Mayo Clinic Radiation Oncology

A randomized trial of 15 fraction vs 25 fraction pencil beam scanning proton radiotherapy after mastectomy in patients requiring regional nodal irradiation

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Protocol Resources

Questions:	**Contact Name:**
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, protocol document, consent form, regulatory issues, forms completion and submission	Rad Onc Study Coordinator

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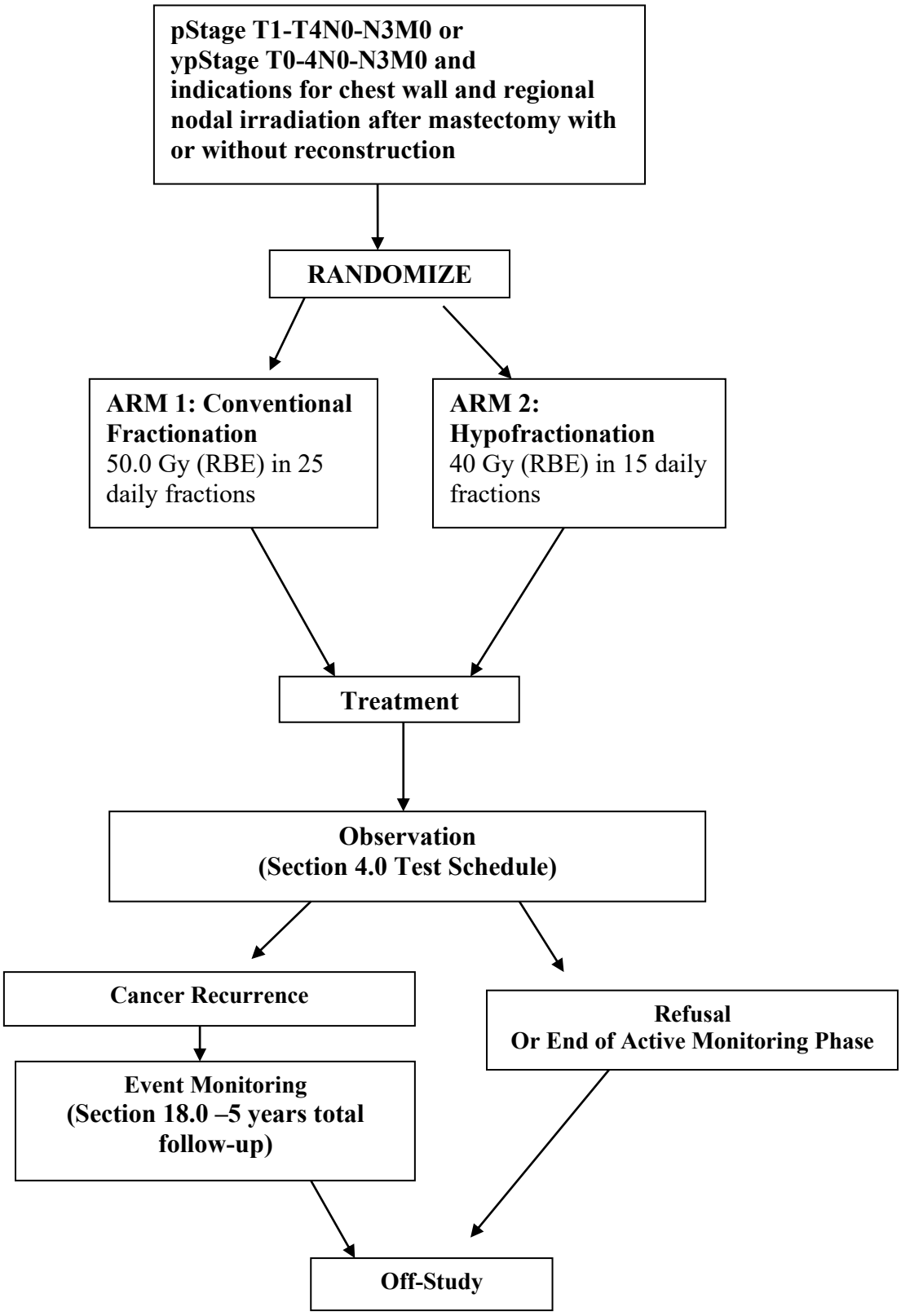
List of Abbreviations

3DCRT	3-D Conformal Radiation Therapy
AE	Adverse Event/Adverse Experience
CBCT	Cone Bean CT
CFR	Code of Federal Regulations
CRF	Case Report Form
CTV	Clinical Target Volume
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IBTR	Ipsilateral breast tumor recurrence
IMRT	Intensity Modulated Radiation Therapy
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
PHI	Protected Health Information
PI	Principal Investigator
PTV	Planning Target Volume
QOL	Quality of Life
RBE	Relative biologic effectiveness
RT	Radiation Therapy
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
XRT	X-ray Radiation Therapy

SCHEMA

Patient Selection



Study Design: This is an open label phase II randomized controlled trial to determine the safety of 15 fraction vs 25 fraction pencil beam scanning proton radiotherapy after mastectomy in patients requiring regional nodal irradiation. Proton therapy is recognized as a standard option for the delivery of radiotherapy for breast cancer.

1.0 Background

1.1 Benefits and Risks of Adjuvant Radiotherapy

Postmastectomy radiotherapy to the chest wall and regional lymph nodes after mastectomy have been shown to result in improvement in rates of recurrence and survival for women with early stage and locally-advanced breast cancer[1]. Despite the oncologic benefits of radiotherapy, however, concerns have been raised regarding the attending toxicity of photon radiotherapy. Data demonstrating late cardiovascular toxicity, particularly for women with left-sided tumors, and risk of secondary malignancy have garnered particular attention in recent years,[2] and these toxicities have been shown to partially offset the cause-specific survival benefit of adjuvant radiotherapy[1, 3].

Cardiovascular toxicity has been studied in great detail and appears to be primarily mediated by a vascular etiology, likely with macro- and microvascular contributions. Correa and colleagues[4] demonstrated a likelihood of left anterior descending artery (LAD) stenosis for women treated with adjuvant radiotherapy for breast cancer in excess of what would be expected for the general population, providing indirect evidence of radiation-mediated coronary artery disease. Darby and co-authors[3] found that the risk of major coronary events (myocardial infarction, coronary revascularization, or death from ischemic heart disease) was related to the mean heart dose and not the LAD, suggesting a microvascular etiology. Notably in that study the increase in cardiac toxicity began within the first 5 years after radiotherapy. Cardiovascular toxicity is likely multifactorial, and multiple dose-volume relationships are important in determining risk of subsequent cardiac disease, including dose to the LAD, heart (mean heart dose and volumetric parameters such as V_{25}) and left ventricle[5].

Adjuvant radiotherapy for breast cancer has also been associated with an elevated risk of developing a secondary malignancy[1]. Specifically, radiotherapy is associated with increased risk of developing and dying from ipsilateral lung cancer[1, 6]. Radiotherapy is also associated with increased risk of developing esophageal and contralateral breast carcinoma[1]. This is a result of inadvertent and unnecessary dose delivered to normal organs adjacent to disease targets. Radiotherapy to the axillary and supraclavicular lymph nodes increases the risk of lymphedema following axillary surgery.[7] Radiotherapy to the breast and chest wall is also associated with breast fibrosis, breast shrinkage, worsening of cosmesis, and arm and shoulder pain.[8, 9] In patients who undergo mastectomy with implant based reconstruction, postmastectomy radiotherapy is associated with higher rates of complication including capsular contracture, unplanned re-operation, and reconstruction failure.[10]

In summary, although adjuvant radiotherapy for breast cancer improves locoregional control and survival, there is strong rationale for the evaluation of novel techniques that reduce unnecessary exposure to normal tissue and novel dose and fractionation regimens which may improve the therapeutic ratio.

1.2 Rationale for Proton Therapy in Breast Cancer

Relative to photons, protons have fundamental physical advantages in the treatment of tumors adjacent to radiosensitive normal structures. By exploiting the Bragg peak of proton beams, clinicians are able to achieve a dose distribution to target tissues similar or better to that accomplished with photons, while reducing unintended dose to nearby normal structures[11, 12]. Thus, interest in the possible benefits of breast cancer radiotherapy with protons is emerging, with hopes of being able to maintain or improve the locoregional control and cause-specific survival with the addition of photon radiation, while reducing toxicity.

MacDonald et al [13] recently published early outcomes for a small cohort of 12 patients treated with proton radiotherapy following mastectomy. All patients received chest wall irradiation and eleven received radiotherapy to the supraclavicular, level 3, and internal mammary lymph node chains. Five of the 12 women had permanent implants at the time of radiotherapy. Nine patients had grade 2 skin toxicity and 3 patients had grade 1 skin toxicity. There was no ≥ grade 3 skin toxicity reported. During treatment 6 patients experienced grade 1 fatigue, 5 patients experienced grade 2 fatigue, and there was one incident of grade 3 fatigue. By 4 weeks follow-up fatigue had completed resolved in all but 1 patient who continued to have grade 1 fatigue. There were no reported cases of pneumonitis. The average mean dose to the heart was 0.44 Gy and the average mean V20 of the lung was 12.7%. Cuaron et al. recently reported the results of treatment of the largest cohort of patients treated with proton therapy for breast cancer.[14] Four patients were treated after lumpectomy, 24 after mastectomy (including 14 patients with implant reconstruction and 1 patient with autologous reconstruction) and 2 patients received proton therapy after wide local excision of a chest wall recurrence. Grade 2 dermatitis occurred in 20 patients (71.4%), 8 of whom (28.6%) also experienced moist desquamation. Grade 2 esophagitis was observed in 8 patients (28.6%). There was 1 grade 3 reconstructive complication. The median mean heart dose was 0.88Gy and the median V20 of the ipsilateral lung was 16.5%. This early data suggests that post-mastectomy proton therapy is feasible and associated with reduced dose to the heart and lung, warranting further study.

