

Pilot Study of Proton Radiation Therapy for Invasive
Breast Carcinoma Following Mastectomy

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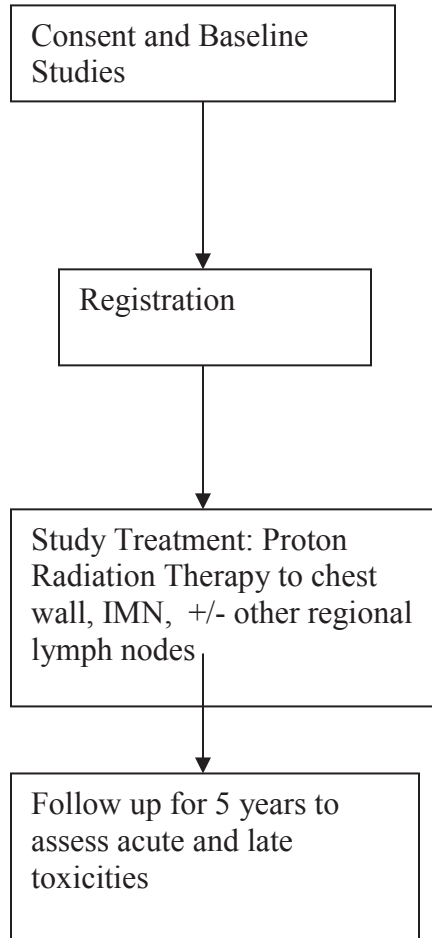


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1. OBJECTIVES

1.1 Study Design

This is a pilot trial to assess the feasibility of using proton radiation to treat breast cancer following surgery (mastectomy or breast-conserving). The intent of this study is to exploit the properties of protons for delivery of radiation therapy to the chest wall and regional lymphatics, including internal mammary nodes, without need for removal or manipulation of breast reconstruction and/or to decrease cardiac exposure to radiation and to form the basis for future studies. This study is intended to determine the feasibility of both double scattered 3D conformal protons as well as intensity modulated proton therapy (IMPT).

1.2 Primary Objectives

1.2.1 To determine the feasibility of using proton radiation for the treatment of invasive breast cancer following surgery (mastectomy or breast-conserving) based on the occurrence of grade 3 or higher radiation pneumonitis or any grade 4 toxicity within 3 months after the completion of radiation treatment. The goal is to enable women with breast reconstruction to undergo radiation therapy without removal or manipulation of reconstruction in order to allow radiation delivery without excessive pulmonary and cardiac dose and to enable patients with unfavorable cardiac anatomy (as defined by $\geq 5\%$ of the heart receives ≥ 20 Gy and/or LAD receives ≥ 20 Gy with conventional planning) to undergo chest wall irradiation with better cardiac sparing.

1.3 Secondary Objectives

1.3.1 The endpoints in these objectives are descriptive and will form the basis for designing future studies. The Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be used for grading toxicities.

- To evaluate the rate and severity of acute skin toxicity
- To evaluate the rate and severity of radiation pneumonitis, a sub-acute toxicity
- To evaluate the rate and severity of late skin toxicity
- To evaluate cosmetic outcome and patient satisfaction with cosmetic outcome

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- To evaluate acute and late toxicity of breast reconstruction following proton radiation
- To evaluate the need for unplanned additional surgery for breast reconstruction
- To evaluate early signs of cardiac effects from radiation therapy using Strain Echocardiogram

1.3.2 To describe the 5 year progression free survival rate of patients with breast cancer treated with proton radiation.

2. BACKGROUND

2.1 Proton Radiation

Radiation therapy (RT) has been proven an essential component of therapy for breast cancer. Unfortunately, radiation also carries substantial risks to surrounding healthy tissues and organs. Well documented side effects of radiation to the breast and/or chest wall include pulmonary and cardiac toxicity due to unavoidable delivery of radiation therapy to the heart and lungs. Proton radiation is a form of particle radiation that can deliver radiation therapy to the chest wall and lymphatics with near complete avoidance of the heart and lung. Proton radiation therapy is currently available at only a handful of radiation treatment centers in the United States. The Massachusetts General Hospital has the longest experience in the US and has been using protons for clinical treatments since 1961. Seven other proton centers have since opened in the United States, five within the past 5 years. Mainly due to limited availability and increased costs, the clinical use of protons has been limited, for the most part, to tumors requiring high doses and/or in close proximity to critical structures (brain, spinal cord, etc) and for the treatment of pediatric malignancies.¹⁻⁵ Over the past several years, the realization of the substantial benefit of this radiation modality has been recognized. Despite substantial capital and operational costs, several proton facilities in both the private and academic sectors are in planning or construction phases. Furthermore, several companies are actively researching more efficient and less expensive machines capable of delivering proton radiation. Given the increased availability of this treatment, it is important to explore in academic centers the potential benefit for additional malignancies, such as breast cancer. While several centers have published comparative planning studies and hypothesize that protons will provide a decrease in acute and late toxicities for patients requiring radiation therapy for advanced breast cancer, no clinical studies have been performed or reported to date for this group of patients. The Paul Scherer Institute in Switzerland plans to open a protocol for delivery of radiation for patients with advanced breast cancer early next year (personal communication, Carmen Ares, M.D.).

Protons are charged particles that enter tissue delivering a small and constant dose until near the end of the proton range where the majority of dose is delivered.⁶ Beyond this

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distal portion of the proton beam no dose is delivered. This enables complete sparing of uninvolved tissues and organs distal to the target volume. This is in contrast to photons that must deliver dose both proximal and distal to region targeted as demonstrated in Figure 1. Proton radiation is prescribed in Gray(RBE) as opposed to Gray, which is used for prescribing photon radiation. This takes into account the slightly higher Relative Biological Effectiveness (RBE) of protons. Thus, for a given prescribed dose the biological effect in tissues is the same for protons and photons and benefits are due to physical properties of the proton beam.^{7,8,9} The benefit of delivering radiation with protons versus photons is derived from the physical properties of the proton particle itself. Protons as are planned in this study will deliver the same dose to target structures. Advanced forms of photon radiation therapy do exist, but are suboptimal as the physical properties of photons necessitate delivery of dose beyond the target. Intensity modulated photon radiation therapy (IMRT) is the most advanced form of photon radiation currently available. IMRT accomplishes excellent conformity to target volumes while decreasing high dose to specified avoidance structures. This is accomplished by a sophisticated computer planning system and delivery of radiation through multiple small fields and beam angles.¹⁰ One of the major disadvantages of IMRT is the increase in low dose to a larger amount of normal tissue. This greater volume of tissue receiving radiation is of particular concern for young patients with a high likelihood of surviving their malignancy and a higher risk of developing a radiation induced malignancy. Low doses to a large volume of pulmonary tissue is also a concern.¹¹⁻¹²

