Phase II Study Assessing the Potential for Reduced Rates of Implant Failure Using Multi-Beam Intensity-Modulated Radiation Therapy for Locally Advanced Breast Cancer Patients With Implant Reconstructions

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND SCHEMA

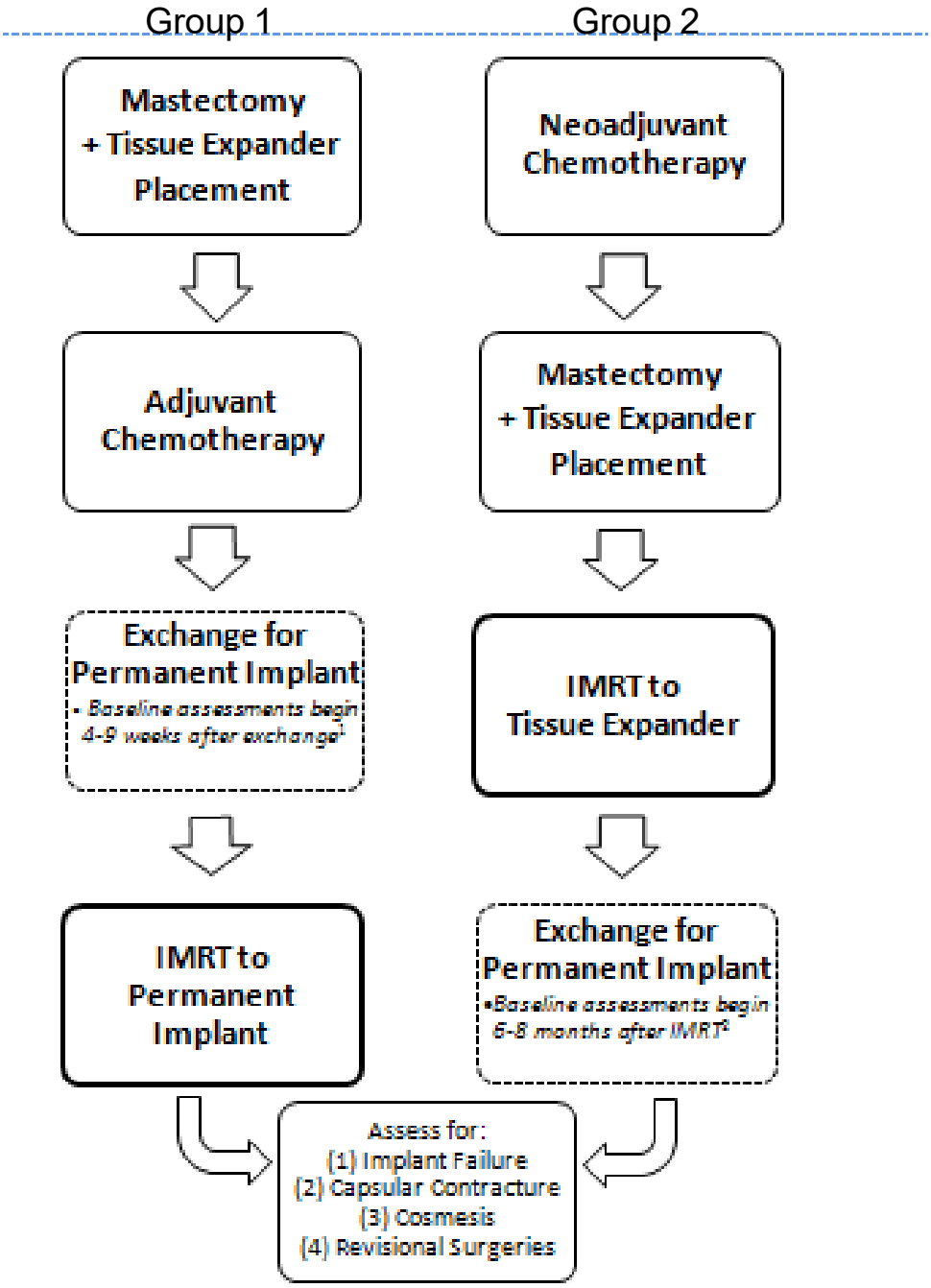
Breast implant failure (defined as removal or replacement with another reconstruction) and capsular contracture are longstanding adverse effects of postmastectomy radiation (PMRT) in patients who have undergone immediate expander/implant reconstruction. These complications can impact cosmesis and quality of life. A prior departmental protocol, IRB #10-025, demonstrated the feasibility and safety of multi-beam IMRT in treating locally advanced breast cancer patients requiring comprehensive PMRT. By permitting the delivery of a more homogeneous radiation dose and fewer and smaller —hot spotsǁ to the implant compared to conventional RT techniques, we hypothesize that multi-beam IMRT can minimize implant-related side effects of RT, leading to improved implant-specific outcomes and cosmesis in breast cancer patients with implant reconstruction undergoing PMRT. Efficacy is the primary endpoint of this study and is defined as relative 30% decrease in implant failure rates following the completion of IMRT. Secondary endpoints are to assess cosmesis, quantify minor revisional surgery rates and to evaluate the correlation between MRI changes in the implant and the degree of capsular contracture as ascertained by standard assessment methods. There are several exploratory endpoints in a subset of the study population: 1) to assess the feasibility of performing a cardiac PET scan in the IMRT treatment position in order to quantify the cardiac dose delivered to the heart 2) to assess early subclinical cardiotoxicity associated with IMRT, utilizing speckle tracking strain echocardiography, ultrasound of the brachial artery, cardiopulmonary exercise testing (CPET), fatigue and quality of life questionnaires and cardiac biomarkers 3) to assess the effect of IMRT on quality of life and fatigue.

The time interval at which follow-up assessments will occur after the intervention (IMRT) will depend on the sequencing of the expander/implant exchange with radiation. Two groups of patients will be evaluated. Group 1 will consist of patients who receive IMRT to the permanent implant and are followed up at 12 ± 2 months and 24 ± 2 months after IMRT. Group 2 will include patients who receive IMRT to the temporary expander and are followed up at 12-18 ± 2 months and 30 ± 2 months after IMRT. This sequencing will be determined prior to study enrollment based on whether the patient received neoadjuvant or adjuvant chemotherapy (see Section 3.0 for further details).

Evaluation for implant failure may occur at any time interval between the completion of IMRT to the end of the study period (24 ± 2 months for Group 1 or 30 ± 2 months for Group 2, after IMRT). Capsular contracture and cosmesis will be assessed at baseline, 12 ± 2 months and 24 ± 2 months for Group 1 or 12-18 ± 2 months and 30 ± 2 months for Group 2, both following IMRT. The patient will be evaluated for capsular contracture by physical exam and an optional breast MRI, and for cosmesis by Breast-Q© questionnaires at these time points. A subset of 10 patients evaluated with cardiac PET scans for exploratory objective #1 will obtain these studies at the time of the RT simulation session and 12-18 months (± 6 months) after the completion of IMRT. A separate subset of 20 patients to be evaluated for exploratory objectives #2 and #3 will complete the study questionnaires and undergo speckle tracking strain echocardiography, ultrasound of the brachial artery, CPET, and cardiac biomarker measurement at baseline and at the post-treatment intervals specified in Section 10.

Target accrual for this study is 130 patients, to be achieved in 3-4 years of accrual.

Schema



[1]**Group 1**: Physical examination by MD, optional Breast MRI, Breast-Q© at baseline (after permanent implant exchange, physical exam and Breast-Q© may be done after the initiation of IMRT), 12 ± 2 months and 24 ± 2 months post-IMRT. Total length of the follow-up time will be 24 ± 2 months post-IMRT.