The work of MacDonald and colleagues was performed using passively scattered protons. A concern with this technique is the high entrance skin dose which may be associated with higher skin toxicity.[15] Scanning beam proton therapy, the technique proposed in this study, offers potential advantages over passively scattered protons including increased conformality with less unintended dose to normal tissues, including the skin.[16] However, this technique is also potentially more sensitive to uncertainties including interfractional as well as intrafractional motion which must be taken into account in treatment delivery. Rigorous clinical studies of scanning beam proton therapy are needed to determine the disease control and toxicity outcomes with this technique and to determine whether the physical dose advantages of proton therapy translate to substantial and lasting improvements in patient outcome.

1.3 Rationale for Hypofractionation in Breast Cancer

The optimal dose and fractionation regimen for postmastectomy radiotherapy remains unknown. The linear-quadratic formula model has emerged as the preferred method of predicting the relationship between fraction size and tissue response of varying radiotherapy regimens. Its origins stem from what has been described as a two-component survival curve for mammalian cells represented by the curvilinear dose-response curve for the log of cell survival.[17] In it, the biologically effective dose (BED) of a given fractionation regimen is related to the α/β ratio in the following equation,

where α represents the $\log_e$ of the cells killed per gray and β is the $\log_e$ of the cells killed per gray squared:

$BED = nd(1 + d/\alpha/\beta)$
d = dose per fraction
n = # of identical fractions

The ratio of α/β is the dose at which the linear and quadratic components of cell killing are the same. In general, early-responding tissues such as skin desquamation have a high ratio whereas late-responding tissues such as dermal contraction have a low ratio and are very sensitive to increases in fraction size.[18] Therefore, patients treated by Macdonald and colleagues and Cuaron and colleagues generally received 50.4 Gy (relative biological effectiveness [RBE]) to the chest wall and 45-50.4 Gy (RBE) to the regional lymph nodes in 1.8 Gy (RBE) fractions using an RBE value of 1.1.[14, 19]

Emerging evidence, however, suggests that the α/β ratio of breast cancer may be low and more in line with that of late responding tissues and therefore breast cancer patients may not benefit from prolonged fractionation regimens.[20, 21] Indeed, the most robust data to date suggesting this relationship has come from the UK Standardization of Breast Radiotherapy (START) trials, two modern breast cancer randomized controlled trials examining various fractionation regimens that have recently been reported with 10-year follow-up. In START-A, a regimen of 50Gy in 25 fractions to the whole breast over 5 weeks was compared with 41.6Gy or 39 Gy in 13 fractions over 5 weeks. There was no significant difference in local-regional relapse between the 41.6Gy and 50Gy regimens (6.3% vs 7.4%, p=0.65) or the 39Gy and 50Gy regimens (8.8 vs 7.4%, p=0.41).[9] Moderate or marked breast induration, telangiectasia, and breast edema was less common in the 39Gy group compared with the 50Gy group, and rates of these toxicities were no different between the 41.6Gy and 50Gy groups. The treatments in each arm were given over the same time period, enabling an estimate of sensitivity of breast cancer to changes in fraction size that was not confounded by differences in treatment time. An α/β ratio for local-regional relapse of breast cancer was determined from a meta-analysis of START-A and the START pilot trial (349 events, 3646 women) as 3.5 Gy (95% CI 1.2-5.7). The α/β ratio for normal tissue toxicity endpoints included 3.5Gy (95% CI 0.7-6.4) for breast shrinkage, 4Gy (2.3-5.6) for breast induration, 3.8Gy (1.8-5.7) for telangiectasia, and 4.7 Gy (2.4-7.0) for breast edema, suggesting that normal tissue toxicity may not be reduced and may even be increased when breast cancer radiotherapy fractionation regimens are prolonged with small daily fractions.

Further evidence suggesting hypofractionated regimens may be attractive for breast cancer came from the START-B clinical trial, in which 50Gy in 25 fractions over 5 weeks was compared with 40Gy in 15 fractions over 3 weeks. There was no difference in local-regional relapse at 10 years between 40Gy and 50Gy groups, (4.3% vs 5.5%, p=0.2) but breast shrinkage, telangiectasia, and breast edema were significantly less common with the shorter fractionation regimen. These data are consistent with the results of the Canadian hypofractionation trial which compared 42.5Gy in 16 fractions in 3.2 weeks to 50Gy in 25 fractions over 5 weeks, and suggest that the use of smaller fractions is of no benefit in terms of tumor control or reduction in toxicity, at least in the doses used in these studies, and may potentially be deleterious.[9, 22]. Interestingly, if one applies an α/β ratio for both normal tissue toxicity and tumor control of 3.5 from START-A, the 40Gy regimen from START-B is equivalent to 44.9Gy in 2 Gy fractions. This may imply

that differences in overall treatment time of a course of radiation therapy may be more important than originally thought.[23, 24].

Only a small minority of patients treated on the START-A and START-B clinical trials had undergone mastectomy or received regional nodal irradiation and none underwent immediate reconstruction. Therefore in North America, 1.8-2 Gy fraction size remains the "preferred" dose in these settings.(NCCN 2014) More data is needed to determine whether patients treated to the chest wall and regional nodes might also benefit from hypofractionated approaches. Moreover, it will be critical to understand whether hypofractionated radiotherapy is feasible in the setting of immediate implant based reconstruction. Finally, there is no data available presently on the role of hypofractionation for breast cancer with scanning beam proton therapy.[13]

Although the use of proton therapy for breast cancer is still in early development, concerns regarding proton therapy have primarily been related to costs, rather than technical feasibility in the clinic. Proton therapy departments are more expensive to build as they require huge accelerators to deliver the beam. Although protons are considered more expensive than conventional forms of radiation, cost-benefit studies have suggested cost-effectiveness in the long term due to decreased long term toxicity.[25, 26] An important driver of cost of both photon and proton radiotherapy is the number of treatments delivered to individual patients. Studies are needed to evaluate whether equivalent or improved outcomes can be achieved with shorter courses of therapy.

The overlying hypothesis of this study is that the low α/β of breast cancer can be exploited with a carefully designed hypofractionated proton therapy regimen in the post-mastectomy setting to further optimize the therapeutic ratio, improve patient convenience, and reduce cost.

2.0 Goals

2.1 Primary

2.1.2 To determine whether the 24 month complication rate (defined as grade 3 or greater late adverse events; and unplanned surgical intervention in patients who undergo mastectomy with reconstruction) of 15 fraction chest wall and regional node pencil beam scanning proton radiotherapy is acceptable relative to 25 fraction chest wall and regional nodal pencil beam scanning proton radiotherapy and worthy of further investigation.

2.2 Secondary

2.21 To evaluate acute and late toxicity

2.22 To evaluate the rate of reconstruction failure (defined as loss of the tissue expander or implant with the inability to replace it resulting in no final reconstruction or conversion to autologous reconstruction or unplanned revision with the addition of autologous reconstruction).[27, 28]

2.23 To determine the 5-year locoregional control, disease free survival and overall survival

2.24 To evaluate fatigue, arm function, and other patient reported outcomes

2.25 To evaluate clinical features, treatment technique, dose-volume parameters, histologic and genetic variants associated with fair and poor cosmetic outcome or unplanned surgical intervention.

2.26 To compare echocardiographic changes, including left ventricular strain pattern, between fractionation regimens

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.12 Age ≥ 18 years

3.13 Histologic confirmation of breast cancer resected by mastectomy with or without immediate reconstruction and chest wall and regional nodal irradiation planned.

3.14 pStage T1-T4N0-N3M0 or ypStage T0-4N0-N3M0
Note: The axilla must be staged by sentinel node biopsy alone, sentinel node biopsy followed by axillary node dissection, or axillary lymph node dissection alone

3.15 ECOG Performance Status (PS) 0 to 2. (Appendix I).

3.17 Radiotherapy must begin within 12 weeks of last surgery (breast or axilla) or last chemotherapy.
Note: Breast implants and expanders allowed

3.18 Able to and provides IRB approved study specific written informed consent

3.19a Ability to complete questionnaire (s) by themselves or with assistance

3.19b Able to complete all mandatory tests listed in section 4.0

3.19c Willing to return to enrolling institution for follow-up (during the active monitoring phase of the study)

3.19d Willing to provide tissue and blood samples for correlative research purposes.

3.19e Rochester and Arizona patients: Willing to sign consent onto the Mayo Clinic Radiotherapy Patient Outcomes Registry and Biobanking study, IRB number 15-000136

3.30 Rochester patients: Willing to sign consent onto Evaluation of cardiac function in patients undergoing proton beam or photon radiotherapy, IRB number 15-007443

3.2 Exclusion Criteria

3.21 Medical contraindication to receipt of radiotherapy.

3.22 Severe active co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.23 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements or providing informed consent.