At this time, the predominant mode of proton delivery is through passive beam scattering methods or “3D conformal” proton therapy. Scattering foils, range compensators, and apertures are designed to deliver a homogeneous dose distribution to the target with optimal dose conformity at the distal target region for each field.⁶ There is some degree of intensity modulation in these proton plans, but increased modulation is possible through pencil beam scanning techniques which became available only recently. Plans that use scanning techniques are referred to as Intensity Modulated Proton Therapy (IMPT) plans.¹³⁻¹⁴ Similar to Intensity Modulated Radiation Therapy (IMRT), IMPT refers to plans that deliver a homogenous dose to the target with the superimposition of individually inhomogeneous fields.⁵ Although this increases the complexity of the plan, it allows for increased dose-shaping capabilities with optimal conformity not only at the distal region of the target but also to the proximal target edge. IMPT may also facilitate the treatment of large areas without matching of fields (which introduces “cold” and “hot” areas at the match line of a plan) and allows for a decrease in the dose to skin if this is desired. For PMRT, the skin and subcutaneous tissue is the target and the goal is to deliver full dose or near full dose. “Bolus” or electron radiation is often used to increase dose to the skin. For this protocol, treatment plans will be established to deliver a dose to the skin comparable to these treatment techniques. Therefore, we do not anticipate greater skin toxicity compared to standard treatment plans, but patients will be monitored closely for this toxicity.

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Despite advances in photon techniques, homogeneous coverage of targets and optimal sparing of cardiac and pulmonary structures can be a challenge, especially for the treatment of locally advanced breast cancer in the setting of breast reconstruction. Clinical data with protons is not available for treatment of whole breast, chest wall, or regional lymphatic irradiation, but studies evaluating the dosimetry for such cases studies have been reported.^{5, 15} Lomax et al, reported results of comparative treatment planning using standard photons, IMRT, and spot scanning proton therapy (IMPT) for radiation of the breast and regional nodes for a patient with left sided breast cancer.⁵ The IMPT plan provided improved target coverage and dose homogeneity, decreased dose to cardiac and pulmonary structures, and provided the lowest integral dose to surrounding tissues. Johansson et al also examined the potential benefit of protons for left sided locally advanced breast cancer.¹⁵ This study evaluated two conventional plans (tangents, and mixed photon/electron technique), IMRT, and 3D conformal proton treatment plans for eleven patients. The authors used normal tissue complication probabilities (NTCP) for evaluation of plans.¹⁶ Mean calculated NTCP values for cardiac mortality and pneumonitis were substantially lower for the proton plan compared to all other plans. Although IMRT reduced the NTCP for the heart, it did not decrease NTCP for radiation pneumonitis in this study. Both conventional and IMRT plans showed increased integral dose as compared to the proton plan. In summary, the authors concluded that proton therapy has the potential to offer a major advantage in decreasing the risk of normal tissue complications in the treatment of left sided node positive breast cancer. At MGH, we have also analyzed plans for both 3D conformal protons and IMPT for the treatment of patients requiring post-mastectomy radiation therapy (PMRT) for left sided breast cancer. Proton plans were compared to treatment plans using partially wide tangent fields (PWTF) and a mixed photon electron (E/P) technique for eight patients. 3D proton plans were superior to PWTF and E/P technique. (Figure 2 & 3). Given the increased number of proton facilities and heightened public awareness of this modality, it is of utmost importance that a clinical trial be performed to evaluate toxicity and clinical outcomes for patients treated with proton radiation (3D-CRT or IMPT) for patients requiring left PMRT. In summary, all studies indicate a decrease in the amount of heart and lung in the treatment field that receives ANY dose of radiation (high dose or low dose). Decades of experience as well as physics research and clinical outcomes indicate that these dose distributions are accurate. Therefore, clinically, this should result in a decrease in toxicity for patients treated with protons. The ultimate question is whether or not the increased cost of protons warrants the decreased risk of side effects. As the number of proton facilities increase, it is likely that the cost of treatment will decrease and that additional centers will explore and administer protons for locally advanced breast cancer. The intent of this study is to establish treatment plans for patients with technically challenging anatomy for adequate treatment planning with modalities that are currently more widely available (photons and electrons). We propose to deliver protons on a clinical trial to patients with implants requiring IMN radiation or for patients with unfavorable cardiac anatomy (as defined by $\geq 5\%$ of the heart receives ≥ 20 Gy and/or LAD receives ≥ 20 Gy with conventional planning) as the patients are the most challenging to adequately treat with standard photon and/or electron radiation therapy. These patients often require removal or manipulation of implant to allow for delivery of

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radiation therapy to the chest wall and regional lymphatics without prohibitive amounts of heart and lung in the treatment field. In addition, we include patients with unfavorable cardiac anatomy. These patients also present a challenge for current treatment techniques.

2.2 Study Disease; Breast Radiation Treatment & Toxicities

Radiation therapy for locally advanced breast cancer has been well established to provide local control and, in some studies, has been shown to provide a survival benefit.¹⁷⁻²⁰ Conventional treatment delivers radiation to the breast/chest wall and draining lymphatics. This increases the complexity of treatment planning. Depending on patient anatomy, it is often technically difficult or impossible to provide homogeneous coverage of the target volume while producing acceptable doses to the heart and lung and it is often necessary to compromise coverage of target volumes in order to avoid toxicity. This is particularly problematic for patients who have undergone breast reconstruction. The rationale for the use of proton radiation for the treatment of breast cancer is to provide adequate coverage of target volumes and to decrease late toxicity by reducing the dose delivered to normal tissues and to allow for patients with breast reconstruction to proceed to radiation without the need for additional procedures to improve anatomy for radiation.

Estimating the risk of late complications for this group of patients is difficult. The latency between radiation treatment and the appearance of long-term side effects is high and therefore lengthy follow-up is necessary to gather adequate data and draw meaningful conclusions. Although many reports of late complications exist, these data are generally from studies utilizing dated techniques. Modern radiation delivery may lower the occurrence of late side effects, but it is too early to perform adequate assessments. We must assume a risk, even with current radiation treatment, and strive to decrease the amount of radiation delivered to areas and organs known to result in late toxicities for breast cancer patients in the past. In addition, new chemotherapeutic agents increase the risks of certain toxicities, thus making the avoidance of radiation dose to the heart and lung more critical.