[2]**Group 2**: Physical examination by MD, optional Breast MRI, Breast-Q © at baseline (after permanent implant exchange and <u>after</u> IMRT), 18 ± 2 months and 30 ± 2 months post-IMRT, as these patients will undergo exchange of the temporary expander for the permanent implant approximately 4-8 months following the completion of radiation (at the discretion of the treating plastic surgeon).Total length of the follow-up time will be 30 ± 2 months post-IMRT.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objective

To evaluate the efficacy of multi-beam IMRT in decreasing the rate of implant failure in breast cancer patients who have undergone two-stage expander/implant reconstruction and require PMRT. Implant failure is defined as a surgery requiring removal or replacement of the prosthesis with another type of reconstruction.

2.2 Secondary Objectives

- To quantify the incidence of moderate to severe capsular contracture
- To quantify the rates of minor revisional surgeries
- To evaluate cosmesis
- To quantify post-radiation volumetric and capsular changes on MRI and correlate these changes with clinical assessments of capsular contracture.

2.3 Exploratory Objectives

- To evaluate the feasibility of performing ^{13}N-NH_3 PET/CT scans within the radiation simulation session and correlate CFR and IMRT dose to the heart.
- To evaluate the effect of IMRT on early subclinical cardiotoxicity, as measured by speckle tracking strain echocardiography, ultrasound of the brachial artery, CPET, fatigue/quality of life questionnaires and cardiac biomarkers.
- To evaluate the effect of IMRT on fatigue and quality of life, as measured by FACT-B and FACIT questionnaires.

3.0 BACKGROUND AND RATIONALE

Enhancement of survival and preservation of quality of life represent two paramount goals in the treatment of breast cancer. The results of a large meta-analysis established the critical role of PMRT therapy plays in improving disease-free survival in locally advanced breast cancer patients [1]. At the same time, breast reconstruction offers psychosocial and cosmetic benefits to patients who undergo mastectomy and is considered an important component of treatment [2]. In spite of the individual merits of PMRT and reconstruction, the optimal integration of the two modalities has been controversial. Radiation is an independent risk factor for complications in patients with implant reconstructions, including a 2-3-fold increase in the risk of significant capsular contracture (Baker grade III or IV), increased rates of reconstructive failure (3-5 fold increase), decreased satisfaction, and decreased cosmetic outcomes [3,4].

Capsular contracture, in particular, is problematic in patients with implant reconstructions who have received radiation, often leading to pain, discomfort and reconstructive failure. After reconstructive surgery which involves the positioning of an implant under the chest wall, capsules of tightly woven collagen fibers commonly form around the implant [5]. In some patients, the interaction between inflammatory cells, extracellular matrix, and fibroblasts leads to an abnormal response, causing thickening and tightness of the capsule and hence, capsular contracture [6,7]. Factors such as radiation, subclinical infections, hematoma or the absence antibiotics during surgery have been proposed as etiologies of capsular contracture, but the contributions of each of these factors to the

development of capsular contracture is unknown [8-10] . Several studies of pharmacologic intervention for capsular contracture have been published, but lacked the evidence to be used as a true therapeutic measure [11,12]. When severe, capsular contracture can compromise the aesthetic outcome and require surgical intervention such as an open capsulotomies, capsulectomy or removal or replacement of the implant.

MSKCC's institutional experience of 151 patients who received PMRT following expander/implant reconstruction, the 7-year permanent implant failure rate was 29%, with the majority of events occurring within 1-2 years after radiation. Infection was a major cause of implant removal, whereas capsular contracture was the most dominant cause for implant replacement. This data is consistent with multiple reports in the literature where capsular contracture remains the most significant long-term risk following irradiation of implant reconstructions, even with improvements in implant technology and surgical techniques over the past decade [13-16]. Recently, additional data from MSKCC has been published by Cordeiro et al [51], which demonstrated that implant failure rate was higher when patients were irradiated to the tissue expander vs. the permanent implant, thereby demonstrating the significance of the timing of radiation therapy relative to reconstruction when assessing reconstructive outcomes.

Existing Methods for Assessing Capsular Contracture and Cosmesis After Implant Reconstruction

To date, the standard tool for estimating the presence and severity of capsular contracture is the Baker scale, which was developed in 1979 and consists of a standardized 4-point scale that integrates the appearance, texture and tenderness of the examined breast. Studies have shown that the Baker score can be subjective and lead to inter-rater (and possible intra-rater) variability [5].

Methods such as measurement of pressures inside the breast pocket using tonometry or other techniques have been attempted. However, none of these tools have gained widespread acceptance. Subsequently, there is difficulty in assessing the extent of capsular contracture, resulting in a wide range of capsular contracture rates reported in the literature [17]. The lack of an objective way to measure capsular contracture has hindered efforts to establish standardized treatment guidelines for capsular contracture.

The use of radiologic tests to quantify capsular contracture appear promising. To date, the only study in which capsular thickness on imaging tests have been correlated with the Baker scoring system is a cross-sectional study of 22 patients who underwent breast reconstruction with implants and followed by clinical assessment of the capsular contractures with MRI to evaluate the radiologic thickness of the capsule. Not all patients received radiation. MRI revealed the distinct appearance of the thickened capsule and correlated well with the Baker scoring system. Parameters measured on MRI included capsular anterior-posterior diameter, left-right diameter and capsular thickness. A statistically proven correlation was found between capsular thickness on MRI and the clinical Baker score (p-values =0.02). A Baker score of I or II correlated with a thinner capsule averaging 1.14 mm, whereas a Baker score of III or IV correlated with a thicker capsule averaging 2.62 mm [18].

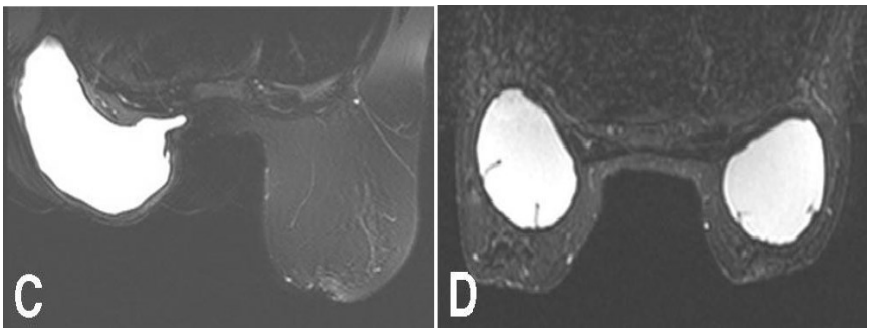


Figure 1. Image C denotes a normal breast capsule on MRI. Image D shows a thickened capsule correlating with capsular contracture. Images adapted from Zahavi et al [18].

Objective assessment of overall cosmesis is also important when comparing aesthetic outcomes in implant reconstruction. The majority of studies assessing cosmesis have relied on photographic analysis by healthcare providers to analyze various measures including symmetry, scars, volume or shape, or they have used non-validated questionnaires which make their findings somewhat less useful. These tools do not address patient perceptions and can either over or underestimate the success rates of various reconstructive surgeries from a cosmetic point of view. Recently, a validated patient reported outcome tool, the Breast-Q © which was developed by investigators at MSKCC[19], has addressed this deficiency. The Breast-Q © will analyze how patients perceive their reconstruction and help guide analysis of outcomes that can then be standardized across centers. A detailed descripton of the Breast-Q © is provided in section 9.3.2.

Sequencing of Radiation with Expander/Implant Reconstruction

We have published that exchanging the expander to the implant prior to the start of radiation therapy is associated with excellent long-term clinical outcomes and acceptable complication rates in patients who received adjuvant chemotherapy [20]. Thus, in these patients (represented in Group 1), our institutional policy is to initiate radiation after the expander has been exchanged for the permanent implant.