3.24 Active systemic lupus or scleroderma.

3.25 Pregnancy or women of childbearing potential who are sexually active and not willing/able to use medically acceptable forms of contraception

3.26 Prior receipt of ipsilateral breast or chest wall radiation that would result in significant overlap of radiation therapy fields. Prior contralateral radiotherapy for breast cancer is allowed.

3.27 Positive margins after definitive surgery

3.28 History of non-breast malignancies (except for in situ cancers treated only by local excision and basal cell and squamous cell carcinomas of the skin) within 5 years prior study entry

3.29 Inflammatory breast cancer

3.29a Recurrent Breast Cancer

3.29b Boosts to the chest wall after mastectomy. Nodal boosts are allowed.

4.0 Test Schedule

Assessments, tests and procedures	**Treatment**			**Observation[7]**
	Baseline[2]	Last day of treatment (+/-2 days)	12 weeks (+/- 8 weeks) post-radiation	12 months (+/- 3 month) post completion of radiotherapy, 24 months (+/- 3 months), 36 months (+/- 3 months), and at 5 years (+/- 3 months)
History and Physical exam (including breast assessment/exam)[1]	X	X	X	X
Mammogram	X[10]			X[11]
Cosmesis ,QOL Outcome Assessment and Breast-Q[16] (see section 11.3 and Appendix)	X[13]	X	X	X
Digital Photograph	X	X	X	X
Review of surgical specimen(s) to confirm eligibility	X[3]			
Echocardiography [9, 14]	X[13]			X[8]
Radiation toxicity assessment (see section 10.4)	X	X	X	X
Serum pregnancy test	X[4]			
Blood specimen[5, 17, R]	X[15]	X	X	X[12]
Surgical tumor specimen[6, 18, R]	X			

1. A general history & physical must be done ≤ 8 weeks prior to registration. This should include an assessment of ECOG performance status (see Appendix I).

2. Following definitive surgical resection and adjuvant chemotherapy if indicated, prior to the start of radiation.
3. Outside pathology must be reviewed at the treating institution.
4. For women of childbearing potential only, must be within 7 days of radiotherapy
5. See section 14 for collection time and preparation of samples
6. See section 17 for collection time and preparation of samples
7. Patients that cannot come back to Mayo Rochester within the time constraints of the follow-up schedule; efforts to obtain outside records and send QOL's to be completed will occur, however the required items may not be captured.
8. Ideally 6-12 months post radiotherapy in HER2 positive patients treated with HER2 directed therapy and in patients treated with anthracycline as part of routine clinical care. Only followed for Echos 1 year post therapy.
9. Co-enrollment on IRB 15-007443 (echo protocol) is required in Rochester while open
10. Completed ≤ 12 months prior to study entry
11. As clinically indicated
12. At 12 months post-treatment visit only to coincide with echocardiography.
13. Should be ≥ 14 days since last chemotherapy
14. After closure of IRB 15-007443 (echo protocol) echocardiography tests will be performed only in left sided patients previously treated with anthracycline and/or HER2 directed systemic therapy. This correlative component will occur at Rochester Mayo only.
15. Baseline blood collection will be drawn through co-enrollment on IRB 15-000136 (Radiation Oncology Outcomes Registry and Biobanking Study).
16. Breast-Q forms to be completed by patient at Observation timepoints.
17. Post radiation blood specimen submission for Rochester site only.
18. Surgical tumor specimen for Rochester site only.

R. Research funded

5.0 Randomization Factors

5.1 Assignment of treatments will be balanced with respect to the presence of immediate reconstruction (mastectomy/immediate reconstruction vs mastectomy/no immediate reconstruction) using a biased-coin minimization algorithm.[29]

6.0 Registration

4.1 Registration will entail confirming patient eligibility and signing the informed consent

4.2 Pretreatment tests/procedures (see section 4.0) will be completed within the guidelines specified on the assessment schedule.

4.3 All required baseline symptoms (see section 10.0) must be documented and graded.

7.0 Protocol Treatment

Doses throughout will be prescribed in Gy (RBE). One Gy will be the equivalent of one Gy (RBE) for proton therapy for the purposes of the descriptions below. Radiation therapy must begin within 12 weeks of the last breast cancer surgery or the last dose of adjuvant chemotherapy and no sooner than 14 days since the last chemotherapy. The dose, schedule, and timing (neoadjuvant vs adjuvant) of chemotherapy and endocrine therapy are at the discretion of the treating oncologists. Concurrent cytotoxic chemotherapy with radiotherapy is not allowed. Use of anti-HER2 therapy during radiotherapy is permitted.

7.1 Radiation Therapy Arm 1

Patients who are randomized to arm 1 will receive conventionally fractionated radiotherapy in daily fractions to the chest wall plus regional nodal area CTV (with setup uncertainty analyses of 3-5mm perturbations along each translation axis and 3% beam range uncertainty). Boosts to the chest wall after mastectomy are not permitted but nodal boosts to sites of initial gross disease are allowed.

7.2 Radiation Therapy Arm 2

Patients who had a lumpectomy or mastectomy and are randomized to arm 2 will receive hypofractionated radiotherapy in daily fractions to the chest wall plus regional nodal area CTV (with setup uncertainty analyses of 3-5mm perturbations along each translation axis and 3% beam range uncertainty). Boosts to the chest wall after mastectomy are not permitted but nodal boosts to sites of initial gross disease are allowed.

7.3 Dose Specifications

7.31 Arm 1 post-mastectomy plus regional nodal irradiation

7.311 Chest wall and regional nodes: 50 Gy (RBE) in 25 fractions of 2 Gy (RBE)

7.32 Arm 2 post-mastectomy plus regional nodal irradiation

7.321 Chest wall and regional nodes: 40.05 Gy (RBE) in 15 fractions of 2.67 Gy (RBE)

7.4 Treatment Technique

7.41 Radiation will be delivered using available scanning beam proton equipment at the treating institution.

7.5 **Localization, Simulation, Immobilization**

7.51 Simulation should be performed with the patient in the supine position

7.52 Patients should be optimally positioned with an immobilization device such as an alpha cradle cast, breast board or other customized immobilization device at the discretion of the treating physician.

7.53 Arm position may be up or down.

7.54 For patients who have an expander in place for reconstruction, the expander should be fully expanded or fully collapsed in order to optimize reproducibility. The expander should remain in the same condition from the time of CT simulation until the completion of radiotherapy.

7.55 The CT should extend cephalad to at least the level of the mandible to include both elbows and extend caudally to encompass the entire lung volume. The CT scan thickness should be ≤5mm.

7.56 External skin markers, which may include permanent tattoos, are recommended for daily set-up.

7.57 KV image guidance will be performed daily. Other imaging modalities, such as CBCT and jVision RT, should be performed based on institutional guidelines.

7.58 Volumetric imaging may be performed with re-planning at the physician's discretion.

7.6 **Treatment Planning**

7.61 For proton planning, 1 en face or 2 oblique fields are generally recommended.

7.62 The use of skin bolus is not allowed

7.7 **Target Volumes**

The definitions for the CTV and normal structures for this protocol will generally follow the RTOG (Radiation Therapy Oncologic Group)-endorsed consensus guidelines for delineation for breast cancer [redacted] with exceptions described below.

7.71 <u>Post-mastectomy chest wall and regional node target volumes (Arms 1 and 2)</u>

Post-mastectomy chest wall and regional node CTV: Includes the chest wall, along with all 3 levels of the axilla, supraclavicular lymph nodes, and internal mammary lymph nodes. The chest wall contour is based on anatomical borders of the chest wall from the RTOG Breast Cancer Atlas but not extending deeper than the anterior surface of the ribs and intercostal muscles except in the vicinity of the internal mammary lymph nodes. The chest wall is also limited anteriorly to exclude the first 3 mm of tissue under the skin. In general, the chest wall CTV should include the mastectomy scar but not cross midline. Expanders, implants, or autologous tissue present for reconstruction is allowed and at least the most peripheral 1 cm should be included in the post-mastectomy chest wall and regional node CTV. In patients with subpectoral implants the implant may be excluded only with permission from the principal investigator or representative. The 3 levels of the axilla should generally follow the RTOG-endorsed consensus guidelines, although the superior border of level II of the axilla should extend to the most cranial CT-slice of the axillary vessels and [30] both the medial and lateral supraclavicular lymph nodes should

be included (Brown et al IJROBP 2015), as described by Dijkema and colleagues.[30] In addition, the internal mammary lymph nodes will be defined as the region of the internal mammary vessels plus an approximate 5 mm medial and 5 mm lateral margin, limited medially by the sternum and posteriorly by the lung and heart. The internal mammary lymph nodes should extend from the cranial CT-slice of the 4th rib to the cranial CT-slice of the jugulo-subclavian junction.[30]. The internal mammary lymph node structure should be incorporated into the CTV but it will also have its own separate individual constraints.

7.8 Critical Structures

7.81 Chest wall skin: Will be defined as the first 3 mm of tissue under the body surface anterior to the CTV and limited superiorly by the slice where the CTV is >5mm from the skin; this is generally at or below the inferior border of the clavicular head).

