleconferences. Each participating site will be responsible for submitting the results and recommendations from the DSMC's six month review to their IRB of record at the time of continuing review.

Study Monitoring and Frequency of Monitoring Visits

The monitoring for this trial will be carried out in full compliance with all Good Clinical Practice (GCP) Guidelines, COMIRB policies and regulations and all applicable federal regulations . This study will monitored for its entire duration until the investigation is completed.

A site initiation visit (SIV) will be conducted for all participating sites prior to enrolling any subjects into this trial to document full training of all study personnel who will be delegated any specific task on the study. This visit includes but is not limited to training on the IRB approved study protocol, regulatory requirements for study conduct including but not limited to GCP guidelines, reporting of adverse events, the review of study personnel's roles and responsibilities, completion of the Delegation of Authority Log and Protocol Training, review of the monitoring plan as outlined in the protocol, and to review data collection and proper source documentation procedures.

The monitor will perform both on-site interim monitoring visits and remote monitoring off-site for all participating sites in this study. Data that is collected during the duration of this trial will be reviewed by the sponsor to identify data discrepancies, inconsistencies or any unclear information both on-site and remotely. In order to reconcile data discrepancies, queries will be sent electronically to the site(s) for data that requires clarification.

Due to the nature of this trial being an interventional radiation Phase II trial, as well as a multi-center IIT (Investigator-Initiated Trial) with the CU Cancer Center as the coordinating site, this study is considered to be high risk and will need consistent routine monitoring visits. An initial monitoring visit will be performed within 2-4 weeks of the first subject being enrolled into the trial. Subsequently, this study will then be monitored every 8-12 weeks on-site, with remote monitoring in-between scheduled on-site visits, as necessary based on the study needs, at all participating sites.

The monitor will perform routine on-site monitoring visits that include but are not limited to:

- Interface with the Principal Investigator at each visit if possible, to discuss any findings, address concerns, and to update the PI and site staff on current study progress.
- Subject source documentation verification and subject eligibility
- Informed Consent review
- Verify radiation treatment
- Protocol adherence
- Review Case Report Forms and the electronic database
- Regulatory documents review
- Review and determine if all Adverse Events and Serious Adverse Events have been appropriately reported within the specified time periods required by the protocol, GCP, the IRB and any other applicable regulatory requirements

After monitoring visits are completed, the monitor will evaluate and summarize the results after each monitoring visit in a written report. This report will include all pertinent findings during the monitoring visit including all identifiable and reportable data and non-compliant problems ongoing in the study and recommend resolutions for noted deficiencies. Any noted deficiencies that are in need of resolution will need a corrective plan of action by the Investigator and/or research staff.

The Investigator will receive a post interim monitoring visit follow-up letter 7 to 10 business days following the completion of the monitoring visit, documenting study progress and any pertinent findings and outstanding action items that need to be resolved. The Investigator will need to sign and date the letter after reviewing, and keep the original on site. The Monitor may review the letter at the next subsequent visit to ensure it has been reviewed, signed and dated by the Investigator in a timely manner.

Upon completion or termination of the study, the sponsor will ensure that each participating site undergo a site Close-out Monitoring visit prior to final closure of the study. The Monitor will assure that all necessary site close-out procedures and activities have been completed which include but are not limited to query resolution, Case Report Form completion, notification to local IRB and regulatory authorities of study closure, record retention arrangements finalized, AE and SAE resolution, and all essential documents are available and present in the Principal Investigator's file. The Monitor will complete a final close-out report documenting completion of the Close-out Monitoring visit and forward a study Close-out follow up letter to the Investigator(s) at the participating site(s) to be reviewed, signed and dated, and file a copy on site for record retention.

Safety and Adverse Event Reporting.

Any Grade 4 or 5 toxicity by CTCAE will qualify as a serious adverse event (SAE). Brachial plexopathy Grade 2 ('moderate symptoms; limiting instrumental ADL') or Grade 3 ('severe symptoms; limiting self-care ADL') and Grade 3 lymphedema ('Severe symptoms; limiting self-care ADL') will qualify as reportable adverse events (AE).