In approximately 30-40% of locally advanced breast cancer cases, upfront surgical down-staging of the tumor with systemic therapy is required and therefore these patients received neoadjuvant chemotherapy, followed by mastectomy with immediate tissue expander placement (represented in Group 2). In such patients, there is often inadequate time to complete expansion, perform exchange and achieve adequate tissue healing prior to initiating radiation. Hence, the exchange procedure for a permanent implant is delayed until approximately 4-8 months after the end of radiation, when the tissues have recovered from radiation injury as determined by the treating plastic surgeon. Radiation is subsequently delivered to the tissue expander and regional lymph nodes.

Over the past several years, over 50% of locally advanced breast cancer patients who receive postmastecomy radiation therapy at MSKCC are treated with comprehensive radiation therapy to the chest wall and regional lymph nodes [departmental statistics]. Regional lymph node irradiation includes the axillary, supraclavicular and internal mammary nodes. PMRT therapy has been shown to positively impact disease free survival and overall survival [21-24]. The most recent meta-analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that adjuvant radiation therapy improved 15-year breast cancer mortality in node positive patients treated with mastectomy and lymph node dissection[1]. Twenty-four of the 25 PMRT studies included in the EBCTCG meta-analysis performed Internal Mammary Node (IMN) irradiation, suggesting that the benefits of PMRT may be

related to their treatment [1]. Interest in IMN irradiation has recently been fueled by the results from the National Cancer Institute of Canada (NCIC) MA-20 trial demonstrating improved distant disease-free survival and a favorable trend in overall survival in breast-conservation patients receiving comprehensive regional node treatment[25].

Despite its clinical benefits, routine irradiation of the IMNs in PMRT remains controversial because of the increased cardiac and pulmonary toxicity that results from targeting the internal mammary nodes, which lie in the first three intercostal spaces in the parasternal region, directly above the heart. Conventional 3D-conformal RT refers to a treatment technique where two tangential beams deliver dose to the chest wall while an anterior oblique beam is used to treat the axillary nodes. It has been shown that when conventional radiation techniques are utilized, the presence of an implant reconstruction can further increase heart and lung doses in patients requiring PMRT, compared to patients who do not have reconstructions[26,27]. The presence of an implant or temporary expander often poses technical challenges in delivering a homogeneous dose to the chest wall secondary to the sharp slope of the implant on the chest wall, compared to a flat chest wall (**Figure 2**).

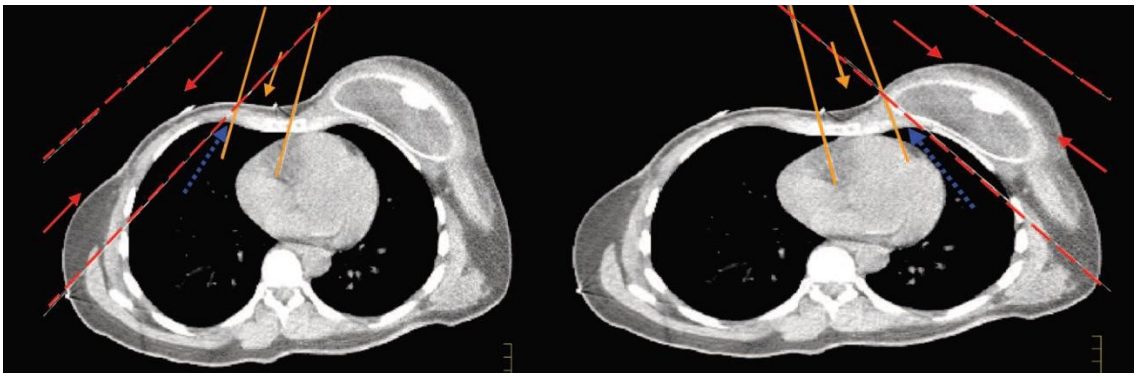


Figure 2. The left panel demonstrates an unreconstructed chest wall. The electrons (orange) targeting the IMNs are junctioned with a ―clean match‖ against the photon tangent beams (red). In contrast, in a patient with an implant reconstruction (right panel), the sharp slope of the implant creates an imperfect match between the electrons and photons, creating a ―cold‖ triangle (blue arrow) region of dose heterogeneity.

3.1 Overview and Rationale of Intensity-Modulated Radiation Therapy (IMRT)

In contrast to the 3-5 beams used in conventional 3D techniques, multi-beam IMRT is an advanced method of delivering radiation that utilizes multiple (8-12) beams spread in an arc over the chest wall, where each beam delivers multiple intensity levels rather than one uniform intensity level to the target. This is achieved by changing the beam aperture during the ―beam-on‖ time with dynamic multileaf collimators. Each beam delivers a different dose to the different parts of the target. The normal surrounding tissue is constrained such that high doses of radiation do not exceed the ―limits‖ set on the normal critical organs. Multi-beam IMRT results in a homogeneous dosimetric plan to the target by eliminating high and low dose regions commonly seen in the junction region between the tangent beams and the anterior oblique beam of 3D-techniques, as well as within the implants.

Previous success has been demonstrated utilizing multi-beam IMRT for locally advanced breast cancer patients in a recently conducted departmental protocol, IRB #10-025 (Pilot Study of Multi-Beam Intensity-Modulated Radiation Therapy for Node-Positive Breast Cancer Patients Requiring Treatment of the Internal Mammary Lymph Nodes). This protocol closed in December 2012 after reaching its

target accrual goal of 116 patients within 30 months of initiation. Sixty percent of the study population consisted of patients with implant reconstructions. All patients were treated with a dosimetrically acceptable plan, thus meeting the criteria for feasibility. The rate of radiation pneumonitis in the entire cohort was 3.5%. Given the safety and the dosimetric advantages offered by this multi-beam, we continue to selectively treat patients with implant reconstructions requiring comprehensive PMRT with this technique.

By delivering a more homogeneous dose to the implant compared to conventional RT techniques, we hypothesize that multi-beam IMRT can reduce complications leading to implant failure and improve cosmesis in breast cancer patients with implant reconstructions requiring PMRT.

3.2 Overview and Rationale of Exploratory Objectives

3.2.1 ^{13}N-NH_3 PET Scans to Estimate Cardiac Dose in Patients Treated with IMRT

Although it has been shown that IMRT limits the high dose delivered to the heart, the trade-off is that, compared to conventional radiation techniques, a higher volume of low dose is delivered to the thorax and heart. In order to quantify the low dose delivered to the heart with IMRT, the study will assess the patients with dynamic PET imaging that are obtained at the time of radiation simulation. Compared to other cardiac imaging modalities, PET has been shown to have improved performance attributable to the better spatial resolution and fewer image artifacts. Moreover, myocardial perfusion imaging with PET results in a lower radiation exposure to patients, on the order of a 20-25% reduction for ^{13}N-NH_3 when compared to the commonly used Tc99m tracers (sestamibi and tetrofosmin). However, the feasibility of performing ^{13}N-NH_3 cardiac PET scans within the RT simulation session has never been shown. The ability to perform the cardiac PET scans on patients in the radiation treatment position would allow optimal co-registration of the PET images with the CT images obtained from simulation. Accurate co-registration of the images at the time of simulation would subsequently enable accurate quantification of the radiation dose delivered to the heart from IMRT.