7.82 Supraclavicular skin (after lumpectomy or mastectomy): Will be defined as the first 3 mm of tissue under the body surface anterior to the Breast/chest wall CTV limited inferiorly by the last slice of "breast skin" and superiorly by the most superior slice of the CTV.

7.83 Heart: To be contoured on all cases. The contour should begin just inferior to the level in which the pulmonary trunk branches into the left and right pulmonary arteries (PA) and should extend to its most inferior extent near the diaphragm. The esophagus, ascending and descending aorta and inferior vena cava should be excluded from the heart contour. The pericardium should be included but not the anterior pericardial fat, if present.

7.84 Left anterior descending (LAD) interventricular branch: To be contoured on left sided cases. "Originates from the left coronary artery and runs in the interventricular groove between the right and left ventricles. If it is difficult to see, raising the level and lowering the window may help (e.g. level 50, window 150)".[31]

7.85 Right coronary artery (RCA). To be contoured on all right sided cases. "Originates from the right side of the ascending aorta. Due to the native heart position in the chest, on axilla CT, it appears to start inferior to the left coronary artery. It moves significantly with cardiac motion, so often the location can seem noncontiguous from axial CT slice to slice, as the position of the AV groove changes."[31]

7.86 Ipsilateral lung: To be contoured on all cases, auto-segmentation with manual verification is permitted

7.87 Contralateral lung: To be contoured on all cases, auto-segmentation with manual verification is permitted

7.88 Total lung: To be contoured on all cases, auto-segmentation with manual verification is permitted

7.89 Esophagus: Should be contoured from its most superior extent at the lower border of the cricoid cartilage to the bifurcation of the trachea.

7.810 Internal mammary lymph nodes: Defined as the internal mammary vessels plus an approximate 3 mm medial and 3 mm lateral margin to include the adjacent soft tissues/fat pad, and limited medially by the sternum and posteriorly by the lung and heart. Should extend from the cranial CT-slice of the 4th rib to the cranial CT-slice of the jugulo-subclavian junction.[30]. Should be incorporated into the CTV but it will also have its own separate individual constraints.

7.811 Contralateral breast: Dose to the contralateral breast will not be constrained in treatment planning and therefore contouring of the contralateral breast is not required in this protocol. However, efforts should be made to limit inadvertent dosing of the contralateral breast.

7.812 Ipsilateral Brachial Plexus: Should be contoured when present in the CTV in addition to 3 slices above the CTV as described by Hall and colleagues.[32]

7.9 Prescription and Normal Tissue Constraints

7.91 For treatment planning, setup uncertainty analyses of 3-5mm perturbations along each translation axis and 3% beam range uncertainty will be performed on the CTV and organs at risk. All CTV target volume parameters must be met under each setup uncertainty analysis. Acceptability of the level of robustness achieved of normal tissue constraints with proton planning will be left to the discretion of the treating physician, provided that all criteria below are met on the planning CT, but will be reported.

7.92 Normal Structures (Note: “of prescription” refers to the non-boost prescription)

Arms 1 and 2

Chest wall and Regional Node CTV

- Per protocol ≥ 95% will receive ≥95% of prescription; Variation Acceptable ≥ 90% receives ≥ 90% of prescription
- Per protocol D.01cc ≤110%; Variation Acceptable D.01cc ≤115%

Normal Structures (Note: “of prescription” refers to the non-boost prescription)

Chest wall skin

- Per protocol D1cc ≤ 96% of prescription; Variation acceptable D1cc ≤ 105% of prescription

Supraclavicular skin

- Per protocol D1cc ≤ 80% of prescription; Variation acceptable D1cc ≤ 90% of prescription

Internal mammary nodes

- Per protocol 95% receives 90% of prescription; Variation Acceptable 90% receives 85% of prescription.

Heart (for left-sided cases only)

- Per protocol mean heart dose ≤ 1.5% of prescription and; Variation acceptable ≤ 3% of prescription

Heart (for right-sided cases only)

- Per protocol mean heart dose ≤ 1.5% of prescription; Variation acceptable ≤ 2% of prescription

LAD (for left-sided cases only)

- Per protocol D0.01cc ≤ 6 % of prescription; Variation acceptable D0.01cc ≤ 30% of prescription.

RCA (for right-sided cases only)

- Per protocol D0.01cc ≤ 6% of prescription; Variation acceptable D0.01cc ≤ 30% of prescription.

Ipsilateral lung

- Per protocol V40 % ≤ 15% (≤ 15% of the ipsilateral lung can receive ≥ 40% of prescription); Variation acceptable V40 % ≤ 20%
- Ipsilateral lung mean dose, V20%, V60%, V80%, and V100% should be recorded

Contralateral lung

- Per protocol V10 % ≤ 10% (≤ 10% of the contralateral lung receives ≥ 10% of prescription); Variation acceptable V10% ≤ 15%

Total lung

- Record total lung V20%, V20Gy, and mean dose

Esophagus

- Per protocol proton D1cc ≤ 72% of prescription; Variation acceptable D1cc ≤ 90% of prescription

Cord

- Per protocol D0.01cc ≤ 80 %

Brachial Plexus

- Per protocol D0.01cc ≤ 102 %
  Variation acceptable ≤ 108%

7.10 Quality Assurance Documentation

7.10.1At a minimum, the first treatment plan per physician will be centrally reviewed by the principal investigator or designee prior to the start of treatment.

8.0 Radiotherapy Dose Modifications Based on Adverse Events

This study has no pre-specified interruptions due to adverse events. Treatment interruptions are discouraged. If radiation needs to be interrupted for > 2 days, this should be approved by the principal investigator or representative and documented.

9.0 Ancillary Treatment/Supportive Care

Skin changes are common complications of breast cancer radiation therapy. Usual care will be provided as per the treating institution's standard of practice. Mepitel film is allowed. If the skin becomes erythematous and/or there is pruritis, topical steroid cream may be prescribed. The addition of antihistamines may be used for severe pruritis. Patients experiencing pain will be prescribed pain medication.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Definitions

Adverse Event- An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event - Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data. All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)- Any unanticipated problem or adverse event that meets the following three criteria:

Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**

Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND

Related: A problem or event is "related" if it is possibly related to the research procedures.

Preexisting Condition- A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At screening, any clinically significant abnormality should be recorded as a preexisting condition. At

the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

10.2 Recording Adverse Events

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting unless as otherwise stated in the table below.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: [redacted])

10.21 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected and if the adverse event is related to the medical treatment or procedure. With this information, determine whether the event must be reported as an expedited report (see Section 10.3).

10.22 Assessment of Attribution
When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:
Definite - The adverse event is clearly related to the agent(s).
Probable - The adverse event is likely related to the agent(s).
Possible - The adverse event may be related to the agent(s).
Unlikely - The adverse event is doubtfully related to the agent(s).
Unrelated - The adverse event is clearly NOT related to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

a. Serious Adverse Events will be reported as part of regular adverse event reporting mechanisms via the data capture system and logged for review reporting.

10.31 Investigator Reporting: Notifying the Mayo IRB:

The IRB requirements reflect the guidance documents released by the Office of Human Research Protections (OHRP), and the Food and Drug Administration (FDA) in early 2007 and are respectively entitled “Guidance on Reviewing and

Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – Improving Human Subject Protection."

10.311 According to Mayo IRB Policy any serious adverse event (SAE) which the Principal Investigator has determined to be a UPIRTSO must be reported to the Mayo IRB as soon as possible but no later than 5 working days after the investigator first learns of the problem/event.

10.312 Non-UPIRTSO – the investigator reports problems or events that do NOT meet criteria of an UPIRTSO in summary format at the time of the next continuing review. The investigator monitors the severity and frequency of subsequent non-UPIRTSOs.

Consider the following information to collect when developing any forms for documentation of adverse events.
Example
Information collected on the adverse event worksheet (and entered in the research database):

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

10.4 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation	Grading scale (if not CTCAE)
Skin and Subcutaneous tissue disorders	Dermatitis Radiation	X	X	CTCAE
	Telangiectasia	X	X	See 10.41

	Breast Edema = CTCAE Vascular Lymphedema	X	X	CTCAE, BCTOS[1]
	Superficial soft tissue Fibrosis	X	X	CTCAE
	Seroma Formation	X	X	CTCAE
	Skin hyperpigmentation	X	X	CTCAE
	Skin hypopigmentation	X	X	CTCAE
Gastrointestinal Disorders	Esophagitis	X	X	
Infections and infestations	Breast infection	X	X	CTCAE
Respiratory, thoracic and mediastinal disorders	Pneumonitis	X	X	CTCAE
General disorders and administration site conditions	Non-cardiac chest pain	X	X	CTCAE

1. BCTOS = Breast Cancer Treatment Outcomes Scale

10.41 Grading Scale for other toxicities

Telangiectasia: Grade 0 – None; Grade 1 – 1cm2; Grade 2 – 2-4cm2; Grade 3 - >4cm2

10.5 Submit via appropriate *reporting mechanisms* the following AEs experienced by a patient and not specified in Section 10.4:

10.52 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.53 Grade 5 AEs (Death)

10.531 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure

10.532 Any death more than 30 days after the patients last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.6 Monitoring and Auditing

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices

10.61 Medical Monitoring
It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10.5 "Monitoring and Auditing"). Medical monitoring will include a regular assessment of the number and type of serious adverse events. Any serious adverse events will be followed up by the sentinel event reporting procedure.