After the first year, adverse events will only be reviewed at the time of per-protocol follow-up visits by study clinicians. Only Grade 3 and higher will be collected and reported.

Retroactive chart reviews are not necessary unless there is an SAE that is identified that had not otherwise been reported.

All **serious adverse events** should be reported to the site research coordinator, site PI, and the study PI, Dr. Fisher at (720) 848-0154.

All serious adverse events will be reported to the COMIRB at the University of Colorado Anschutz Medical Campus according to institutional guidelines, and to the CU Cancer Center DSMC, as stated herein.

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

The definition of "related" being that there is a reasonable possibility that the RT caused the adverse experience.

An adverse event is UNEXPECTED when the specificity or severity is not consistent with the current expectations of biopsy complications being extremely uncommon.

Data Security

Paper records:
All paper records containing the patient's information will be stored in a locked file in a secure location in the Department of Radiation Oncology. Only members of the research team will have access to these records.

Electronic records:
Study data will be collected and managed using an electronic database. The database will be a secure system with audit capabilities.

All study related electronic files will only be made available to personnel involved in the study through the use of access privileges and passwords.

E. Potential Scientific Problems:
As with any prospective, single-institution study, sufficient patient accrual is a potential scientific problem that may limit statistical power. Over the last two years, we have treated 142 potentially eligible patients at the University of Colorado Denver. While some eligible patients will undoubtedly decline enrollment, we do expect this study to be particularly attractive to patients given that the proposed treatment is two weeks shorter than standard therapy. It is estimated that this trial will accrue, on average 8 patients per month over all sites, 5 patients per month at the UC Denver campus, and 1-2 patients per month at North and South campuses. Based on our required sample size of 106 patients (justification below), it will take approximately 18-22 months to complete accrual once the study is open at all three campuses.. The primary endpoint will be reported after all patients have been followed for one year.

Accrual.
If accrual is slower than expected and at least 50 patients reach one year of follow-up while total accrual is still fewer than 100 patients, then barriers to accrual will be reconsidered and corrective measures taken. We will also evaluate our event rate at that time to determine whether our 95% confidence interval will satisfactorily exclude the unacceptable event rate of 50% set forth a priori (see sample size justification – Section F.c.), understanding that our limited sample size in this situation may limit statistical power and result in an unacceptably wide confidence interval.

Study Duration, Completion or Termination.

Criteria for Removal of Patients from the Study.
Patients will be removed from protocol for any of the following:

1. Withdrawal of consent for any reason.
2. Inability to comply with study procedures.
3. Any illness that prevents treatment continuation, or interferes with treatment
4. If PI and/or subject decides to discontinue treatment for reason(s) other than an AE
5. Death, or subject is lost to follow-up
6. At PI's discretion.

Study Duration.
We estimate it will take approximately 2 years to complete enrollment for this study. Along with the 5 year QOL questionnaire, the total duration of the study is estimated to take approximately 7.5 years.

F. Data Analysis Plan:

(a) Definition of primary endpoint: Composite endpoint of six binary outcomes at one year. These are defined below with an estimated composite event rate of 40%. Each event will count equally, and a composite event will be scored only once per patient.

1. lymphedema – an increase in inter limb arm circumference of at least 10% in the lower arm or the upper arm, or both, compared with the contralateral arm at the same time point, will be judged to be clinically significant lymphedema. Arm circumference 15 cm above the medial epicondyle (upper arms) and 15 cm below the medial epicondyle (lower arms) will be measured at 6, 12, 36, and 60 months by clinicians.
2. shoulder stiffness – reported by patient questionnaire [EORTC QLQ-C3014 and breast-cancer module (BR23)].
3. symptomatic rib fracture – diagnosed by evidence of a correlative lesion on plain film or CT.
4. ischemic heart disease – new development of angina with corresponding EKG changes, or myocardial infraction
5. pneumonitis – CTCAE ≥ Grade 2 (requires steroids).
6. brachial plexopathy – CTCAE ≥ Grade 2 (symptomatic, limits ADLs).