Earlier radiation trials reported an increase in morbidity and mortality due to cardiac disease, predominantly in patients treated for left sided breast cancer.^{15, 21-22} Some authors even suggest that increased mortality from ischemic heart disease was the reason for the absence of a survival benefit for patients treated in the earlier post-mastectomy radiation trials.²³⁻²⁴ More recent post-mastectomy studies utilizing modern techniques and fractionation schedules have demonstrated survival benefits and no increase in cardiac mortality to date.²⁵⁻²⁶ After computed tomography (CT)-based radiation treatment planning was developed, the relationship between radiation dose, volume of heart irradiated, and cardiac outcomes could be more closely evaluated. It has generally been established that the risk of cardiovascular disease increases with increasing mean heart dose. Doses in excess of 30 to 40 Gy to small volumes of the heart are felt by some authors to increase a patient's risk of cardiovascular disease and may lead to increased

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cardiac events.²⁷ Doses of 25 Gy have been shown to induce temporary perfusion defects and ≥ 5 -6% of the heart receiving ≥ 25 -27 Gy has been accepted by some to define “unfavorable cardiac anatomy” based on correlation of this heart volume to the Stockholm trial for patients with left sided tumors that showed a high rate of cardiac morbidity and mortality.^{15, 21-22, 28-29} There is emerging data that doses to specific parts of the heart, such as the coronary arteries, may be more important in predicting cardiac outcomes.³⁰ Strain echocardiogram has recently shown promise as an accurate and relatively inexpensive study to determine myocardial abnormalities in the left ventricle for doses > 3 Gy immediately post radiation and at 2 months following radiation.³¹ Control patients receiving right sided radiation did not show any changes on post radiation studies. Pericarditis is a very rare toxicity, occurring in $<1\%$ of patients, but may lead to hospitalization.³² In addition, the increased use of cardiotoxic chemotherapy over the past several years adds yet another confounding factor to determining the effect of radiation therapy on cardiac outcomes. Doxorubicin and Herceptin, particularly when used in combination, are known to increase the risk of cardiac disease.³³⁻³⁴ These agents were not included in the chemotherapeutic regimens used in the aforementioned trials. Currently, Doxorubicin and Herceptin are both included in standard chemotherapeutic regimens and are often administered in combination.³⁵ It is not fully known how radiation therapy in the setting of these agents will affect cardiovascular outcomes. Maximal cardiac sparing achieved through proton therapy has the potential to decrease this risk by decreasing mean heart dose as well as volume receiving 40 Gy and 25 Gy (Figure 2 & 3).

Symptomatic radiation pneumonitis is a sub-acute side effect of radiation for treatments involving lung tissue.³⁶ When irradiating the chest wall and regional lymphatics, 20-30% ipsilateral lung may receive radiation to a dose of 20 Gy. With implants in place, this dose may be even higher and this is one reason why it may be recommended that implants be removed or reconstruction be delayed. In addition, recent literature for patients being treated for lung cancer report the importance of large volumes of lung receive low dose irradiation (5 Gy or 10 Gy).¹² Although the meaning of this for patients with breast cancer is less clear, it is important to note the techniques using electron radiation and/or some IMRT techniques generally decrease the volume of lung receiving 20 Gy, but increase the volume of lung receiving lower doses of radiation. Protons are capable of reducing both high and low doses of radiation to the lung. (Figure 3). Radiation pneumonitis is reported in approximately 1-5% of patients treated for breast cancer without concurrent chemotherapy.^{33, 37-38} However, the risk of radiation pneumonitis has been shown to increase with treatment of the regional lymph nodes and/or concurrent chemotherapy and rates as high as 20% have been reported in patients treated with concurrent paclitaxel and radiation.³⁹⁻⁴¹ Radiation pneumonitis generally resolves without treatment, but may require hospitalization or a course of steroids. The incidence of RP as reported by several recent series that utilized both modern chemotherapy and radiation therapy techniques are summarized below. The majority of these reports have used the Radiation Therapy Oncology Group (RTOG) acute lung morbidity scoring system to describe the severity of RP:

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	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
RTOG ACUTE LUNG MORBIDITY SCORING CRITERIA	No Change	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents/dyspnea with minimal exertion	Severe cough, no response to narcotic antitussives or dyspnea at rest/clinical or radiological evidence of acute pneumonitis/intermittent O ₂ or steroids may be required	Respiratory insufficiency/continuous oxygen or assisted ventilation	Fatal

The following retrospective studies report on incidences of RP after adjuvant radiation for breast cancer. It is important to note that only two of the series included patients who required internal mammary lymph nodes.^{37, 39} Voduc reported a 2% incidence of grade 2-3 RP using the RTOG scale in a group of 77 women with breast cancer treated at the British Columbia Cancer Agency (BCCA). No grade 4 or 5 events occurred. All patients had lymph node–positive disease with negative estrogen receptor expression and underwent surgery, adjuvant doxorubicin/cyclophosphamide for four cycles followed by four cycles of paclitaxel (AC,T) followed by radiation therapy. This study represents a patient population who were treated with the systemic regimen that most of these patients in the proposed study will receive. Yu and Buchholz reported the MD Anderson Cancer Center (MDACC) incidence of RP in a Phase III study comparing neoadjuvant four cycles of paclitaxel followed by four cycles of 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) versus eight cycles of FAC.³³ Of 524 patients treated in the study, 189 also received radiation therapy. RP was scored using the RTOG scale. Clinically evident pneumonitis was observed in 5% of the paclitaxel-FAC group and 4.5% of the FAC-only group (difference not significant). Only two patients of 189 required steroids, one other required narcotics, and none were hospitalized. Taghian et al. from the Massachusetts General Hospital (MGH) reported RP rates in 41 breast cancer patients treated with mastectomy and axillary lymph node dissection followed by four cycles of adjuvant doxorubicin/cyclophosphamide followed by four cycles of paclitaxel.³⁹ Radiation therapy to the chest wall and regional lymphatics was given concurrently with paclitaxel in 21 patients and sequentially in the remainder. In contrast to the BCCA and MDACC experiences, an incidence of 14.6% (6 of 41 patients) grade 2-3 RP using the RTOG scale was observed at the MGH regardless of the sequencing. Five of the events were grade 3 and no grade 4-5 events occurred. Lind et al reviewed Duke’s experience with RP in a cohort of breast cancer patients treated with breast-only radiation therapy versus comprehensive radiation therapy.³⁷ In 319 patients who received radiation to the breast alone the RP rate was 0.9%. When comprehensive radiation therapy was employed, the RP incidence increased to 4.1% (12 of 294 patients). All 12 patients were

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treated with oral corticosteroids. There were neither hospitalizations nor deaths from pneumonitis, which means that the incidence of 4.1% may be regarded as the incidence of RTOG grade 3 events. The Duke report predated the widespread use of taxane chemotherapy, but AC chemotherapy or cyclophosphamide, methotrexate, and 5-fluorouracil was given to 42% of the group, which resulted in a RP rate of 3.8%. Beal and McCormick reported a small series of 38 node-positive breast cancer patients treated with surgery, adjuvant (AC, T), followed by comprehensive radiation therapy at MSKCC.³⁸ No cases of RP were seen in this group after a median follow-up of 28 months. However, none of the patients in this study required irradiation of the internal mammary lymph nodes.