10.62 Internal Data and Safety Monitoring Board

The trial will be reviewed by the Radiation Oncology Research Executive Board on a yearly basis to assess accrual, adverse events, and any endpoint problems. Any safety issues requiring protocol changes will be communicated through protocol amendments. The Mayo Clinic Cancer Center (MCCC) Data Safety and Monitoring Board (DSMB) is responsible for reviewing the accrual and safety for this trial at least twice a year, based on reports provided by the MCCC Statistical Office..

11.0 Treatment Evaluation

11.1 Patients will be evaluated at baseline, then according to the Assessment Schedule (Section 4.0)

11.2 At the time of reevaluation, patients will be classified in the following manner:

11.2.1 No evidence of disease (NED).

11.2.2 Recurrence of disease (REC). Recurrence must be confirmed by biopsy.

11.2.3 The site of recurrence (or failure) will also be collected and classified as local vs. regional vs. distant recurrence. The specific site of failure will also be collected as well.

11.2.4 Secondary Treatment. The date of the first retreatment and extent of retreatment post-recurrence (i.e. secondary resection or re-irradiation for primary disease), will be collected. Pathology, if available, and operative reports are required to be submitted per Section 18.0.

11.3 Cosmesis evaluation and Patient Reported Outcomes

11.3.1 Digital photographs should be performed according to the schedule outlined in section 4.0 and should include three poses: from the front with hands on hips, both oblique and lateral views with hands behind the back. Recommended framing should go from the sternal notch to the umbilicus. If possible, patients should be photographed against a solid colored background such as a white sheet.

11.3.2 The Breast Cancer Treatment Outcome Scale (BCTOS) is a self-report instrument that has high reliability and validity and will be used for evaluating patient-rated cosmesis according to the schedule outlined in section 4.0.

11.3.3 The 4 point (excellent, good, fair, poor) adaptation of the Harvard Cosmesis Scale will be used by nursing staff to grade cosmesis in women who undergo reconstruction.

11.4 Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) will be used for patient self-reporting of toxicities in the CTCAE.

Other Patient Reported Outcome questions (fatigue, pain, arm function etc.)

Unplanned surgical intervention and Reconstruction Failure will be adjudicated by a plastic surgeon and a general surgeon.

***Note the Outcomes assessments will be collected through clinical mechanisms by the Mayo Clinic Radiotherapy Patient Outcomes Registry and Biobanking study These will then be correlated with analysis from this study.**

11.5 Cardiopulmonary function testing

11.5.1 Echocardiography is a noninvasive tool that enables the detection of cardiovascular disease as a result of radiotherapy. Echocardiography can detect pericardial disease, left ventricular systolic and diastolic dysfunction , coronary artery disease suggested by resting or stress-induced regional wall motion abnormalities, and valvular heart disease.[33] Furthermore, echocardiographic strain rate imaging, a measure of regional myocardial function, has previously been reported to detect subclinical decline in cardiac function in the anterior wall of patients treated with radiotherapy for left-sided breast cancer.[34] Echocardiography will be used to detect clinical or subclinical cardiovascular disease as a result of radiotherapy.

12.0 Descriptive Factors

- Breast Quadrant: upper inner, upper outer, lower inner, lower outer
- AJCC Stage
- Tumor Size

13.0 Treatment/Follow–up Decision at Evaluation of Patient

Follow-up data will be collected and entered after the observation phase outlined in section 4.0. If the patient is still alive after 5 years have elapsed from the on-study date, no further follow-up is required by this protocol.

13.1 Patients who have a recurrence while receiving therapy or during observation will go to the event-monitoring phase and be followed

13.2 Patients who discontinue treatment or observation for reasons other than recurrence will go to the event-monitoring phase and be followed

13.3 Patients who will not receive any radiation treatment or who will receive radiation treatment elsewhere will move to event monitoring phase.

13.4 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

11.5 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

Collection Tube	Volume to Collect per Tube (Number of Tubes to Collect)	Timepoint: Last day of treatment (+/- 2 days)	Timepoint: 12 weeks post-radiation (+/- 2 days)	Timepoint: 12 months post-treatment visit (+/- 3 months)
EDTA tubes	10 mL (1)	X	X	X
No additive tubes (for Serum)	10 mL (1)	X	X	X

The baseline sample will be obtained through co-enrollment in Radiation Oncology Patient Outcomes Registry and Biobanking Study, IRB#15-00136. All other samples will be drawn according to the test schedule and summary table above. Collect and process last day of treatment, 12 weeks post-radiation, and 12 months post-treatment, blood/blood products according to table 14.1. Label specimen tube(s) with protocol number, study patient ID number, and time and date blood is drawn.

14.2 BAP will process and store specimens per standard operating procedures.

14.3 Bloods will be collected prospectively and stored until funding sources have been

secured to investigate exploratory analyses described in section 16.64

15.0 Drug Information

Not Applicable

16.0 Statistical Considerations and Methodology

This is an open label phase II randomized controlled trial to determine the safety of 15 fraction vs 25 fraction scanning beam proton radiotherapy after mastectomy in patients requiring regional nodal irradiation.

16.1 Primary Endpoint:

16.1.2 Primary endpoint: 24 month complicate rate, defined as the percentage of women randomized who develop one or more of the following events:

1) grade 3 or higher late adverse events
2) unplanned surgical intervention (not including planned serial fat grafting) in patients who undergo mastectomy with reconstruction.

16.2 Secondary Study Endpoints: The secondary aims of this study are to characterize acute and late adverse events including grade ≥ 2 pneumonitis and reconstruction failure rate, assess patient self-reported cosmesis, evaluate fatigue, breast pain, arm function and other patient reported outcomes, compare the locoregional control, disease free, overall survival. Blood will be collected for future studies exploring dose volume and genomic predictors of adverse cosmesis and biomarkers of cardiotoxicity.

The following definitions are used for the secondary endpoints of interest:

- *Acute adverse events* (up to 90 days post-RT): any adverse event, regardless of attribution, that occurs in the first 90 days post-RT.
- *Late adverse events* (up to 5 years post XRT): any adverse event that occurred after the first 90 days post-RT and up to 5 years post-RT.
- *Reconstruction failure* (up to 5 years post XRT): loss of the tissue expander or implant with the inability to replace it resulting in no final reconstruction or conversion to autologous reconstruction or revised with the addition of autologous reconstruction.[27, 28]
- *Patient Reported Outcomes/Quality of life:* Elements of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) will be used for patient self-reporting of toxicities. The Breast Cancer Treatment Outcomes Scale (BCTOS) will be used to measure patient reported functional status (pain, mobility). Other measures of fatigue, pain, and arm function are listed in the appendix.
- *Patient self-reported cosmetic outcomes:* the patient self-reported outcome will be assessed using a modified Harvard Cosmesis Scale and a modified BCTOS at baseline, 2 years, and 5 years.
- *Panel assessed cosmetic outcome:* in addition to patient self-reported and physician reported outcomes, cosmesis will be assessed by a panel of breast cancer medical providers using digital photographs from baseline and at 2 years. The Panel will be blinded to treatment allocation.

- *IBTR:* this is defined as local recurrence from trial registration as a first event at 5 years. IBTR is defined as both invasive and non-invasive breast cancer involving the same breast parenchyma as the original tumor.
- *Regional recurrence:* invasive breast cancer in the axilla, regional lymph nodes, chest wall, and skin of the ipsilateral breast at 5 years.
- *Distant recurrence:* metastatic cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer at 5 years.
- *Invasive disease free survival:* this is defined as the time from study registration until the occurrence of one of the events in a composite endpoint. This endpoint includes invasive IBTR, regional invasive breast cancer recurrence, distant breast cancer recurrence, death due to any cause, contralateral invasive breast cancer, and second primary non-breast invasive disease.
- *Overall survival:* is defined as the time from registration to death due to any cause.

16.4 Sample Size Determination

The proposed trial design is a randomized phase II trial with a 1:1 randomization ratio with the stratification variable noted in section 5.1. The primary endpoint for this trial is the 24-month complication rate, as defined above. The study will plan to enroll a total of 72 evaluable patients. An evaluable patient is defined as a patient who receives any dose of the protocol-defined radiotherapy. In this trial, we will accrue and randomize up to 96 patients over 3 years to account for ineligibility, cancellations (withdrawals prior to protocol therapy), major treatment violations, or other reasons, and treat a total of 82 patients in order to ensure 72 evaluable patients at 24 months.