3.2.2 Assessing the Effect of IMRT on Early Subclinical Cardiotoxicity in Breast Cancer Patients

External beam radiation has been shown to cause chronic impairment of endothelium-dependent vasodilatation in humans in vivo, specific to arteries that received radiation [28]. Post-radiation cascade consists of loss of endothelial cells and increase in inflammatory response, which lead to micro- and macrovascular damage. Endothelial cell dysfunction is the initial and key insult in radiation-induced heart disease and is an important component of premature atherogenesis. The development of plaque formation from atherosclerosis leading to a cardiac event is a long process. Identification of early surrogate endpoints for the development of long-term cardiac morbidity after breast RT is therefore warranted. However, sensitive and reliable metrics for assessing early subclinical cardiotoxicity in patients treated with radiation are lacking.

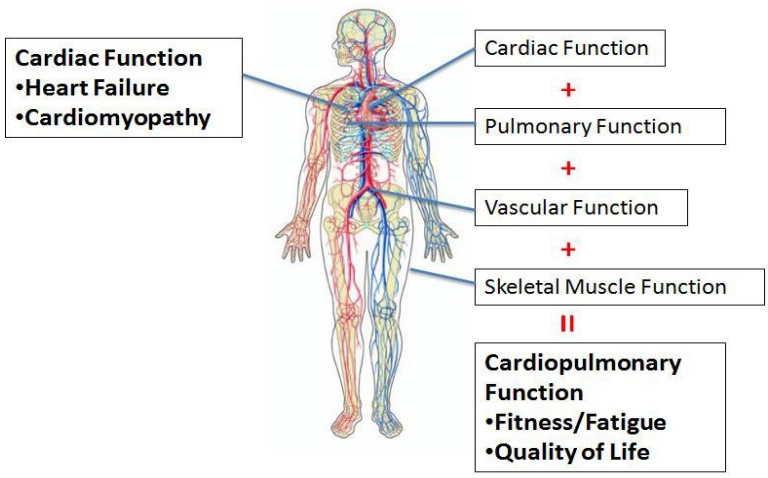


Figure 3: Cardiopulmonary function is assessed by multiple organ systems

3.2.2.1 Strain Echocardiogram

Developments in echocardiographic imaging, such as speckle tracking strain echocardiography, have permitted a more accurate assessment of regional myocardial function. Speckle tracking echocardiography-derived strain imaging is a novel imaging modality that measures myocardial deformation and provides a more sensitive and quantitative assessment of cardiac contractile function than conventional 2D echocardiographic indices [29]. Strain echocardiogram is a highly reproducible and objective measurement that is superior to measures such as ejection fraction or fractional shortening in the detection of early subclinical myocardial dysfunction and has been shown to be useful in the early diagnosis of trastuzumab- associated cardiotoxicity [30,31]. An expert consensus statement from the American Society of Echocardiography in 2014 has recommended the inclusion of strain imaging for the evaluation of patients in preparation for, during, and after cancer therapy [32]. A pilot study in 30 breast cancer patients demonstrated the feasibility of strain echocardiography in evaluating early RT-induced cardiac changes, however this study was limited by older techniques that are currently not used in the United States [33].

3.2.2.2 Flow-Mediated Dilatation (FMD) Measurements via Ultrasound of the Brachial Artery

Endothelial dysfunction can also be measured by a process called flow-mediated dilatation (FMD), which describes the manner in which the endothelium responds to vasculature sheer stress [34]. Invasive methods of measuring endothelial dysfunction include sympathetic activation by cold pressor resting, dilator response to increased blood flow and dilatation in response to nitroglycerin. Each of these methods has been shown to be an independent predictor of poor prognosis, even after adjustment for traditional cardiovascular risk factors and the presence of atherosclerosis itself. A non-invasive and reliable method of studying FMD has been described by Celermajer and colleagues, in which flow is increased through the brachial artery by inducing post-ischemic dilatation in the downsteam vascular bed of the distal forearm [35]. A cuff placed around the proximal forearm was inflated to higher than systolic pressure and produced ischemia in the distal vascular bed. After the

release of the cuff pressure, a sudden increase of blood flow into the dilated vascular bed occurred. The resulting increase in sheer stress in the upstream conduit artery causes dilatation of the brachial artery, which was measured by an ultrasound device, with dilatation reflecting increase in arterial endothelial nitrous oxide release [36]. This method is non-invasive, repeatable and reproducible, but requires specialized training to perform the ultrasound, which has limited broader utilization. Certified exercise physiologists within the MSK Cardio-Oncology Research Program (under the direction of Dr. Lee Jones) will perform these measurements.

3.2.2.3 Cardiopulmonary Exercise Testing/VO_2 peak Measurements

It is possible that cardiac imaging tests and flow-mediated dilatation may be unsensitive predictors of cardiotoxicity. Cardiovascular reserve, as measured by cardiopulmonary exercise testing (CPET), is considered the gold standard assessment of exercise capacity and provides assessment of peak oxygen consumption ($VO_{2\ peak}$)[37]. Dr. Lee Jones and his team have had over 10 years experience of investigating the efficacy of supervised exercise training trials in patients with cancer across the entire cancer survivorship continuum, including breast cancer patients. The information gathered by this exploratory objective will be important in understanding to what extent IMRT reduces cardiovascular reserve, and the extent to which IMRT may impact the recovery of cardiovascular reserve in the sub-acute setting after treatment.

3.2.2.4 Cardiac Biomarkers

Cardiac biomarkers, particularly troponins, also have the potential to identify patients at risk for cardiotoxicity during early pre-clinical stages. Elevation of serum cardiac troponin levels in asymptomatic patients after administration of anthracycline-based chemotherapy have been shown to predict subsequent deterioration of myocardial function [38]. In contrast, very limited data exists on the role of cardiovascular biomarkers in the detection of RT-induced cardiotoxicity. The levels of multiple cardiovascular biomarkers that are mechanistically relevant to cardiotoxicity will be examined in this protocol. NT-proBNP is an established biomarker for the diagnosis and prognosis of heart failure, and high sensitivity troponin-I (hsTnI) has been used to measure myocardial injury and to predict incident LV dysfunction among patients receiving chemotherapy [39]. Endothelin is involved with the vascular regulatory system and may have prognostic value in patients with heart failure [40]. Matrix metalloproteinase (MMP)-2 and 9 and their tissue inhibitors (TIMP) play a major role in left ventricular remodeling and the development of heart failure[41-43]. Inflammatory markers, including high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-6, and tumor necrosis factor-alpha (TNF-α) are elevated in patients with heart failure as well as patients with asymptomatic left ventricular dysfunction, raising the possibility that inflammation may contribute directly in the pathogenesis of heart failure [44,45]. This study will explore the utility of multiple novel biomarkers to identify patients at risk for cardiotoxicity following chemotherapy and radiation therapy to the chest wall and regional lymph nodes.

3.2.3 Assessing the Effect of IMRT on Quality of Life in Breast Cancer Patients

Although radiation to the chest wall and lymph nodes for breast cancer is a well-tolerated treatment, the effect of radiation on functional status of patients has not been well quantified. Fatigue levels and quality of life may also be important indicators of cardiopulmonary dysfunction in patients who have received radiation therapy.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a Phase II trial examining the efficacy of multi-beam IMRT in reducing implant failure rates (primary endpoint), as well as the secondary endpoints of cosmesis, incidence of capsular contracture and minor revisional surgeries, and the correlation of MRI changes with clinical assessments of capsular contracture in breast cancer patients with implant reconstruction receiving PMRT. We will test the hypothesis that the 2-year probability of implant failure will be reduced by a relative 30% or greater compared to our aforementioned published experience of implant failure following PMRT with conventional radiation techniques.