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Summary of Retrospective Studies Reporting RP After Breast RT:					
Author	Institution	Publication Year	n	Overall RP Reported (RTOG Grade)	Subset with RTOG Grade 3
Taghian	MGH	2001	41	14.6% grade 2-3	12%
Lind	Duke	2002	294	4.1% grade 3	4.1%
Voduc	British Columbia	2004	77	2% grade 2-3	2%
Yu	MDAH	2004	189	5% grade 2-3	1%
Beal	MSKCC	2005	38	0%	0%

In order to assess the feasibility endpoint in the proposed study, we are most interested in capturing incidences of RP that requires corticosteroids or hospitalization (RTOG grade 3-5). However, no series reported any fatalities or grade 4 events from RP after breast RT, so serious pneumonitis in this population appears to be limited to RTOG grade 3 events. The weighted average for grade 3 RP in these series using the RTOG scale is around 3.3%. Again, not all of the reported series included patients who required internal mammary lymph node radiation.

The National Cancer Institute (NCI) has advocated use of the CTCAE in clinical trials. Relevant sections from the CTCAE version 4 are available in Appendix 1. Therefore, in capturing treatment-related pulmonary toxicities secondary to our proposed treatment, we will use the CTCAE adverse events scale listed above. CTCAE toxicities >3 appear to correspond to the level of treatment-related pulmonary events that we are interested in using for the infeasibility end point and correspond most closely with grade 3-5 toxicities on the old RTOG scale. For the feasibility endpoint, we will score all cases of pneumonitis, but are most interested in those treatment-related pulmonary toxicity events that are greater than or equal to grade 3. Although we will score the level of toxicity over time for all patients, for purposes of determining infeasibility, we are only interested in the number of patients who experience grade 3-5 pulmonary toxicity. A given patient either has or does not have such an event, in which case she will be scored as a failure for this endpoint if present.

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There is limited data on second malignancy following the treatment of breast cancer, but available studies do indicate an increased risk.⁴² Radiation-induced sarcomas have been reported with rates ranging between 0.2 to 0.48 percent at 10 to 15 years.⁴³⁻⁴⁴ Increased rates of lung cancer and squamous cell carcinoma of the esophagus have also been reported.^{42, 45-48} Although the risk of a radiation induced malignancy is relatively small, considering the large number of patients treated and the gravity of a second malignancy, it cannot be ignored. Young patients are at particularly high risk of second malignancy.

Breast reconstruction is considered an integral part of treatment for breast cancer and should be discussed and offered to women undergoing mastectomy. For patients undergoing mastectomy, reconstruction offers benefits of improved psychosocial well being and body image⁴⁹. Many different types of reconstruction are available, but they can be categorized into 2 major groups; 1) prosthetic implants, including saline or silicone implants that can be placed in a one step procedure or with an expander placed at the time of mastectomy and permanent implant placed during a separate surgical procedure and 2) autologous implants using the patient's own tissue. What type of reconstruction is chosen depends on several factors including patient anatomy, comorbidities, need for radiation, and patient preference. The decision to proceed with immediate or delayed reconstruction also depends on several factors, including radiation. Benefits to immediate reconstruction include the need for only one surgical procedure, psychological benefits, and cost. The potential disadvantages include the negative impact on radiation planning⁵⁰⁻⁵². Some radiation oncologists recommend that reconstruction always be delayed for patients receiving radiation therapy due to interference with radiation delivery with standard photon and electron techniques.⁵⁰ In addition, many centers have seen an increase in the rate of contralateral prophylactic mastectomy and these cases create a particular challenge for radiation planning.⁵³⁻⁵⁴ The properties of protons will allow for radiation therapy for these patients without compromise of treatment plan or need for additional procedures to reduce the size of the implant or remove the implant (Figure 4 &5). Protons are delivered en face similar to electrons, but have the ability to treat to greater depths and with less scatter. Electrons can be used to treat the chest wall superficially in cases without an implant in place, but they cannot treat to a sufficient depth to reach the chest wall beneath an implant. Photons may be used, but it is often difficult to use optimal angles, particularly when bilateral implants are in place. Immediate breast reconstruction has advantages of providing greater psychosocial benefits compared with delayed reconstruction by allowing patients to awake from surgery with at least a partially reconstructed breast in place. This has been shown to provide patients with improved body image and self esteem and less anxiety, depression, and impairment of sexual attractiveness. Immediate reconstruction has also been shown to provide better esthetic results and often allows for more options for the type of reconstruction and is less costly than delayed reconstruction. Some studies indicate that pedicled transverse rectus abdominis myocutaneous flap (TRAM) tolerate postmastectomy RT very well and delivery of radiation may be less technically challenging with TRAM reconstruction compared to prosthetic reconstruction.^{50, 55-57}. Prosthetic based implants are also feasible in the setting of postmastectomy RT. While some studies report feasibility and outcomes with permanent implant placement prior to

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radiation, many advocate for placement of a tissue expander at the time of mastectomy and exchange of the expander for permanent implant following radiation to allow for manipulation of expander for radiation if needed. Others advocate that exchange of the implant prior to radiation will result in a decreased rate of complications because of the avoidance of performing an operation in an already irradiation field (Ho, A, abstract ASTRO 2010).⁵⁸ In any case, many women undergo immediate reconstruction due to preference or because the need for radiation is not known at the time of surgery. Proton radiation will allow for these patients to avoid additional procedures necessary to deliver radiation and potentially improve quality of life and cosmetic outcome as a result. Because the dose delivery is more homogeneous with protons, there may also be a benefit in cosmesis due to decreased “hot spots”.

2.3 Rationale

A major goal of breast oncologists as well as national and international breast oncology cooperative groups is to decrease late toxicities for patients with curable malignancies. Given the relatively high disease free and overall survival rates for breast cancer, improving functional outcomes by decreasing the long term complications of radiation therapy is a major goal. Many women now undergo reconstruction prior to radiation therapy. Technical limitations of widely available radiation techniques often lead to the need for additional manipulation of the breast reconstruction or even removal of breast reconstruction or implant prior to radiation therapy. This can impact quality of life, and self image for the patient, decrease the chance of a cosmetically acceptable result, and is more costly. The physical properties of protons allow for delivery of radiation without compromise with breast reconstruction in place. Cardiac exposure is still a major concern for patients with unfavorable cardiac anatomy. Given anticipated long term survival for many of these patients and risks of cardiac disease from chemotherapeutic and targeted agents used for care, it is important to decrease exposure to radiation. Protons will decrease cardiac exposure to radiation.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

- 3.1.1 Participants must have histologically confirmed invasive breast cancer confined to the breast and regional lymphatics (supraclavicular, axillary, internal mammary lymph nodes).
- 3.1.2 Participants must have completed definitive breast surgery (mastectomy or breast-conserving)+/- reconstructive surgery with referral for definitive chest wall radiation therapy. Patients with breast reconstruction are eligible if it determined

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by the referring or treating radiation oncologist that plan would be suboptimal without manipulation of breast implants. For patients without reconstruction, they must meet eligibility by having unfavorable cardiac anatomy defined as $\geq 5\%$ of the heart receives ≥ 20 Gy and/or LAD receives ≥ 20 Gy with conventional planning. Participants do not need to have measurable disease. Most patients will not have measurable disease at the time of treatment.