This study is designed as a non-inferiority/superiority "hybrid" design using the approach of Freidlin et al.[36] It is estimated that approximately 2/3 of the patients will undergo reconstruction. For patients who undergo mastectomy with immediate reconstruction, the rate of unplanned surgical complications at the Mayo Clinic is ~15% (personal communications with Dr. Jacobson and Dr. Lemaine 6/2014), comparable to what has been reported in the literature in the modern era.[27]. The rate of grade 3 or greater late toxicity in this population is expected to be ≤1 % (Whelan ASCO 2011). For the purpose of designing this trial, we will assume a 10% complication rate in the control arm. We consider that a 10% increase of this rate in the experimental arm would be acceptable (i.e. a non-inferiority margin of 10%). Based on the results of the START-B clinical trial[9], it is also plausible that toxicities in the experimental arm may even be reduced with the shortened fractionation schedule. Therefore, a marginal *decrease* in complication rate in the experimental arm to 5% (i.e. marginal benefit margin of 5%) may be reasonably expected. Denote p_0 and p_1 as the 24-month complication rate in the control arm and experimental arm, respectively. The null hypothesis is that the complication rate in the experimental arm is inferior to the control rate of 10% by more than 10% (i.e. H_0: p_1-p_0 > 10%). The alternative hypothesis is that the complication rate in the experimental arm is non-inferior to the control rate of 10% (i.e. H_A: p_1-p_0 < 10%).

The primary analysis will occur after a minimum of 2-years following the enrollment of the last evaluable patient. The 24-month complication rate for each treatment arm will be estimated using exact binomial method along with a 1-sided 95% confidence limit. The approach of Freidlin et al. allows sequentially testing the hypotheses of non-inferiority and superiority in the same trial. Specifically, we will first test the non-inferiority hypothesis based on non-inferiority (NI) margin of 10%. If the upper bound of the 1-sided 95% confidence limit for ($p_1 - p_0$) is larger than 10%,

then inferiority (of the experimental arm) cannot be ruled out. Otherwise, if the null hypothesis is rejected in favor of non-inferiority, then a test of superiority will be performed. Specifically, if the upper bound of the 1-sided 95% confidence limit for ($p_1 - p_0$) is smaller than 0%, then superiority of the experimental arm is concluded; otherwise, if the upper bound of the 1-sided 95% confidence limit for (p1 – p0) exceeds 0% but does not exceed 10%, non-inferiority without superiority will be concluded. No multiple-comparison adjustment is required for the two hypotheses tests.[36]

The operating characteristics of the proposed design are evaluated by carrying out 5,000 simulations. Using a one-sided type I error rate of 0.05 (corresponding equivalently to constructing a 1-sided 95% confidence limit), a study of 72 evaluable patients will have 80% power to reject the null hypothesis that the 24-month complication rate in the experimental arm is higher than that of the control arm by more than 10% (i.e. rule out inferiority) under the alternative hypothesis that the complication rate in the experimental arm is 5% less than that of the control arm (i.e. superiority). However, the design will have only 41% power when the two treatment arms are equivalent (i.e. the complication rate is 10% for both arms).

16.6 Analysis Plan

The primary analysis will occur after a minimum of 2-years following the enrollment of the last evaluable patient.

16.61 Primary Analysis: The primary analysis will be to estimate the difference in the complication rate (grade 3+ toxicities, and unplanned surgical interventions) between the experimental arm and the control arm, which is defined as 24-month complication rate in experimental arm minus that in the control arm. All patients meeting the eligibility criteria who have signed a consent form and started treatment will be in the primary analysis. The complication rate will be estimated using a binomial estimator in both experimental arm and control arm, and a one-sided 90% confidence interval of the difference will be computed with normal approximation.

16.62 Secondary Analyses

16.621 *Acute adverse events (up to 90 days post-RT)*: All patients who were registered to the study and started treatment will be included in the acute adverse event analysis. An acute adverse event is an AE, regardless of attribution, that occurs up to 90 days post-RT. The maximum grade for each type of acute AE will be recorded for each patient. Data will be summarized as frequencies and relative frequencies by treatment arm. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.622 *Late adverse events and reconstruction failure*: All patients who were registered to the study and started treatment will be included in the late adverse event and reconstruction failure analysis. A late adverse event is an AE, regardless of attribution, that occurs at least 90 days post-RT and up to 5 years post-RT. The maximum grade for each type of late AE will be recorded for each patient. Data will be summarized as frequencies and

relative frequencies by treatment arm. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.623 *Quality of life*: The subscales of the BCTOS, elements from CTCAE-PRO, and other patient reported measures such as fatigue, breast pain, breast shape, and arm related morbidity outlined in the appendix will be summarized as the mean ± SD and median (minimum value, maximum value). Changes in the QOL measurements from baseline will be determined at each follow-up visit and measured by treatment arm. The comparison of the changes at each time point between the two treatment arms within each cohort will be done with a paired t-test or Wilcoxon signed rank test, whichever is appropriate.

16.624 *Cosmesis*: The values of the cosmesis instruments (patient self-reported and panel-assessed) will be summarized with the frequencies and confidence intervals of fair or poor cosmesis events at baseline, 2 years, and 5 years by treatment arm.

16.625 *IBTR incidence*: The IBTR cumulative incidence will be estimated using a competing risks method (Gooley et al.) by treatment arm. The competing risks will be regional/distant breast cancer recurrence and death.

16.626 *Regional recurrence incidence*: The regional breast cancer recurrence cumulative incidence will be estimated using a competing risks method (Gooley et al.) by treatment arm. The competing risks will be local/distant breast cancer recurrence and death.

16.627 *Distant recurrence incidence*: The distant breast cancer recurrence cumulative incidence will be estimated using a competing risks method (Gooley et al.) by treatment arm. The competing risks will be local/regional breast cancer recurrence and death.

16.628 *Disease-free survival*: DFS is defined as the time from registration until the time of disease recurrence or death due to any cause. The DFS will be estimated with a Kaplan-Meier estimator and curve by treatment arm. Estimates will be given for specific time points along with 95% CIs.

16.629 *Overall survival*: The OS will be estimated with a Kaplan-Meier estimator and curve by treatment arm. Estimates will be given for specific time points along with 95% CIs.

16.63 Exploratory Analyses: 2D and 3D strain parameters will be analyzed after radiotherapy compared to baseline and will be cmopared between patients undergoing conventional versus hypoofractionated radiotherapy. Continuous variable will be compared using unpaired t tests and nonimal variables will be compared using contingency tables and Chi square analyses.

16.64 Correlative Analyses:

16.641 Cardiac toxicity

Cardiac toxicity remains an important late effect of radiotherapy for breast cancer.[3, 34, 37, 38] Echocardiography is a noninvasive tool that enables the detection of cardiovascular disease as a result of radiotherapy. Echocardiography can detect pericardial disease, left ventricular systolic and diastolic dysfunction , coronary artery disease suggested by resting or stress-induced regional wall motion abnormalities, and valvular heart disease.[33] Ideally, cardiac toxicity could be predicted prior to the onset of clinical symptoms to enable an earlier opportunity for risk stratification, surveillance, and preventative interventions that reduce risk. Echocardiographic strain rate imaging, a measure of regional myocardial function, has previously been reported to detect subclinical decline in cardiac function in the anterior wall of patients treated with radiotherapy for left-sided breast cancer.[34]

Patients requiring regional nodal irradiation, including treatment of the internal mammary lymph nodes, are at highest risk of developing radiation induced late cardiac complications such as coronary artery disease and myocardial infarction.[39] This is a result of a higher mean dose to the heart when dose the internal mammary lymph nodes are targeted.[3] Furthermore, many high risk patients are exposed to anthracyclines and HER2 directed therapies such as trastuzumab and pertuzumab which are also associated with cardiovascular toxicities [40]. Therefore, assessment of therapy-induced cardiac toxicity will be performed as outlined in section 4.0.

Cardiac imaging modalities have limitations such as cost and operator-dependency. In contrast, serum biomarkers are operator- independent and are a potentially lower cost, non-invasive means of predicting cardiac toxicity. In one prospective study of women undergoing adjuvant radiotherapy for breast cancer, mean cardiac troponin I (TnI) levels, a highly sensitive marker or cardiac damage, were significantly elevated after photon radiotherapy in left-sided patients compared to baseline, but not in right-sided patients.[34] However, other studies have not shown cardiac troponins to consistently be of clinical utility in this setting.[41, 42]. The natriuretic peptide N-terminal pro-B-type naturetic peptide (NT-proBNP) has also been shown to be elevated in left-sided breast cancer patients after photon radiotherapy for breast cancer.[42] Similar to the case of cardiac troponins, results have been mixed and inconsistent.[41] There is no information available regarding the effects of scanning beam proton radiotherapy for breast cancer on these cardiac biomarkers. Blood will be drawn according to the schedule in section 4.0 to assess cardiac troponins and natriuretic peptides. Changes across time will be evaluated.
In addition, blood will be stored for future testing of emerging biomarkers of radiation induced cardiac toxicity.

16.643 Molecular and Genomic Predictors of Fibrosis and Reconstruction Toxicity

Predictors of fibrosis and reconstruction failure are poorly understood. If a subset of patients at high risk of complications could be identified, their treatment could be personalized. Factors previously associated with worsened cosmesis after breast conserving therapy include inferior tumor location, large excision volume,

the presence of postoperative breast complications, higher dose (including radiotherapy boost), inhomogeneity, and use of concurrent chemotherapy.[43-45] We will analyze clinical and dose volume parameters correlated with increased risk of fibrosis and reconstruction failure following proton radiotherapy. However, clinical and dose-volume factors alone are not sufficient to explain the patient to patient variation in late toxicity following a course of radiation therapy.[46, 47] Indeed, patient specific molecular and genomic features may also be of significant importance in determing variation in normal tissue radiation response following breast cancer radiotherapy.