4.2 Intervention

4.2.1 Mastectomy with Immediate Tissue Expander Placement

Patients will undergo mastectomy and axillary dissection with immediate tissue expander placement. As is the current practice at MSKCC, patients receiving adjuvant chemotherapy will undergo expansion during chemotherapy, with exchange for a permanent implant to be performed approximately one month after chemotherapy and radiation to begin approximately one month after exchange. Patients who receive neoadjuvant chemotherapy will undergo ―rapid expansion‖ of the expander and begin radiation at least 4 weeks following surgery, although it may be performed sooner if the patient has recovered from surgery and the treating physician deems it safe to proceed with treatment. In these patients, exchange for the permanent implant will occur at the discretion of the treating plastic surgeon (approximately 4-8 months after the end of radiation).

4.2.2 Multi-beam IMRT

Multi-beam IMRT will be performed approximately one month (but no sooner than 2 weeks) after exchange in Group 1. Multi-beam IMRT will be performed at least 4 weeks after mastectomy in Group 2, although it may be performed sooner if the patient has recovered from surgery and the treating physician deems it safe to proceed with treatment. The target volume for IMRT will be contoured according to guidelines specified in Appendix 2. All patients will receive 50-50.4 Gy in 25-28 fractions, which is the standard dose and fractionation for breast IMRT in our department. Prior to each daily treatment, the reproducibility of the patient's position will be verified by kilovoltage (kV) x-rays or Align RT®, an FDA-approved in-room video-based localization system.

A subset of 10 left-sided patients will receive ^{13}N-NH_3 PET scans within the radiation simulation session. A CT for coronary calcium scoring and a low-dose CT for attenuation correction will also be obtained at this time. Myocardial blood flow will be measured during rest and at peak stress with ^{13}N-NH_3 as a perfusion tracer. A follow-up ^{13}N-NH_3 PET study with low-dose CT for attenuation correction will be obtained 12-18 months (± 6 months) post-IMRT.

4.2.3 MRI

MRI studies will be strongly recommended but not required. At the time of study consent, if a patient chooses not to participate in the the portion of the study that recommends MRIs, then they will not be approached about follow-up MRIs following radiation.

Baseline MRI**:** MRI scans will be performed at the baseline assessment point and acquired on the Philips 3T scanner (70 cm bore size diameter), located in the Department of Radiation Oncology Main

Campus. All MRIs will be performed in the prone position with a dedicated 16-channel prone breast coil. The scanning field-of-view will include both breasts and coverage will encompass supraclavicular region excluding the descending thoracic aorta.

The following 5 sequences will be obtained for silicone implants. All MRIs will include the bilateral breasts.

1) Axial non-fat-saturated 3D T1-weighted fast field echo (FFE) (TR/TE = minimum/2.3 ms)

2) Axial non-fat-saturated 3D T2-weighted turbo spin echo (TSE) (TR/TE = 2000/minimum ms)

3) xial 2D IR water saturation (silicone is hyperintense) (TR/TE = minimum/65 ms)

4) Axial fat-saturated 3D T1-weighted FFE image (silicone is hypointense and water is hyperintense) (TR/TE = minimum), and

5) Contrast-enhanced dynamic axial fat-saturated 3D T1-weighted FFE (TR/TE=minimum)

For saline implants, the 4 sequences will include:

1) Axial non-fat-saturated 3D T1-weighted FFE (TR/TE = minimum/2.3 ms)

2) Axial non-fat-saturated 3D T2-weighted TSE (TR/TE = 2000/minimum ms)

3) Axial fat-saturated 3D T1-weighted FFE (TR/TR = minimum), and

4) Contrast-enhanced dynamic axial fat-saturated 3D T1-weighted FFE

There will be a total of four dynamics at a temporal resolution of ~ 60-90 seconds. All sequences will be acquired with an isotropic voxel size of 1x1x1 mm^3 except the axial 2D IR water saturation sequence, which will be acquired with a voxel size of 1x1x3 mm^3.

The total scan duration will be approximately 30 minutes for both silicone or saline implants.

Follow-up MRIs**:** Subsequent MRIs will be performed in the prone position with a dedicated 16-channel breast coil. Parameters similar to baseline MRIs will be used for sequences. If a patient is unable to receive the baseline and/or follow-up MRI, or if either MRI produces images of insufficient quality for evaluation, the patient may still participate in and be evaluated for the rest of the study.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Multi-beam IMRT has been proven to be a feasible and safe method of PMRT delivery for locally advanced breast cancer patients. Following mastectomy and immediate implant-based reconstruction, multi-beam IMRT will be utilized to treat the chest wall, expander or permanent implant, and axillary, supraclavicular and internal mammary lymph nodes. The radiation dose (50-50.4 Gy/25-28 fractions in approximately 5-6 weeks), treatment-planning and delivery aspects are according to departmental guidelines for breast IMRT.

Concurrent biologic therapy (Trastuzumab, Tamoxifen or Aromatase Inhibitors) with radiation therapy will be permitted, but concurrent cytotoxic chemotherapy will not.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. Females who are ≥ 18 years of age with a life expectancy estimated to be at least 2 years

2. Histologically-confirmed invasive breast cancer by MSKCC
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
4. Status post mastectomy with surgical assessment of axillary nodes
5. Immediate reconstruction with tissue expander (Group 2) or permanent implant (Group 1) prior to RT performed at MSKCC
6. If PMRT is recommended, the treatment fields will include the axillary, supraclavicular, and internal mammary nodes

6.2 Subject Exclusion Criteria

1. Absence of a breast reconstruction prior to RT (placement of tissue expander is sufficient for group 2)
2. Pregnant or breastfeeding
3. Psychiatric or addictive disorders that would preclude obtaining informed consent or filling out Breast-Q© questionnaires
4. Prior radiation therapy to the ipsilateral breast/nodes or thorax

The criterias outlined above apply to the patients enrolled to meet the primary objective of the study. Additional criteria for patients in the cardiac substudy portion of the protocol are outlined in Section 7.1.2.

7.0 RECRUITMENT PLAN (Limited Waiver of Authorization)

Patients will be identified at consultation in the Radiation Oncology clinics for their eligibility. The investigators take due notice of the National Institutes of Health (NIH) policy concerning inclusion of women and minorities in clinical research populations**.**

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, they will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the

patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, the study will seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

It is estimated that between 200-300 eligible patients are treated in the Department of Radiation Oncology per year, including the Main campus and satellite facilities. On average, 20-25 eligible patients are under treatment at any moment, providing a large pool of patients who could be eligible for this study. Based on these estimates as well as the accrual history with IRB protocol #10-025, it is predicted that the study will meet the target accrual goal of 130 patients within three to four years.

7.1 Voluntary Studies: Assessment of Cardiotoxicities and Quality of Life

Patients enrolled in this protocol are eligible to volunteer to be evaluated in of one of the sub-studies below. Participation in these adjunct interventions is strictly voluntary and not required to assess the primary endpoint of the protocol, which is assessment of implant failure rates.

Given the large population of breast cancer patients who receive neoadjuvant chemotherapy for breast cancer and our departmental policy of pre-operatively evaluating such patients for radiation, the study plans to identify and recruit the patients needed for n=10 patients required for the ―controll group (Group 2B). Potential candidates will be identified at the time of pre-operative consultation in the radiation oncology department. It is customary for patients who have received neoadjuvant chemotherapy to be seen in a subsequent new visit following surgery, in order to discuss how response to chemotherapy impacts radiation treatment recommendations. At that time, if radiation therapy is not recommended, the patient will be offered enrollment onto the control arm (no RT) of the sub-study assessing early cardiotoxicity.