3.1.3 Age ≥ 18 at the time of diagnosis

3.1.4 Life expectancy of greater than 12 months.

3.1.5 ECOG performance status ≤ 2 (Karnofsky $\geq 60\%$, see Appendix A).

3.1.6 Diagnostic Imaging Baseline mammography prior to surgery is required. For patients with lymphatic involvement Computed Tomography (CT) scan of the chest, CT of the abdomen, and bone scan and/or Positron Emission Tomography (PET)/CT scan are required prior to delivery of chemotherapy. For most patients, this will be months prior to radiation. For patients with low burden nodal disease only mammography prior to surgery will be required.

3.1.7 Because radiation is known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.8 Ability of the patient or the patient's legal guardian to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Patients will be ineligible if any prior therapeutic radiation therapy > 200 cGy has been delivered to the target volume.

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- 3.2.2 Patients will be ineligible if surgery and chemotherapy was completed ≥ 20 weeks from the planned start date of radiation therapy or if the patient is referred for radiation therapy after a relapse of prior ipsilateral breast cancer. Surgery can exceed 20 weeks if the patient undergoes chemotherapy following surgery.
- 3.2.3 Individuals with a history of a different malignancy are ineligible except for the following circumstances. Individuals with a history of other malignancies are eligible if they have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy. Individuals with the following cancers are eligible if diagnosed and treated within the past 5 years: cervical cancer *in situ*, and basal cell or squamous cell carcinoma of the skin.
- 3.2.4 Pregnant females are excluded. Female subjects of childbearing potential must indicate to their physician that there is not a possibility of being pregnant at the time of enrollment or have a negative pregnancy test prior to initiation of radiation therapy.
- 3.2.5 Patients who received investigational chemotherapy prior to radiation therapy are excluded from this study.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

We do not expect the inclusion and exclusion criteria to either over or under-represent minorities, or underrepresented populations. This protocol does not exclude males, but will enroll primarily females as breast cancer occurs predominantly in women.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's

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protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. If a participant must be registered during off-hours or holidays, call the QACT registration line at [REDACTED] and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.
2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at [REDACTED]

Exception: DF/PCC Affiliate sites must fax the entire signed consent form including HIPAA Privacy Authorization and the eligibility checklist to the Network Affiliate Office. The Network Affiliate Office will register the participant with the QACT.

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.
5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks of radiation are described in Section 6 (Expected Toxicities and Delays).

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5.1 Pre-treatment Criteria

- 5.1.1 Diagnostic Imaging: Patients with lymph node involvement must have a metastatic work up that includes Computed Tomography(CT) scan of the chest, abdomen and pelvis and bone scan or Positron Emission Tomography (PET)/CT scan.
- 5.1.2 Cardiology: Echocardiogram including Strain echocardiogram will be performed for all patients. Echocardiogram data will be collected prior to radiation therapy (or within first week of treatment), within 4 weeks after completion of radiation therapy, and 2 months after radiation therapy.
Echocardiography: Conventional two-dimensional (2D) and Doppler echocardiography will be obtained in standard views. Tissue Doppler imaging will be acquired using standard views. Imaging parameters will be optimized and the frame rate will be set greater than 150 frames/sec for acquisition of tissue Doppler imaging. Echocardiographic loops of at least 3 beats will be recorded. Echocardiograms will be read in the conventional manner and reported in the subject's medical record. TDI-derived parameters, such as myocardial velocities, strain, strain rate and torsion, will be analyzed offline using customized computer software (EchoPac, GE Healthcare, Milwaukee, WI).
- 5.1.3 Pathological review of surgical specimen at the Massachusetts General Hospital or other DF/HCC institution.
- 5.1.4 Complete History and Physical Examination
- 5.1.5 CBC with differential. TSH at baseline. Biomarkers will be obtained with baseline routine labs and in follow with routine labs at 2 additional follow up visits (at 4 weeks after radiation therapy and 2 months after radiation therapy): Approximately 5 cc of blood will be taken for each measurement of BNP and NTproBNP, and 5 cc of blood for ultrasensitive troponin. Blood will be spun at 3000 rpms for 10 minutes, the plasma aliquotted into daughter tubes and stored at -80. BNP levels will be measured with a twosite dual-monoclonal immunochemiluminescent assay (ADVIA Centaur® BNP, Bayer Diagnostics, Tarrytown, NY) using the ADVIA Centaur immunoassay system. NT-proBNP levels will be measured with an electrochemiluminescence sandwich immunoassay (Elecsys® ProBNP, Roche Diagnostics Inc, Indianapolis, IN) using the Roche 2010 system. For non acutely dyspnic subjects aged <75 years of age, the upper limit of normal is considered 125 pg/ml (manufacturers recommendations). Troponin I will be measured using a new generation

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technique that has shown increased sensitivity compared to routine measurements (Architect STAT troponin assay, Abbot Diagnostics).

5.1.6 Photography: (optional) to objectively track cosmetic outcome.

5.2 Radiation Administration

5.2.1 Treatment Volume Parameters

The ICRU 50 recommended terminology will be used to define the radiation treatment parameters. The definitions of clinical tumor volume (CTV) will vary according to the tumor location, stage of disease, response to pre-radiation therapy, and histology.

The GTV corresponds to the gross tumor. This study does not include tumors with gross disease.

The CTV corresponds to the area that is likely to be microscopically involved with tumor.

All patients must have target volumes (chest wall and regional lymphatics) contoured. All contours should be performed according to Radiation Therapy Oncology Group (RTOG) guidelines. These guidelines are available online at <http://www.rtog.org/atlas/breastCancer/main.html>. In addition, the left ventricle and region of the left anterior descending artery will be contoured.

An additional margin to account for penumbra is to be determined for specific beam parameters at the Francis H. Burr cyclotron. The additional margin needed to account for penumbra depends on the depth of the tumor in the tissue being treated, size of the field, and field arrangement.

5.2.2 Timing of the radiation therapy

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Radiation therapy should be initiated no later than 20 weeks following chemotherapy and surgery. Surgery can exceed 20 weeks if the patient undergoes chemotherapy following surgery. Radiation should not be started earlier than 3 weeks following Taxane based chemotherapy.