Cytokines and growth factors are involved in the radiation response and tissue remodelling and may serve as predictive factors for normal tissue damage. For example, levels of transforming growth factor β1 (TGF- β1) vary substantially between individuals and has previously been associated with radiation fibrosis in early-stage breast cancer patients.[48] TGF- β1 is a multi-functional cytokine that attracts fibroblasts and stimulates collagen production.[49] Although basal levels may be important, expression levels of this protein are induced within an hour or less after exposure to ionizing radiation and therefore TGF- β1 induction following radiation may be a better functional marker of an elevated fibrotic response.[50, 51] Therefore, blood will be drawn pre-treatment and on the last day of radiotherapy 1 hour following the final fraction. The pre and post radiotherapy levels of TGF- β1 and other proteins in the fibrotic response will be compared and correlated with toxicity.

Mounting evidence also suggests that genetic variation may play an important role in determining susceptibility to radiation toxicity.[52] Radiogenomics is an emerging field aimed at studying genetic differences associated with variability in the effectiveness and toxicity of radiation.[47] We plan to use a candidate gene approach[47] to investigate the association of single nucleotide polymorphisms (SNPs), previously correlated with normal tissue toxicity, fibrosis, and reconstruction failure. For example, in addition to TGF- β1, SNPs in the XRCC1 (codon 241) and XRCC1 (codon 399) genes, the protein products of which function in the DNA repair pathways of base excision repair and homologous recombination, respectively, have been correlated with increased risk of subcutaneous fibrosis following breast cancer radiotherapy. [redacted] laboratory at the Mayo Clinic has used a genome-wide association approach in human lymphoblastoid cell lines to identify radiation response biomarkers. C13orf34, MAD2L1, PLK4, TPD52, and DEPDC1B were identified and functionally validated as modifiers of radiation response. These promising findings, however, require further clinical validation, potentially as part of a meta-analysis of patients treated with breast cancer radiotherapy.[47, 53]

BRCA1 and *BRCA2 (BRCA1/2)* germline mutations are responsible for the majority of hereditary breast cancer. The protein products encoded by *BRCA1/2* are essential members of the homologous recombination (HR) DNA repair pathway. *PALB2, ATM, CHEK2*, and *NBN* are other breast cancer predisposition genes that play important roles in HR. Emerging evidence suggests that HR-deficient cells are hypersensitive to protons.[54] Compared to x-rays, DNA repair is delayed following proton irradiation in HR-deficient, but not in wild-type cells.[55] Protons result in more clustered DNA DSBs, complex chromosomal aberrations, and an increased frequency of sister chromatid exchanges than x-

rays.[56, 57] These results suggest that the quality of DNA damage caused by protons has a greater requirement for DNA repair by HR. We will use emerging sequencing assays of known breast and ovarian cancer predisposition genes to develop preliminary data on whether patients with germline HR gene alterations are at increased risk of toxicity from proton therapy.[58] Flash frozen and paraffin embedded tumor and adjacent normal tissue will also be available through the breast spore to determine the impact of field effect cancerization toxicity outcomes.[59, 60] DNA will be extracted and HR gene sequencing analyses will be performed on tumor and adjacent normal tissue. Although event rates will likely be too low for definitive conclusions to be drawn, the impact of HR deficiency on disease control outcomes will also be assessed, potentially as part of a pooled analysis of breast, prostate, and pancreatic tumors treated with x-ray and particle therapy from multiple institutions. The final design of these future studies will depend on the event rates observed, cost and state of technology at the time.

16.7 Data & Safety Monitoring

16.71 Data and Safety Monitoring Plans: The Mayo Clinic Cancer Center (MCCC) Data Safety and Monitoring Board (DSMB) is responsible for reviewing the accrual and safety for this trial at least twice a year, based on reports provided by the MCCC Statistical Office..

16.72 Adverse Event Stopping Rules: The stopping rules specified below are based on knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below. The following rule will be evaluated for each arm separately.

Accrual will be temporarily suspended if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

- If 3 or more patients in the first 15 treated patients experience a grade 3 or higher adverse event, besides acute dermatitis, that is at least possibly related to treatment within 90 days post treatment.
- After the first 15 patients have been treated: if $\geq 20\%$ of all patients experience a grade 3 or higher adverse event, besides acute dermatitis, that is at least possibly related to treatment within 90 days post treatment.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.9 Inclusion of Women and Minorities

16.91 This study will be available to all eligible patients, regardless of race, or ethnic origin.

16.92 There is no information currently available regarding differential effects of this regimen in subsets defined by race, or ethnicity, and there is no reason to expect such differences to exist..Although the planned analysis will, as always, look for differences in treatment effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.93 The geographical region served by the Mayo Clinic, has a population which includes approximately 5% minorities. We expect about 5% of patients will be classified as minorities by race and about 100% of patients will be women.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	Process at Site? (Yes or No)
Diagnostic	Mandatory (as available through the breast SPORE registry)	Formalin Fixed and Flash Frozen tumor and adjacent normal	TBD	Yes
Mastectomy	Mandatory (as available through the breast SPORE registry)	Formalin Fixed and Flash Frozen tumor and adjacent normal	TBD	Yes

*If no tissue available from mastectomy surgery, obtain diagnostic slides

17.2 Patients will be consented to have tissue collected through the Breast SPORE registry available for future research studies associated with this protocol. No tissue will be collected or altered in any way under this IRB .

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s) -

CRF	**Treatment** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤2 weeks after registration
Patient Eligibility	
Demographics	
On-Study	
On Study: Neoadjuvant Chemotherapy	
Surgery	
Pathology of Ipsilateral Breast	
Breast Reconstruction	
Adjuvant Therapy	
Adverse Events- Baseline	
Specimen Submission: Blood (Baseline)	*6 months after accrual
Specimen Submission: Tissue (Baseline)*	

CRF	Treatment (Compliance with Test Schedule Section 4.0)
Patient Status: Baseline	
Patient Assessment	
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

Test Schedule Material(s)

CRF	End of Treatment	12 weeks post/Observation Phase[4]	Event Monitoring[5]
Radiation Therapy	X		
Post Mastectomy Therapy: Chest Wall	X		
Radiation Therapy: Regional Nodes	X		
Patient Assessment	X	X	
Specimen Submission: Blood (post rad tx)	X		
Adverse Events Solicited	X	X	
Adverse Events: Other	X[2]	X[2]	
Off Treatment	X[2]	X[2]	
Patient Status Form	X	X	X
Specimen Submission: Tissue (Recurrence)		X[2]	
Consent Withdrawal	X[2]	X[2]	
Lost to Follow-up	X[2]	X[2]	
Breast/Chest Wall Radiotherapy Questionnaire[3]	X	X	

1. Complete at each evaluation during Active Treatment (see Section 4.0).
2. When applicable
3. Survey will need to be entered manually if has not alternately been scanned or entered electronically
4. Active monitoring observation phase, post radiation (+/-2 days), 12 weeks (+/- 4 weeks), 12 months (+/- 30 days), annually for 4 years (+/-3 months, total 5 years follow-up). If patient progresses within observation, they will move to the event monitoring phase where they will be followed until 5 years of follow-up information has been completed from the end of treatment timepoint
5. If patient has a recurrence prior to being off radiation therapy for 5 years, continue to follow yearly.

18.3 Data Handling and Record Keeping

18.31 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

(This information is contained within the Mayo IRB Informed Consent Template Section 14)

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

18.32 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Source documents are kept in a secure location that is locked and requires approved access.

18.33 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

18.37 Records Retention

The investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The investigator will retain the specified records and reports for;
1. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" [redacted]

19.0 Study Finances

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: Venipuncture, additional echocardiography

19.3 Other budget concerns: The Mayo Clinic Radiation Oncology Unit is funding the study and will cover costs related to running the study

20.0 Publication Plan

The principal investigators hold primary responsibility for publication of the results of this study and approval from the principal investigators must be obtained before any information can be used or passed on to a third party.

21.0 References

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Appendix I

ECOG PERFORMANCE STATUS

Grade	
0	Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work (Karnofsky 70-80).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50 percent of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50 percent or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
5	Dead

Appendix 2

MC1631

MC#: _____ Scoring Nurse: _____ Date: _____

Right Breast

Overall Score: 3 Excellent
2 Good
1 Fair
0 Poor

Left Breast

Overall Score: 3 Excellent
2 Good
1 Fair
0 Poor

A= Asymmetry
3 Excellent
2 Good
1 Fair
0 Poor

B= Breast Shape
3 Excellent
2 Good
1 Fair
0 Poor

N= Nipple deformation
3 Excellent
2 Good
1 Fair
0 Poor

S= Skin condition
3 Excellent
2 Good
1 Fair
0 Poor

W= Wound scar
3 Excellent
2 Good
1 Fair
0 Poor

Total score = _____

A= Asymmetry
3 Excellent
2 Good
1 Fair
0 Poor

B= Breast Shape
3 Excellent
2 Good
1 Fair
0 Poor

N= Nipple deformation
3 Excellent
2 Good
1 Fair
0 Poor

S= Skin condition
3 Excellent
2 Good
1 Fair
0 Poor

W= Wound scar
3 Excellent
2 Good
1 Fair
0 Poor

Total score = _____

Appendix 3

BREAST-Q™
RECONSTRUCTION MODULE (POST OPERATIVE) 2.0

The following questions are about your breasts and breast reconstruction surgery. After reading each question, please circle the number in the box that best describes your situation. If you are unsure how to answer a question, choose the answer that comes closest to how you feel. Please answer all questions.