7.1.1 Ammonia PET Scans to Correlate IMRT Dose to the Heart

Patients who meet the exclusion criteria listed below (in addition to those listed in section 6.0) will be approached regarding volunteering to receive a ^{13}N-NH_3 PET/CT scan during RT simulation, as well as 12-18 months ($\pm$ 6 months) after completion of RT. Ten volunteer patients are expected (n=10, all left-sided), but the study has budgeted enough scans for twelve patients, in the event that a patient is lost to follow-up/expires and cannot have the second scan, or declines the second scan.

Any of the following excludes a patient from the PET/CT subset:

a. Age >60 years old at time of diagnosis

b. Diabetes mellitus

c. Hyperlipidemia

d. Obesity

e. Personal history of cardiac illness

f. Planned IMRT to the right reconstructed breast

7.1.2 Detection of Early Subclinical Cardiotoxicities (Following IMRT)

A total of 20 patients will be required for this voluntary portion of the study:

7.1.2.1 Group 2A

Group 2A (n=10) are patients who will be receiving intensity-modulated radiation therapy to the (reconstructed) breast and regional lymph nodes. They will be approached regarding volunteering to receive the evaluations for assessment of cardiotoxicity and functional performance status outlined in Section 10.0. These evaluations will be performed 0-4 weeks prior to radiation therapy and 2-4 weeks after completion of radiation therapy.

7.1.2.2 Group 2B

Group 2B (n=10) are patients who are receiving neoadjuvant chemotherapy and mastectomy, evaluated by Radiation Oncology for consideration of RT but do not receive RT. These 10 patients will serve as a control population against which to compare the effect of IMRT on early subclinical cardiotoxicity, and will be approached to receive the identical evaluations for assessment of cardiotoxicity as the 10 patients in the experimental group who do receive IMRT. The assessments for the control group will be performed at similar post-operative intervals as the experimental group: 4-8 weeks after surgery and at 15-20 weeks after surgery.

For breast cancer patients who receive neoadjuvant chemotherapy, it is customary for the Department of Radiation Oncology to preliminarily evaluate at a time point prior to the receipt of mastectomy. This allows adequate time for planning and sequencing of treatments, in the event that the patient opts for immediate reconstruction. After the mastectomy, the patient is seen for a second, subsequent new visit, at which time final pathology from the mastectomy is available to guide definitive treatment recommendations. We will plan to identify potential candidates for both the control and experimental arms at the first new visit prior to surgery and follow up with/ enroll eligible volunteers at the second visit.

Patients in Groups 2A and 2B must meet the following inclusion criteria:

a. Normal cardiac function (left ventricular ejection fraction ≥ 50%)

b. Able to complete an acceptable baseline CPET, as determined by the absence of remarkable ECG findings or other inappropriate response to exercise

c. Able to achieve an acceptable peak baseline CPET, as defined by <u>any</u> of the following criteria:

i. achieving a plateau in oxygen consumption, concurrent with an increase in power output;

ii. a respiratory exchange ratio ≥ 1.10;

iii. attainment of maximal predicted heart rate (HR_{max}) (i.e within 10 bpm of age-predicted HR_{max} [HR_{max}=220–Age(years)]);

iv. volitional exhaustion, as measured by a rating of perceived exertion (RPE) ≥ 18 on the BORG scale.

d. Medical clearance from attending oncologist or attending radiation oncologist to undergo a symptom-limited cardiopulmonary exercise test.

Any of the following will exclude a patient from participating in Group 2A or 2B:

a. Any of the following contraindications to cardiopulmonary exercise testing

- Acute myocardial infarction within 3–5 days of any planned study procedures;
- Unstable angina;
- Uncontrolled arrhythmia causing symptoms or hemodynamic compromise;
- Recurrent syncope;
- Active endocarditis;
- Acute myocarditis or pericarditis;
- Symptomatic severe aortic stenosis;
- Uncontrolled heart failure;
- Acute pulmonary embolus or pulmonary infarction within 3 months of any planned study procedures;
- Thrombosis of lower extremities;
- Suspected dissecting aneurysm;
- Uncontrolled asthma;
- Pulmonary edema;
- Room air desaturation at rest ≤ 85%;
- Respiratory failure;
- Acute non-cardiopulmonary disorders that may affect exercise performance or be aggravated by exercise (i.e., infection, renal failure, thyrotoxicosis); or
- Mental impairment leading to inability to cooperate.

b. Lymphedema of the upper extremities, as detected on history and physical

c. Any condition that, in the opinion of the investigator, would preclude safe and adequate test performance

8.0 PRE-TREATMENT EVALUATION

Groups 1 and 2, will have a baseline clinical evaluation 3-10 weeks after permanent implant exchange, both by the radiation oncologist and by the plastic surgeon. For Group 1, baseline evaluations will take place shortly before or during IMRT (but the baseline MRI must be completed prior to the start of IMRT). For Group 2, MRI and baseline evaluations will take place approximately 6-8 months after completion of IMRT. The baseline procedures include:

- History and physical exam by a radiation oncologist and a plastic surgeon, including clinical evaluation for implant failure, revisional surgeries, capsular contracture and cosmesis
- Breast-Q© questionnaire
- MRI of the breast (strongly recommended, but not required)
- CBC (Complete Blood Count)
- FACT-B and FACIT questionnaires (only Groups 2A and 2B)

However, at the discretion of the plastic surgeon, the baseline clinical evaluation by plastic surgeon may occur at any time point between the exchange surgery and 10 weeks post-surgery.

The research team will collect baseline demographic data that may relate to possible variability in the study population. Data to be collected includes details on chemotherapy, hormone therapy and surgery.

9.0 TREATMENT/INTERVENTION PLAN

9.1 Multi-Beam IMRT-Simulation

Multi-beam IMRT will be performed in the Department of Radiation Oncology on an outpatient basis. Patients will be evaluated by the radiation oncology team and then undergo CT simulation (with contrast is strongly recommended for all patients, but only required for patients enrolled in the optional ^{13}N-NH_3 cardiac PET scan subset) for IMRT. At the time of simulation, the patients will be positioned in an immobilization device and undergo a CT scan (slice spacing 2 mm), scanning from C4/5 to the inferior border of the wired breast field, capturing the entire lungs. The isocenter will be placed on a slice at the midpoint between C4-C5 and the inferior border of the breast field. Anteriorly and posteriorly, the point should be placed into the chest wall.

A subset of 10 patients with left-sided breast cancer will undergo a CT for radiation treatment (RT) planning (standard for patients receiving radiation), as well as an ^{13}N-NH_3 PET myocardial perfusion scan at the time of the RT simulation session. The rest/stress PET procedure will be performed as follows: A low-dose CT (~40 mA) will be acquired over one PET field-of-view (FOV) centered over the heart, which will be used for attenuation correction of the subsequent PET images. ECG-gated dynamic ^{13}N-NH_3 PET studies at rest and during stress will follow immediately. First, the resting dynamic PET acquisition will commence simultaneously with intravenous injection of ~8 mCi of ^{13}N-NH_3. PET images will be acquired in 3D dynamic mode for a total of 10-15 minutes. Approximately five minutes after the completion of the resting study, the patient will receive a bolus intravenous injection of regadenoson 0.4 mg over ~20 seconds for the vasodilator stress procedure. Approximately 2 minutes after injection of regadenoson, the stress dose of ^{13}N-NH_3 (~12 mCi) will be injected intravenously and dynamic PET imaging will commence simultaneously for a total of 10-15 minutes. An ECG-gated CT scan for calcium scoring assessment will be performed immediately before or after the PET study.

9.2 Treatment and Set-up

Treatment will be delivered over approximately 5-6 weeks in 25-28 fractions, utilizing 6 MV photons. A daily bolus will be applied over the chest wall. The number of gantry angles used for the multi-beam IMRT plan will be optimized for each patient but will generally range between 6-12 beams. The

radiation oncologist will delineate the PTV (planning target volume), according to guidelines specified in Appendix 3.