5.2.3 Patient Simulation

Patient set-up and immobilization will be determined prior to obtaining the planning CT scan. The type of immobilization will be determined by the treating physician, but treatment should be delivered in the supine position.

Patient set-up reproducibility is critical for both conventional radiotherapy and proton radiotherapy and the use of daily imaging with diagnostic quality imaging will be performed. For photon therapy, it is most common to perform weekly portal images that are not always of diagnostic quality.

Respiratory gating is allowed, but not required. The decision to use this technique will be at the discretion of the treating radiation oncologist. Proton radiation should be less sensitive to breathing motion as it is delivered with en face fields rather than tangent fields.

To avoid treatment delays resulting from the machine being down, photon beam radiation can be administered. The maximum dose delivered by photons will be 20% of the prescribed dose. Treatment delays will be allowed if a serious adverse event occurs due to protocol therapy. Treatment delays will also be allowed for patients who experience a serious adverse event not related to protocol therapy (e.g. concurrent chemotherapy requiring hospitalization for neutropenia).

5.2.4 Dose Specification and Schedule

The dose prescribed to the chest wall should be 45-50.4 Gy(RBE) to the chest wall and 45-50.4 Gy(RBE) to the regional lymphatics. Ninety-five percent of the target volume should receive 45-50.4 Gy(RBE) at the discretion of the physician. The chest wall incision may receive an additional 10 Gy with electron radiation at the discretion of the treating physician, but incision boost is not required. Questions regarding dose fractionation should be discussed by contacting [REDACTED]

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Treatments will be typically administered once per day, 5 days per week. Doses will be prescribed to the appropriate isodose line encompassing the CTV such that the gradient within a volume is +7% to -5%. Dose will be reported in Gy(RBE), Gray Radiobiological Equivalent (where 1 Gy(RBE)= proton dose Gy x RBE [radiobiological effective dose], RBE = 1.1). A RBE of 1.1 has been selected for protons and is based on RBE determinations in animal and cell culture systems.⁸

5.2.5 Proton Radiation Parameters and Quality Assurance

The FHBPTC cyclotron produces a 230 MeV proton beam. The energy can be degraded to an appropriate energy to treat the desired depth. For treatment, intensity modulation of the proton beam may also be used for shaping of the beam and conformation to the target volume. Apertures and Lucite compensators may be used for shaping of protons and to conform to the distal aspect of the target volume.

Pre-treatment port films should be compared with a digitally reconstructed radiography (DRR) from the treatment planning system. Film or digital images will be taken prior to each treatment in accordance with the proton center's standard practice for all patients. These images are used to verify the position of the patient and the aperture. These digital images are permanently stored electronically for each patient. A physicist will perform dose verification for all treatment plans/fields.

5.3 General Concomitant Medication and Supportive Care Guidelines

Concomitant chemotherapy as dictated by protocol or the treating physician is allowed. All appropriate non-investigational supportive care medications or treatments may be used for optimal symptom management.

5.4 Duration of Therapy

Duration of therapy will be defined by protocol or dictated at the discretion of the treating physician.

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue as planned until finish or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,

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- Unacceptable adverse event(s),
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

5.5 Duration of Follow Up

Participants will be followed for at minimum 5 years after completion of study treatment or until death, whichever occurs first. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.6 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.5 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator (or Protocol Chair), [REDACTED]

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
<https://phsexchweb.partners.org/exchweb/bin/redir.asp?URL=http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm>. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE. If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used.

All radiation related grade 2 and greater adverse events experienced by participants will be collected from the time of the start of radiation and throughout the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

It is anticipated that toxicities will be decreased with proton radiation.

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6.1 Possible Toxicities

Possible short-term side effects, during or shortly after radiation therapy. These are reversible.

- ❑ skin: redness, tanning, irritation (common); breakdown under breast or in armpit (variable)
- ❑ fatigue (variable)
- ❑ poor wound healing (variable)
- ❑ pneumonitis, with cough and fever (rare; occurs mostly in the first 3 months after radiation)
- ❑ radiation pericarditis (left breast only) (very rare)

Unlikely long-term side effects, many months or years after radiation therapy. These may not be reversible.

- ❑ skin changes (rare)
- ❑ rib fracture (rare)
- ❑ arm or hand swelling, influenced by additional surgery and chemotherapy (variable)
- ❑ shoulder stiffness, influenced by additional surgery (rare)
- ❑ arm weakness and/or numbness (brachial plexopathy) (very rare)
- ❑ secondary cancer many years from now (very rare)
- ❑ cardiac disease

6.2 Toxicity Management

All appropriate non-investigational supportive care medications or treatments (e.g. topical ointments, pain medications, etc.) may be used for optimal symptom management.

6.3 Dose Modifications/Delays

Doses of radiation used are considered standard, i.e., this is not a dose escalation study, and interruption of radiation is not anticipated. Delays or interruptions of radiation therapy will be at the discretion of the treating physician, but the primary investigator should be notified if the number of days exceeds 3. Dose modifications for side effects should not be made without informing the primary investigator.

Proton radiation for invasive breast carcinoma will be considered to be feasible following surgery (mastectomy or breast-conserving) if the rate of grade 3 or higher radiation pneumonitis within 3 months of treatment were no more than 5%, within the range associated with conventional techniques of adjuvant radiation. In addition to radiation pneumonitis, the feasibility of proton radiation will also be compromised by any grade 4 effect occurring within 3 months of treatment, skin toxicity and pericarditis. If 2 or more

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of the initial 12 patients were to experience grade 3 or higher radiation pneumonitis or any grade 4 toxicity within 3 months of finishing radiation, accrual will not continue further. The probability of stopping early is only 12% if the underlying rate of grade 3 or higher radiation pneumonitis or any grade 4 toxicity were truly 5%. Otherwise, the protocol will proceed to enroll a total of 26 patients and declare the feasibility of proton radiation if no more than 3 of them were to experience grade 3 or higher radiation pneumonitis or any grade 4 toxicity within 3 months after treatment.

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7. STUDY CALENDAR

Baseline evaluations are to be conducted within 6-weeks prior to start of protocol therapy. Scans must be done ≤ 12 weeks prior to the start of chemotherapy if delivered or radiation therapy if no chemotherapy is delivered. In the event that the participant's clinical condition is deteriorating, laboratory evaluations should be repeated within 48 hours.

Tests and Observations	Pre-study	During Radiation	Follow Up (1)
Informed Consent and registration	X		
Pathology Review (DF/HCC)	X		
Medical History	X		
Physical Exam	X		X
Echocardiogram (2)	X		X(2)
Imaging	X (3)		As clinically indicated
Toxicity/AE Assessment		X weekly	X
Data Sheets			X (4)
Labs (5)	X		X
Optional Photography	X	X	X

Notes:

(1) Follow up schedule is at 4 weeks and 2 months, and 6 months after treatment, then at 12 months and annually to five years after treatment. Labs are only collected at the first two follow up visits (4 weeks and 2 months). Visit window for follow up is +/- 3 weeks for the 4week and 8 week follow up visits, then +/- 6months for the 6month and annual visits.