1. With your breasts in mind, in the past 2 weeks, how satisfied or dissatisfied have you been with:

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a.	How you look in the mirror clothed?	1	2	3	4
b.	The shape of your reconstructed breast(s) when you are wearing a bra?	1	2	3	4
c.	How normal you feel in your clothes?	1	2	3	4
d.	The size of your reconstructed breast(s)?	1	2	3	4
e.	Being able to wear clothing that is more fitted?	1	2	3	4
f.	How your breasts are lined up in relation to each other?	1	2	3	4
g.	How comfortably your bras fit?	1	2	3	4
h.	The softness of your reconstructed breast(s)?	1	2	3	4
i.	How equal in size your breasts are to each other?	1	2	3	4
j.	How natural your reconstructed breast(s) looks?	1	2	3	4
k.	How naturally your reconstructed breast(s) sits/hangs?	1	2	3	4
l.	How your reconstructed breast(s) feels to touch?	1	2	3	4
m.	How much your reconstructed breast(s) feels like a natural part of your body?	1	2	3	4
n.	How closely matched your breasts are to each other?	1	2	3	4
o.	How your reconstructed breast(s) look now compared to before you had any breast surgery?	1	2	3	4
p.	How you look in the mirror unclothed?	1	2	3	4

BREAST-Q™

RECONSTRUCTION MODULE (POST OPERATIVE) 2.0

Please check that you have answered all the questions before going on to the next page

This question is about breast reconstruction using IMPLANTS. If you do not have an implant(s) please skip to question 3. If you do have an implant(s), please answer question 2 below.

2. In the past 2 weeks, how satisfied or dissatisfied have you been with:

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a.	The amount of rippling (wrinkling) of your implant(s) that you can see?	1	2	3	4
b.	The amount of rippling (wrinkling) of your implant(s) that you can feel?	1	2	3	4

3. We would like to know how you feel about the outcome of your breast reconstruction surgery. Please indicate how much you agree or disagree with each statement:

		Disagree	Somewhat Agree	Definitely Agree
a.	Having reconstruction is much better than the alternative of having no breast(s).	1	2	3
b.	I would encourage other women in my situation to have breast reconstruction surgery.	1	2	3
c.	I would do it again.	1	2	3
d.	I have no regrets about having the surgery.	1	2	3
e.	Having this surgery changed my life for the better.	1	2	3
f.	The outcome perfectly matched my expectations.	1	2	3
g.	It turned out exactly as I had planned.	1	2	3

Please check that you have answered all the questions before going on to the next page

BREAST-Q™
RECONSTRUCTION MODULE (POST OPERATIVE) 2.0

4. With your breasts in mind, in the past 2 weeks, how often have you felt:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time
a.	Confident in a social setting?	1	2	3	4	5
b.	Emotionally able to do the things that you want to do?	1	2	3	4	5
c.	Emotionally healthy?	1	2	3	4	5
d.	Of equal worth to other women?	1	2	3	4	5
e.	Self-confident?	1	2	3	4	5
f.	Feminine in your clothes?	1	2	3	4	5
g.	Accepting of your body?	1	2	3	4	5
h.	Normal?	1	2	3	4	5
i.	Like other women?	1	2	3	4	5
j.	Attractive?	1	2	3	4	5

5. Thinking of your sexuality, since your breast reconstruction, how often do you generally feel:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time	Not Applicable
a.	Sexually attractive in your clothes?	1	2	3	4	5	N/A
b.	Comfortable/at ease during sexual activity?	1	2	3	4	5	N/A
c.	Confident sexually?	1	2	3	4	5	N/A
d.	Satisfied with your sex-life?	1	2	3	4	5	N/A
e.	Confident sexually about how your breast(s) look when unclothed?	1	2	3	4	5	N/A
f.	Sexually attractive when unclothed?	1	2	3	4	5	N/A

Please check that you have answered all the questions before going on to the next page

BREAST-Q™
RECONSTRUCTION MODULE (POST OPERATIVE) 2.0

6. In the past 2 weeks, how often have you experienced:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time
a.	Neck pain?	1	2	3	4	5
b.	Upper back pain?	1	2	3	4	5
c.	Shoulder pain?	1	2	3	4	5
d.	Arm pain?	1	2	3	4	5
e.	Rib pain?	1	2	3	4	5
f.	Pain in the muscles of your chest?	1	2	3	4	5
g.	Difficulty lifting or moving your arms?	1	2	3	4	5
h.	Difficulty sleeping because of discomfort in your breast area?	1	2	3	4	5
i.	Tightness in your breast area?	1	2	3	4	5
j.	Pulling in your breast area?	1	2	3	4	5
k.	Nagging feeling in your breast area?	1	2	3	4	5
l.	Tenderness in your breast area?	1	2	3	4	5
m.	Sharp pains in your breast area?	1	2	3	4	5
n.	Shooting pains in your breast area?	1	2	3	4	5
o.	Aching feeling in your breast area?	1	2	3	4	5
p.	Throbbing feeling in your breast area?	1	2	3	4	5

Please check that you have answered all the questions before going on to the next page

BREAST-Q™

RECONSTRUCTION MODULE (POST OPERATIVE) 2.0

This question is about NIPPLE reconstruction. If you did not have nipple reconstruction, please skip to question 11. If you did have nipple reconstruction, please answer question 10 below.

10. In the past 2 weeks, how satisfied or dissatisfied are you with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. The shape of your reconstructed nipple(s)?	1	2	3	4
b. How your reconstructed nipple(s) and areola(s) look?	1	2	3	4
c. How natural your reconstructed nipple(s) look?	1	2	3	4
d. The color of your reconstructed nipple/areolar complex?	1	2	3	4
e. The height (projection) of your reconstructed nipple(s)?	1	2	3	4

Please check that you have answered all the questions before going on to the next page

Appendix 4

BREAST-Q™
MASTECTOMY MODULE (POSTOPERATIVE) 2.0

After reading each question, please circle the number in the box that best describes your situation. If you are unsure how to answer a question, choose the answer that comes closest to how you feel. Please answer all questions.

1. With your breast area in mind, in the past 2 weeks, how satisfied or dissatisfied have you been with:

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a.	How you look in the mirror clothed?	1	2	3	4
b.	How comfortably your bras fit?	1	2	3	4
c.	Being able to wear clothing that is more fitted?	1	2	3	4
d.	How you look in the mirror unclothed?	1	2	3	4

2. With your breast area in mind, in the past 2 weeks, how often have you felt:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time
a.	Confident in a social setting?	1	2	3	4	5
b.	Emotionally able to do the things that you want to do?	1	2	3	4	5
c.	Emotionally healthy?	1	2	3	4	5
d.	Of equal worth to other women?	1	2	3	4	5
e.	Self-confident?	1	2	3	4	5
f.	Feminine in your clothes?	1	2	3	4	5
g.	Accepting of your body?	1	2	3	4	5
h.	Normal?	1	2	3	4	5
i.	Like other women?	1	2	3	4	5
j.	Attractive?	1	2	3	4	5

Please check that you have answered all the questions before going on to the next page

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3. In the past 2 weeks, how often have you experienced:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time
a.	Neck pain?	1	2	3	4	5
b.	Upper back pain?	1	2	3	4	5
c.	Shoulder pain?	1	2	3	4	5
d.	Arm pain?	1	2	3	4	5
e.	Rib pain?	1	2	3	4	5
f.	Pain in the muscles of your chest?	1	2	3	4	5
g.	Difficulty lifting or moving your arms?	1	2	3	4	5
h.	Difficulty sleeping because of discomfort in your breast area?	1	2	3	4	5
i.	Tightness in your breast area?	1	2	3	4	5
j.	Pulling in your breast area?	1	2	3	4	5
k.	Nagging feeling in your breast area?	1	2	3	4	5
l.	Tenderness in your breast area?	1	2	3	4	5
m.	Sharp pains in your breast area?	1	2	3	4	5
n.	Shooting pains in your breast area?	1	2	3	4	5
o.	Aching feeling in your breast area?	1	2	3	4	5
p.	Throbbing feeling in your breast area?	1	2	3	4	5

Please check that you have answered all the questions before going on to the next page

BREAST-Q™
MASTECTOMY MODULE (POSTOPERATIVE) 2.0

4. Thinking of your sexuality, how often do you generally feel:

		None of the time	A little of the time	Some of the time	Most of the time	All of the time	Not Applicable
a.	Sexually attractive in your clothes?	1	2	3	4	5	N/A
b.	Comfortable/at ease during sexual activity?	1	2	3	4	5	N/A
c.	Confident sexually?	1	2	3	4	5	N/A
d.	Satisfied with your sex-life?	1	2	3	4	5	N/A
e.	Confident sexually about how your breast area looks when unclothed?	1	2	3	4	5	N/A
f.	Sexually attractive when unclothed?	1	2	3	4	5	N/A