Two techniques are currently available in the Department of Radiation Oncology and will be employed to verify setup accuracy prior to each treatment:

1) AlignRT employs three ceiling-mounted stereostopic camera units to produce high-resolution and accurate 3D surface image referenced to the treatment isocenter. At each treatment fraction, the system images the current patient position instantaneously. State-of-the-art surface-matching software registers these data to the reference surface within seconds. Couch shifts are displayed to show discrepancies between existing and ideal treatment positions. New coordinates for the optimal couch position are then displayed and may be applied. This system has been FDA-approved. Further information regarding this approval is available on the website:
http://www.visionrt.com/site_files/AlignRT%20SE%20FDA%20Clearance%20Letter.pdf

A 2-step setup procedure has been established to minimize breast tissue deformation. First, the patient's arm and chin will be aligned to match simulation position with real-time AlignRT guidance, to minimize difference in muscle stretching. Then the patient's chest wall surface (including the ipsilateral reconstructed breast and 1/3 of contralateral breast) will be used as the region of interest for alignment.

2) An orthogonal pair of KV images allows optimal visualization of bony anatomy as well as clips in the axilla or the port in a tissue expander. One Trilogy, two 2100EX linear accelerators, and two True Beam linear accelerators with on-board KV imagers are available in the department. Bony landmarks, such as anterior ribs, should be used for alignment at the setup.

9.2.1 Treatment interruptions

In the event that a patient must miss a scheduled treatment for non-toxicity related reasons (ie: weather, sickness, family emergencies, etc) the treatment visit will be made up at the end. If the patient misses more than 5 consecutive treatments, they will be removed from the protocol and considered inevaluable.

9.3 Assessment of Secondary Objectives

9.3.1 Capsular Contracture

Two methods will be employed to assess capsular contracture. These include the current standard assessment tool, the Modified Baker score, and MRI. All follow-up assessments will be compared to the baseline assessments. For all patients, the radiation oncologist should perform the baseline physical evaluation 3-10 weeks after the patient's exchange surgery.

Baker Scoring System (See Appendix 1)

All patients will be assigned a Baker Classification score at baseline and at each follow-up interval by the radiation oncologist and plastic surgeon. The Baker score is a standardized 4-point scale, which integrates the texture and appearance of the breast. Grade I is a normal-appearing, soft breast (a Grade IA breast cannot be detected as an implant, while the implant of a Grade IB breast can be detected by physical examination or inspection); Grade II refers to breast implants that are firm but

appear normal; Grade III includes implants that are firm and appear abnormal; Grade IV capsular contracture is the most severe and includes breasts that are hard, painful, and appear abnormal often with severe distortion [46].

Breast MRI

Longitudinal MR studies will be evaluated for capsular contracture.

9.3.2 Cosmesis

The Breast-Q©'s Reconstruction Module will be tailored specifically to assess patient-reported cosmesis for patients with implant reconstructions following IMRT. With a focus on the post-operative period, the module will evaluate changes over time in four of the six subthemes identified by Breast-Q: (1) Psychosocial well-being; (2) Physical well-being; (3) Satisfaction with breasts; and (4) Satisfaction with outcome. Each subtheme will be evaluated using one or more scales. Each scale is independently scored into a value that ranges from 0 to 100, with higher score indicating greater satisfaction or better health-related quality of life. The time estimated to complete the questionnaire is 10 minutes. Additional details regarding the tailored Breast-Q are shown below:

	Post-operative Reconstruction Module, 51 items		
Subtheme	Scales/Items	Response format	Recall Period
Psychosocial well-being	Psychosocial well-being, 10 items	5-point Likert-like scales from 1 —None of the time‖ to 5 —All of the time‖	In the past 2 weeks.
Physical well-being	Physical well-being, 16 items	5-point Likert-like scales from 1 —None of the time‖ to 5 —All of the time‖	In the past 2 weeks.
Satisfaction with breasts	Satisfaction with breasts, 16 items; Satisfaction with breasts (implant only), 2 items	4-point Likert-like scales from 1 —Very dissatisfied‖ to 4 —Very satisfied‖	In the past 2 weeks.
Satisfaction with outcome	Satisfaction with outcome, 7 items	3-point Likert-like scales from 1 —disagree‖ to 3 —Definitely agree‖	None

The development phase of the Breast-Q© reported all scales to have Cronbach's alphas that ranged from 0.87 to 0.98. Test-retest reliability, as measured by intraclass correlation coefficients, ranged from 0.85 to 0.98. Item response theory (Rasch) analysis was used for item reduction and scale development. In the item reduction analysis, 48% of field-test items were eliminated. Validation studies examining convergent and discriminant validity of the new measure relative to multiple existing measures (i.e. EORTC BR-23, BIS, BEQ, SF-36, PAR, BIBCQ, BSAS) are currently underway.

9.4. Assessment of Exploratory Objectives

9.4.1 Subclinical Cardiotoxicity

A subset of 20 patients with breast cancer receiving neoadjuvant chemotherapy will undergo additional assessments for evaluation of subclinical cardiotoxicity and functional performance status. These procedures are not part of routine assessments for patients receiving breast radiation and therefore will be performed on a strictly voluntary basis. All of these assessments are non-invasive and their safety and feasibility have been demonstrated in breast cancer patients who have received

chemotherapy[37]. Prior to completion of these assessments, participants will be instructed to adhere to certain fasting, substance, and activity guidelines. These guidelines are outlined in detail in Appendix 5.

9.4.2 Speckle Tracking Strain Echocardiography

From the standard 2D echocardiogram, three apical views acquired at an increased frame rate (80 frames per second) will be used for offline semi-automated speckle tracking strain analysis (Echopac, GE Medical Systems). The methods of image acquisition and strain measurements with speckle tracking have been previously described [47]. Longitudinal strain and strain rate curves will be generated for each segment, and peak global longitudinal strain will be calculated as the average value of the peak systolic strain values for all the segments within the three standard apical views. The timing of the aortic valve closure will be used to designate end-systole. A parasternal short axis view at the level of the papillary muscle will be used to obtain peak global radial and circumferential systolic strain and strain rate by averaging the peak strain value in all 6 segments of the parasternal short axis view. For strain analysis, all echocardiograms will be interpreted by a single echocardiographer blinded to whether or not patient received IMRT, 2D LVEF results, and prior strain values (study investigator: Anthony Yu). A non-sequential test ID will be assigned for each examination, identifiers and clinical information removed.

9.4.3 Cardiopulmonary Exercise Testing (CPET)

In order to determine exercise capacity, a symptom-limited cardiopulmonary exercise test to assess peak oxygen consumption ($VO_{2\ peak}$) will be performed. VO_{2peak} will be evaluated using an electronic motorized treadmill test with 12-lead ECG monitoring (Mac ® 5000, GE Healthcare) performed by certified exercise physiologists.

Cardiopulmonary exercise testing is a well-established assessment of exercise capacity and provides assessment of peak oxygen consumption (VO_{2peak}) [48]. Expired gases will be analyzed continuously by a metabolic measurement system (Parvo Medics, TrueOne 2400).

During the test, participants will begin walking on a treadmill at a participant-specific designated speed at 0% grade for approximately 2 minutes. The speed and/or grade will be increased every 1–2 minutes until exhaustion or a symptom-limited peak is achieved measured by peak oxygen consumption (VO_{2peak}) ($mL{\cdot}kg^{-1}min^{-1}$).