(b) Definition of secondary outcomes/endpoints:

1. axillary recurrence – Recurrent disease presentation within axillary lymph node levels I, II, or III. Note that supraclavicular region is not included in this endpoint as in AMAROS historically.

2. local-regional failure free survival – time from date of enrollment to earlier of clinical detection of any ipsilateral recurrent disease to the breast/chest wall or regional lymph nodes (levels I, II, III, supraclavicular, and internal mammary lymph nodes) or death.
3. distant metastasis-free survival – time from date of enrollment to earlier of clinical detection of metastatic disease beyond the breast/chest wall and regional lymph nodes or death.
4. overall survival – time from date of enrollment to date of death from any cause.
5. quality of life [EORTC QLQ-C3014 and breast-cancer module (BR23)].

(c) Analytic plan for primary objective: This analysis will be performed after all patients have been entered and followed for a minimum of one year. All eligible patients (as defined above) that begin protocol treatment will be included in the analysis.

A non-inferiority margin of 10% was chosen after extensive consultation with multiple radiation oncologists. Note this margin is an absolute difference between the toxicity event rate of standard treatment (assumed to be 40%) and that of proposed treatment, where a higher rate indicates treatment is more toxic. The sample size calculation is based powering the study with 80% power and 5% significance level. The sample size is dependent on the actual absolute difference between the toxicity event rate of standard treatment and that of the proposed treatment. When it is assumed that the actual toxicity event rate of proposed treatment is 2% lower (absolute difference) than that of standard care, a total number of 106 patients accomplishes abovementioned power. If less than 44 patients out of 106 are observed to have adverse event, we will conclude that the proposed treatment is non-inferior to standard treatment. Assuming an estimated drop-out rate of 5% of patients lost to follow-up, the calculated total number of patients will be inflated accordingly to 112.

The initial treatment report will contain the following:
1. study accrual rate;
2. tabulation of all cases entered, and any patients excluded from the analysis with reasons for exclusion;
3. distribution of important prognostic baseline variables;
4. compliance rates of treatment delivery with respect to the protocol prescription;
5. observed results with respect to the primary endpoint described above.

G. Summarize Knowledge to be Gained:

This prospective study will provide valuable information on the safety and tolerability of hypofractionated, short-course radiotherapy after surgery for breast cancer patients. Based on previously published reports in analogous but slightly different scenarios, we hypothesize that hypofractionation will prove to be as good or better than conventionally fractionated radiation that takes 50% (two weeks) longer to administer. However, it is important to document this thoroughly in a prospective manner with informed consent. Detailed information on the safety and efficacy of hypofractionation in the modern era of 3D treatment planning is needed and will prove instructive to design of subsequent randomized, multi-institution Phase III trials. If ultimately proven safe and effective, further transition of national practice care patterns toward a hypofractionated approach would result in substantial societal cost savings with respect to healthcare expenditures and resource utilization.[16]