(2) Echocardiogram including Strain echocardiogram will be performed for all patients. Echocardiogram data will be collected prior to radiation therapy (or within first week of treatment), at 4 weeks after completion of radiation therapy, and 2 months after radiation therapy. Conventional two-dimensional (2D) and Doppler echocardiography will be obtained in standard views. Tissue Doppler imaging will be acquired using standard views. Imaging parameters will be optimized and the frame rate will be set greater than 150 frames/sec for acquisition of tissue Doppler imaging. Echocardiographic loops of at least 3 beats will be recorded. Echocardiograms will be read in the conventional manner and reported in the subject's medical record. TDI-derived parameters, such as myocardial velocities, strain, strain rate and torsion, will be analyzed offline using customized computer software (EchoPac, GE Healthcare, Milwaukee, WI).

(3) Diagnostic imaging required pre-study:

- Baseline mammography prior to surgery
- For patients with lymphatic involvement Computed Tomography (CT) scan of the chest, CT of the abdomen, and bone scan and/or Positron Emission Tomography (PET)/CT scan are required. For patients with low burden nodal disease, these scans are not required.

(4) The Patient Evaluation form and the Physician Data Therapy forms will be considered optional with the intent to complete at all follow up study timepoints and missed forms will not be considered as constituting protocol deviations or violations.

(5) Standard clinical labs including CBC with differential; TSH at baseline; Biomarkers will be assessed only at the times of echocardiography. Approximately 5 cc of blood will be taken for each measurement of BNP and NTproBNP, and 5 cc of blood for ultrasensitive troponin. Blood will be spun at 3000 rpms for 10 minutes, the plasma will be aliquotted into daughter tubes and stored at -80. BNP levels will be measured with a twosite dual-monoclonal immunochemiluminescent assay (ADVIA Centaur® BNP, Bayer Diagnostics, Tarrytown, NY) using the ADVIA Centaur immunoassay system. NT-proBNP levels will be measured with an electrochemiluminescence

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sandwich immunoassay (Elecsys® ProBNP, Roche Diagnostics Inc, Indianapolis, IN) using the Roche 2010 system. For non acutely dyspnic subjects aged <75 years of age, the upper limit of normal is considered 125 pg/ml (manufacturers recommendations). Troponin I will be measured using a new generation technique that has shown increased sensitivity compared to routine measurements (Architect STAT troponin assay, Abbot Diagnostics). Labs will be performed in conjunction with routine labs obtained pre- and post- treatment only at 3 time points, prior to radiation therapy, 4 weeks after radiation therapy, and 2 months after radiation therapy.

8. MEASUREMENT OF EFFECT

The patients on this study will not have measurable disease at the time of radiation therapy. These patients will be followed for disease recurrence.

8.1 Antitumor Effect– Solid Tumors

8.1.1 Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for response. Only those participants who have completed study treatment, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of study treatment will also be considered evaluable.

8.1.2 Progression-Free Survival

Tumor control is not the primary objective of this Pilot Study. Participants will be followed for toxicities and Progression-Free Survival (PFS), which is defined as the duration of time from start of treatment to time of objective disease progression.

Progressive disease will be defined as the appearance of one or more new lesions. Disease progression will be assessed at follow up by clinical exam, and may be further assessed by imaging as determined by the treating investigator.

9. ADVERSE EVENT REPORTING REQUIREMENTS

9.1 General

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Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
<https://phsexchweb.partners.org/exchweb/bin/redir.asp?URL=http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm>. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Adverse events experienced by participants will be collected and reported from initiation of study treatment, throughout the study, and within 30 days of the last dose of study treatment. Participants who experience an ongoing adverse event or related to study procedures and/or study treatment beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

9.2 Definitions

9.2.1 Adverse Event (AE)

An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

9.2.2 Serious adverse event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:

- is fatal or life-threatening;

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- requires or prolongs inpatient hospitalization;
- results in persistent or significant disability/incapacity;
- constitutes a congenital anomaly or birth defect; or
- jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

9.2.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

9.2.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

9.2.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

9.2.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.

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- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

9.3 Recording Adverse Events

Adverse event information will be obtained at each contact with the participant. All adverse events will be recorded on the appropriate study-specific case report forms (CRFs).

9.4 Reporting Adverse Events

Each adverse event will be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local policies, and federal guidelines and regulations as appropriate.

It is the responsibility of the participating investigator to notify the Principal Investigator (or Protocol Chair), IRB, and others of all serious adverse events as required in the protocol.

The Principal Investigator (or Protocol Chair) will provide information with respect to adverse events and safe use of the study treatment (e.g., safety reports, Action Letters) to all participating investigators as soon as the information becomes available.

9.5 Sponsor Notification by Investigator

9.5.1 Serious Adverse Event Reporting Requirements

All events meeting the criteria for Serious Adverse Event (see Section 11.2.2) that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported as serious adverse events.

The participating investigator must report each serious adverse event, regardless attribution, to the Principal Investigator (or Protocol Chair) within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of

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Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of study treatment
Toxicity/Adverse Event Report Form	Weekly during study treatment; Within 10 days of protocol-defined follow up
Lab Form	Within 14 days of protocol required labs
Measurement/Response Form	Within 14 days of registration; within 10 days of protocol-defined follow up
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

10.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet as required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

10.3 Monitoring

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All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

11. REGULATORY CONSIDERATIONS

11.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

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11.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

11.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- ICH Consolidated Good Clinical Practice: Guidelines (E6)
www.fda.gov/cder/guidance/iche6.htm
- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
 - Title 21 Part 11 – Electronic Records; Electronic Signatures
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
 - Title 21 Part 50 – Protection of Human Subjects
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
 - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
 - Title 21 Part 56 – Institutional Review Boards
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
 - Title 21 Part 312 – Investigational New Drug Application
www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- Institutional research policies and procedures
www.dfhec.harvard.edu/clinical-research-support/clinical-research-operations-cro/policies-and-procedures

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It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

11.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

11.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

12. STATISTICAL CONSIDERATIONS

We propose to enroll a total of 96 patients in three cohorts following the study design indicated in 12.1 to evaluate independently the feasibility of intensity modulated proton therapy (IMPT) and 3D conformal protons following mastectomy or breast-conserving surgery. The separate cohorts will ensure adequate patient numbers for achieving reasonable precision in the assessment of acute, sub-acute and late toxicities associated with each proton technique in the specific population. The accrual goal includes 20% inflation to account for patients unevaluable or lost to follow-up so that adequate precision is maintained for longer-term endpoints. The target accrual has been adjusted based on the observed data among mastectomy patients with at least 6 months follow-up, including the completeness of strain echocardiogram testing.