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Appendix A

Study Calendar	
Visit	**Studies performed**
Baseline (prior to RT start)	• Consent • History and Physical Exam, including weight and height • Toxicity grading by CTCAE • Lymphedema measurement (bilateral) • Shoulder mobility measurement (goniometer – four excursions) • TSH lab • EORTC QLQ-C30 and BR.23 questionnaire
Radiation On-Treat Visit - Week 1	• Toxicity grading by CTCAE
Radiation On-Treat Visit - Week 2	• Toxicity grading by CTCAE
Radiation On-Treat Visit - Week 3	• Toxicity grading by CTCAE
Radiation On-Treat Visit - Week 4 (if applicable)	• Toxicity grading by CTCAE
Follow-Up Six-Months (+/- 30 days from RT end)	• History and Physical Exam, including weight • Toxicity grading by CTCAE • Lymphedema measurement (bilateral) • Shoulder mobility measurement (goniometer – four excursions) • EORTC QLQ-C30 and BR.23 questionnaire
Follow-Up One-Year (+/- 30 days from RT end)	• History and Physical Exam, including weight • Toxicity grading by CTCAE • Lymphedema measurement (bilateral) • Shoulder mobility measurement (goniometer – four excursions) • TSH lab • EORTC QLQ-C30 and BR.23 questionnaire
Follow-Up 36 months (+/- 60 days from RT end)	• History and Physical Exam, including weight • Toxicity grading by CTCAE • Lymphedema measurement (bilateral) • Shoulder mobility measurement (goniometer – four excursions) • TSH lab • EORTC QLQ-C30 and BR.23 questionnaire
Follow-Up 60 month (+/- 60 days from RT end)	• History and Physical Exam, including weight • Toxicity grading by CTCAE • Lymphedema measurement (bilateral) • Shoulder mobility measurement (goniometer – four excursions) • TSH lab • EORTC QLQ-C30 and BR.23 questionnaire

Study (Non-SOC) Calendar

15 (+/- 4) treatments

◄ July		~ August 2015 ~				September ►
Sun	**Mon**	**Tue**	**Wed**	**Thu**	**Fri**	**Sat**
						1
2	**3** Radiation (267cGy)	**4** Radiation (267cGy)	**5** Radiation (267cGy) On Treat Visit (anytime week 1)	**6** Radiation (267cGy)	**7** Radiation (267cGy)	**8**
9	**10** Radiation (267cGy)	**11** Radiation (267cGy)	**12** Radiation (267cGy) On Treat Visit (anytime week 1)	**13** Radiation (267cGy)	**14** Radiation (267cGy)	**15**
16	**17** Radiation (267cGy)	**18** Radiation (267cGy)	**19** Radiation (267cGy) On Treat Visit (anytime week 1)	**20** Radiation (267cGy)	**21** Radiation (267cGy)	**22**
23	**24**	**25**	**26**	**27**	**28**	**29**
30	**31**	**Notes:**				

Principal Investigator: **Christine M. Fisher, MD**
COMIRB No: **15-1329**
Version Date: **May 03, 2018**

Study Title: ***Hypofractionated, Comprehensive Radiation Therapy for Node-Positive Breast Cancer***

You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

This study is being done to learn more about a particular dose of radiation treatment for breast cancer that is completed in a shorter amount of time than what has traditionally been used to treat breast cancer.

You are being asked to be in this research study because you have already had surgery for breast cancer and some cancer cells were found in the lymph nodes that drain the breast tissue.

Other people in this study

Up to 112 people from your area will participate in the study.

Up to 150 people around the country will be in the study.

What happens if I join this study?

If you join the study, you will receive a shortened course of radiation treatment that will last approximately four weeks, instead of the traditional six-week course that women have typically received in your situation. The six-week course has been standard for effective treatment and has acceptable toxicity. We want to determine if a shorter course can maintain efficacy as the longer course with acceptable toxicity. The shorter course you will receive is designed in a way that it is intended to be equivalent to the longer course. This shorter course has been tested in breast radiation alone when the chest wall and armpit can be avoided because of concern of increased toxicity. However, because cancer cells were found outside of just the breast, you require radiation to a larger area of your chest, armpit, and shoulder than has been completely tested with this experimental dose.

Study Procedures

- ***Informed Consent***
  Before any study procedure takes place, this informed consent document will be discussed with you and you will be given a copy of this document.

- ***Patient Demographics, Medical and Cancer History***
  Before you start the study we will record your date of birth, race, ethnicity, and complete medical history. This history will look at the background and progress of your cancer and the prior therapies you have received for your disease.

- ***Physical Examination***
  A physical examination will be completed as part of your standard of care. This examination will include, at minimum, a bilateral breast/chestwall, lymph node, and upper extremity exam.

- ***Vital Signs***
  We will take your blood pressure, heart rate, respiratory rate and temperature.

- ***Performance Status***
  We will assess how well you are performing your daily activities.

- ***Concomitant Medications***
  Your study doctor will let you know which medications you can and cannot take while taking part of this study, from the time you sign informed consent through the 60 month follow up.

- ***Blood sample***
  These tests are sometimes referred to as safety labs so the study doctor can be sure it is safe for you to take part in this study and to be given treatment. Serum pregnancy tests will be performed in women who are able to become pregnant. A positive pregnancy test prior to being given treatment will exclude you from starting or continuing to take part in the study.

- ***Measurement of Swelling (Lymphedema)***
  The circumference of both arms is measured in clinic with a paper tape measure.

- ***Shoulder Mobility Measurement***
  The range of motion of your shoulder is measured in clinic with a small tool called a goniometer. This simple tool looks similar to a ruler.

- ***Mammogram***
  A mammogram is an x-ray picture of the breast. The x-ray images make it possible to detect tumors that cannot be felt. In this study, you will have a mammogram about 12 months after you have completed your radiation treatment. The results of this mammogram will be used to look at any change that may have occurred since your prior mammogram.

- ***Questionnaires for quality of life and body image***
  You will be asked to complete two questionnaires at each of the following visits in order to assess your quality of life and body image: screening, 6 month follow-up visit, 12 month follow-up visit, 36 month follow-up visit, and 60 month follow-up visit.

Study Visits

***Screening* (about One Hour)**

After you sign this consent form you will have the following done to see if you can be in this study:

- Review your medical and cancer history
- Physical exam
- Vital signs
- Performance status
- Blood draw:
  - Thyroid stimulating hormone (TSH)
  - Pregnancy test (if applicable)
- Review of medications
- Measurement of arm swelling
- Shoulder mobility measurement
- Quality of life and body image questionnaires

Treatment

Week 1 – Week 4 (about 15 minutes each visit).
While on the study you will receive radiation treatment five times per week. At one of these visits each week, you will also see your study doctor for the following assessments (about 15 minutes each visit):

- Vital signs
- Performance status
- Review of medications
- Assessment of side effects
- Radiation treatment

Follow-Up (about Thirty minutes)

- Review your medical and cancer history
- Physical exam

- Performance status
- Review of medications
- Measurement of swelling
- Shoulder mobility measurement
- Review of side effects
- Quality of life and body image questionnaires
- Blood test for thyroid stimulating hormone (12, 36, and 60 months)
- Mammogram (12 months)

How long will this study last?

Participation in this study will last about five years.

What are the possible discomforts or risks?

Below are the risks of breast radiation. The significant concern with this study is that this short course might be associated with increased frequency and severity of side effects.

Radiation Therapy Risk

Radiation therapy is a way of destroying cancer tissue while preserving as much of the surrounding healthy tissue as possible.

This procedure will give you radiation in much larger amounts than you would normally get from your usual imaging x-rays. However, the radiation will be concentrated in areas where you have cancer. Both the study treatment and the standard radiation treatment recommended without this study fall in the same place on this scale.

By getting this therapy, you have some risk of developing a second type of cancer. The actual risk to you depends on many things, such as the amount of radiation you receive and how susceptible your cells are to radiation. These things are difficult to determine, but the risk of developing a second type of cancer is generally low, 5-7 per 1000.

There is a risk that you could have side effects from the radiation treatment. Discomforts you may experience while in this study include:

<u>Short-term risks - common, but rarely serious</u>

- Temporary fatigue
- Skin irritation or redness
- Sore throat

<u>Long-term risks – uncommon, but potentially serious</u>

- Weakness of ribs on the treated side

- Skin changes to include tightening or darkening of the skin
- Increased risk of swelling in the arm
- Increased stiffness of your shoulder
- A low risk of damage to underlying organs such as your heart or lungs
- It is possible that treatment on this study might make eventual breast implant placement more difficult due to potential scar tissue, if applicable.
- Damage to the nerves the control the arm
- The small risk of a secondary cancer caused by the radiation

Here are important points about side effects:

- The study doctor does not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.
- In this study, there is a risk of acute toxicity due to the increased radiation dose for the four-week treatment.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the treatment to try to reduce side effects.