12.1 Study Design/Endpoints

This is a pilot study substituting proton radiation for photon radiation, seeking to show the feasibility of proton radiation and to assess the rate of acute, sub-acute and late toxicities during and after proton radiation to the left chest wall and regional lymphatics. It is anticipated that patients undergoing proton radiation will not have increased toxicity compared to patients who have historically undergone photon radiation.

Proton radiation will be considered to be feasible as adjuvant treatment for invasive breast carcinoma in each cohort following surgery if the rate of grade 3 or higher radiation pneumonitis within 3 months of treatment were no more than 5%, within the range associated with conventional techniques of adjuvant radiation. In addition to radiation pneumonitis, the feasibility of proton radiation will also be compromised by any grade 4 effect occurring within 3 months of treatment, as well as skin toxicity and pericarditis. If 2 or more of the initial 12

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patients were to experience grade 3 or higher radiation pneumonitis or any grade 4 toxicity within 3 months of finishing radiation, accrual to a cohort will not continue further. The probability of stopping early is only 12% if the underlying rate of grade 3 or higher radiation pneumonitis or any grade 4 toxicity were truly 5%. Otherwise, the cohort will proceed to enroll a total of 26 patients and declare the feasibility of proton radiation if no more than 2 of them were to experience grade 3 or higher radiation pneumonitis or any grade 4 toxicity within 3 months after treatment. The two-stage design provides 81% power to accept that proton radiation is associated with a 5% rate of grade 3 or higher radiation pneumonitis or any grade 4 toxicity in a treated cohort. However, the probability is only 20% for declaring the feasibility of proton radiation if the underlying rate grade 3 or higher radiation pneumonitis or any grade 4 toxicity were truly 15%.

12.1.1 Sample Size/Accrual Rate

We estimate an annual enrollment of 16-20 patients based on the existing referral patterns and proton slot availability over 3 years of active accrual. Since protocol enrollment began in August 2011, the accrual rate has been about 15 patients per year, thus increasing the accrual goal from 58 to 64 post-mastectomy patients is projected to take another 4-5 months. Based on existing referral patterns of patients following breast-conserving surgery, we estimate the intact breast cohort will require 5-6 months to enroll the cohort goal of 32 patients. All patients will be followed for an additional 5 years to allow for the assessment of late toxicities and progression-free survival.

12.1.2 Stratification Factors

Protocol accrual will be stratified by proton technique (3D conformal and IMPT) and by surgery procedure (mastectomy and breast-conserving). Post-mastectomy patients will be enrolled in sequential cohorts, while patients with intact breast will only be treated with IMPT. In general, primary and secondary endpoints will be analyzed separately for each proton cohort.

12.2 Analysis of Secondary Endpoints

Secondary endpoints of this study will be analyzed as follows:

- 12.2.1 Exact binomial methods will be used to construct 95% confidence intervals for estimating the rates of acute, sub-acute and late toxicities during and after proton radiation to the left chest wall and regional draining lymphatics. The precision provided by a sample size of 26 patients is associated with a maximum half-width of 20%, but the 95% confidence intervals will be narrower in practice, as the observed toxicity rates are expected to be generally low. The same methods will also be used to analyze the post-radiation outcomes of breast reconstruction, including the rates of implant complication, contracture, infection, unplanned cosmetic surgeries.
- 12.2.2 Progression-free survival is defined as the duration from the start of radiation to the date of objective disease progression or death due to any cause, whichever is earlier. Progression-free survival will be estimated using Kaplan-Meier methodology. The 5-year

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progression-free survival rate will be reported and a 95% confidence interval for this rate will be calculated using Greenwood's formula. Patients who do not experience a progression and are still alive will be censored at their date of last contact.

- 12.2.3 Data from the strain echocardiogram will be analyzed for each parameter, including myocardial velocity, strain, strain rate and torsion. ANOVA methods will be used to analyze the pre- and two post-radiation measurements, using linear contrasts to test the significance of cardiac function changes over time. Fixed effects may be incorporated to explore subgroup differences defined by patient and treatment factors, for example, dose level.

12.3 Reporting and Exclusions

- 12.5.1 **Evaluation of toxicity.** All participants will be evaluable for toxicity from the time of their first treatment.
- 12.5.2 **Evaluation of response.** Although patients will not have measurable disease at the time of treatment and therefore response is not an endpoint of this study, all patients will be followed for disease recurrence.

13. PUBLICATION PLAN

The results should be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of data collection.

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15. APPENDICES

Appendix A. Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-	20	Very sick, hospitalization indicated. Death not imminent.

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	care. Totally confined to bed or chair.	10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

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Toxicity CTCAE version 4.0 from <http://ctep.cancer.gov>

Condition	Short Name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fatigue (lethargy, malaise, asthenia)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	--
Radiation dermatitis	Radiation dermatitis	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Dysphagia	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g. altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
Fibrosis-deep connective tissue	Fibrosis-deep connective tissue	Increased density, "spongy" feel	Increased density with firmness or tethering	Increased density with fixation of tissue; operative intervention indicated; interfering with ADL	Life-threatening; disabling; loss of limb; interfering with vital organ function	Death
Pneumonitis/Pulmonary Infiltrates	Pneumonitis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O2 indicated	Life-threatening; ventilatory support indicated	Death
Dyspnea (Shortness of Breath)	Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion but unable to walk 1 flight of stairs or 1 city block (0.1 km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
Hypoxia	Hypoxia	--	Decreased O2 saturation with exercise (e.g. pulse oximeter <88%); intermittent supplemental oxygen	Decreased O2 saturation at rest, continuous oxygen indicated	Life-threatening; intubation or ventilation indicated	Death
Cough	Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic medication indicated	Symptomatic and significantly interfering with sleep or ADL	--	--
FEV1	FEV1	90-75% of predicted value	<75-50% of predicted value	<50-25% of predicted value	<25% of predicted value	Death

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Pulmonary Fibrosis (radiographic changes)	Pulmonary fibrosis	Minimal radiographic findings (or patchy or bi- basilar changes) with estimated radiographic proportion of total lung volume that is fibrotic of < 25%	Patchy or bi-basilar changes with estimated radiographic proportion of total lung volume that is fibrotic of 25 - <50%	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50 - <75%	Estimated radiographic proportion of total lung volume that is fibrotic is ≥75%; honeycombing	Death
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Remark: Fibrosis is usually a “late effect seen >3 months after radiation or combined modality therapy (including surgery). It is thought to represent scar/fibrotic tissue. It may be difficult to distinguish from pneumonitis that is generally seen within 3 months of radiation or combined modality therapy.

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