Risks of Pregnancy

Radiation may involve risks to the embryo or fetus. You should not become pregnant while on this study. It is important to let your treating doctor know if you think you might be pregnant.

Risk of Loss of Confidentiality

There is a risk that the study approach may not be better, and could possibly be worse, than the usual approach for your cancer. There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

The study may include risks that are unknown at this time.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about the treatment of breast cancer using a shorter course of radiation therapy. However, there is no guarantee that your health will improve if you join this study. Also, there could be risks to being in this

study. If there are risks, these are described in the section describing the discomforts or risks.

Are there alternative treatments?

There may be other ways of treating your breast cancer. These other ways include the standard six weeks of radiation treatment to the same area. You could also choose to get no treatment at all, although this would not be recommended.

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study at any time, and your doctor will still take care of you.

Who is paying for this study?

This research is being sponsored by University of Colorado Denver and the University of Colorado Cancer Center.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

You will need to pay for your standard clinical care not covered by your insurance company according to the details of your insurance plan which includes deductibles and co-payments. However, it will not cost you anything to be in the study, and you will not be charged extra for taking part in this study. We will obtain prior authorization from your insurance company before providing any treatment, but this is not a guarantee of payment. Because radiation of this type is generally billed per week of treatment and this treatment is completed sooner than standard radiation therapy, we anticipate that overall this type of treatment will be less expensive than the standard six week course of radiation.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled. You should talk to your treating doctor before making a decision to leave the study to discuss other choices that may be available to you.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason. Also, the lead principal investigator of this study may stop the study at any time.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call the PI for this study at your hospital:

- University of Colorado Hospital, during normal business hours please call Dr. Christine Fisher at (720) 848-0293. After hours, you should call the main hospital number (303)724-5000 and ask for the "Radiation Doctor On-Call."
- Poudre Valley Hospital, please call Dr. Joshua Petit at (970) 482-3328. This number is answered 24 hours a day.
- Memorial Hospital, please call Dr. Jane Ridings at (719) 365-6800. After hours, you should call the main hospital number (719) 365-5000.

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Christine Fisher, MD. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Fisher at (720) 848-0293. You can also ask your treating Radiation Oncologist. You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Fisher with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital
- Poudre Valley Hospital
- Memorial Hospital – Colorado Springs

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Christine Fisher, MD
University of Colorado Denver
1665 Aurora Court, Suite 1032
Campus Mail Stop F-706
Aurora, Colorado 80045-0508

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you.
- People at the Colorado Multiple Institutional Review Board (COMIRB).
- The study doctor and the rest of the study team.
- Officials at the institution funding and conducting this research and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research.

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

The Investigator (or staff acting on behalf of the Investigator) will use your information for the research outlined in this consent form. They will also make all or some of the following health information collected about you in this study available to Poudre Valley Hospital and Memorial Hospital.

Information about you that will be seen, collected, used and disclosed in this study:

- Name and demographic information (age, sex, ethnicity, address, phone number, etc.).
- Portions of your previous and current medical records that are relevant to this study, including but not limited to diagnosis(es), history and physical, laboratory or tissue studies, radiology studies, procedure results.
- Research visit and research test records.

What happens to data that is collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data collected from you during this study are important to this study and to future research. If you join this study:

- The data given by you to the investigators for this research no longer belong to you.
- Both the investigators and any sponsor of this research may study your data collected from you.
- If data are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

[Signatures on Next Page]

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study: I will get a signed and dated copy of this consent form.

Signature: _____ Date: _____

Print Name: _____

Consent form explained by: _____ Date: _____

Print Name: _____

Signature Line for witness is required for consent of non-reading subjects and consent using a short form.

Witness Signature: _____ Date: _____

Witness Print Name: _____

Witness of Signature ☐

Witness of consent process ☐