All participants will be monitored continuously with 12-lead ECG during exercise and five minutes of recovery. During exercise, oxyhemoglobin saturation will be monitored continuously using finger pulse oximetry, while blood pressure will be measured manually by auscultatory sphygmomanometer approximately every two minutes (± 1 minute). This protocol has been previously demonstrated to be appropriate for measuring VO_{2peak} in our prior studies of early-stage and advanced cancer patients. [22,23]

The CPET may be terminated at the discretion of the exercise physiologist if abnormal ECG findings or abnormal response to exercise is observed, or if acceptable test criteria — as outlined in Section 7.1.2.2 — are not met.

Exercise physiologists within the Cardio-Oncology Research Program (CORP) at MSKCC will perform all cardiopulmonary exercise tests. All personnel are trained to read (but not interpret) exercise ECGs and are trained in Basic Life Support (BLS) or Advanced Cardiovascular Life Support (ACLS).

The completion of the subclinical cardiotoxicity assessments will be conducted in the CORP Integrative Physiology Laboratories at Memorial Hospital, the Rockefeller Outpatient Pavilion at 53rd Street, or the Sidney Kimmel Center for Prostate and Urologic Cancers. Participants will be given an opportunity to eat a light snack following their fasted assessments. Participants will be encouraged to bring their own snack; however, the CORP team will also have extra snacks, such as granola bars, available in case participants are unable to bring their own.

9.4.4 Flow-Mediated Dilatation (FMD) via Ultrasound of the Brachial Artery

Endothelial cell dysfunction will be assessed using a commercially–available high-resolution ultrasound and a 7.5MHz linear array transducer (HP Sonos 2000). Brachial artery assessments (a surrogate of systemic nitric oxide-bioavailability) will be obtained in longitudinal view, approximately 4cm proximal to the olecranon process, in the anterior/medial plane, during the five minutes of forearm occlusion, and following cuff release (hyperemia). In patients who have received unilateral modified radical mastectomy, measurements will be performed preferably on the contralateral upper extremity. Due to the potential confounding effects, participants will be asked to adhere to fasting, substance, and activity guidelines prior to the assessment. These guidelines are defined in Appendix 5.

9.4.5 Quality of Life (QoL) and Fatigue

QOL will be assessed using the Functional Assessment of Cancer Therapy – Breast (FACT-B) scale developed for the assessment of patient symptoms and QOL in breast cancer patients. FACT is a general quality of life instrument intended for use with a variety of chronic illness conditions and was originally validated in a general cancer population that included breast cancer patients.

FACT-B is a 27-item compilation of general questions divided into four primary QOL domains: physical well-being, social/family well-being, emotional well-being, and functional well-being. This instrument has been under development since 1987 and represents the generic core questionnaire that is often combined with cancer site-specific questionnaires. FACT-B is located in Appendix 6.

FACT-B is scored by summing the individual scale scores, with higher scores indicating better quality of life. Each domain, as well as the overall QOL score is calculated according to the scoring instructions for FACT. Briefly, after reversing the scoring of negatively worded items (so that a higher score always indicated a favorable response), item responses are summed. The average value of the items for a subscale is computed for missing values, as long as >50% of the questions in the subscale were answered.

In addition to FACT-B, fatigue will be assessed using the 13-item FACIT-fatigue scale for the assessment of fatigue in cancer patients [49]. The FACIT (Functional Assessment of Chronic Illness Therapy) Measurement System has multiple disease, treatment and condition-specific subscales that will be used to complement the FACT-B questionnaire. FACIT is located in Appendix 7.

FACT-B and FACIT-fatigue QOLs will be administered post-CPET to patients in groups 2A and 2B only.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Group 1 (IMRT to Permanent Implant)

12 months (± 2 months) after completion of IMRT:

- Clinical evaluations by the radiation oncologist and plastic surgeon
- Breast-Q© questionnaire (Appendix 4)
- Optional MRI of breast

12-18 months (± 6 months) after completion of IMRT:

- Follow-up ^{13}N-NH_3 PET/CT
  For patient subset who received cardiac ^{13}N-NH_3 PET/CT during simulation

24 months (± 2 months) after completion of IMRT:

- Clinical evaluations by radiation oncologist and plastic surgeon
- Breast-Q© questionnaire (Appendix 4)
- Optional MRI of breast

10.2 Group 2 (IMRT to Tissue Expander)

12-18 months (± 6 months) after completion of IMRT:

- Follow-up ^{13}N-NH_3 PET/CT
  For patient subset who received cardiac ^{13}N-NH_3 PET/CT during simulation

18 months (± 2 months) after completion of IMRT:

- Clinical evaluations by the radiation oncologist and plastic surgeon
- Breast-Q© questionnaire (Appendix 4)
- Optional MRI of breast

30 months (± 2 months) after completion of IMRT:

- Clinical evaluations by radiation oncologist and plastic surgeon
- Breast-Q© questionnaire (Appendix 4)
- Optional MRI of breast

10.2.1 Group 2A (IMRT to [Reconstructed] Breast participating in sub-study)

2-4 weeks after completion of IMRT:

- Follow-up strain echocardiogram
- CPET
- Flow-mediated dilatation (FMD)
- cardiac biomarkers for assessment of early cardiotoxicity
- FACT-B (Appendix 6) and FACIT-fatigue (Appendix 7) questionnaires for assessment of QOL and fatigue

10.2.2 Group 2B (Mastectomy and no RT participating in sub-study)

4-8 weeks post-surgery:

- Follow-up strain echocardiogram
- CPET
- Flow-mediated dilatation (FMD)
- cardiac biomarkers for assessment of early cardiotoxicity

- FACT-B (Appendix 6) and FACIT-fatigue (Appendix 7) questionnaires for assessment of QOL and fatigue

15-20 weeks post-surgery:

- Follow-up strain echocardiogram
- CPET
- Flow-mediated dilatation (FMD)
- cardiac biomarkers for assessment of early cardiotoxicity
- FACT-B (Appendix 6) and FACIT-fatigue (Appendix 7) questionnaires for assessment of QOL and fatigue

Group 1: IMRT to Permanent Implant

Protocol Activity	**Screening**		**Treatment**		**Post-Treatment Follow-Up** *After IMRT completion*		
Study Week(s)/ Months	0-4 weeks	3-10 weeks	Day 1[f]	2-4 weeks	12 months	12-18 months	24 months
Visit Window	before IMRT	after exchange surgery[e]	during IMRT	during IMRT	± 2mo	± 6 mo	± 2mo
Evaluation by Radiation Oncologist[a]		X			X		X
Evaluation by Plastic Surgeon[a]		X[b]			X[c]		X[c]
MRI at the MSKCC main campus[d]		X			X		X
BreastQ Questionnaire		X			X		X
CBC	X			X			
IMRT			X	X			
Pregnancy Test[h]	X						
^{13}N-NH_3 PET/CT[g]		X				X	

a) Evaluation includes assessment of capsular contracture and cosmesis
b) May occur at any time point between the exchange surgery and 10 weeks after exchange surgery.
c) Follow-up clinical evaluations by the plastic surgeon can be from the completion of IMRT or the date of exchange surgery. This will ensure that patients are seen routinely as per standard care and will ease the schedule to accommodate changes in scheduled appointments.
d) The MRI is an optional assessment but highly recommended
e) This may be before IMRT or just after the start of IMRT
f) Patients will be fully registered prior to start of Radiation Treatment (refer to section 15.0)
g) ^{13}N-NH_3 PET/CT for subset of 10 patients who agreed to participate. Baseline occurs during radiation simulation. Follow-up scan occurs 12-18 months (± 6 months) after the completion of IMRT.
h) Pregnancy Test: Serum pregnancy is required 14 days prior to RT. A urine pregnancy test is also accepted (if performed, must be done at set-up)..

Group 2 and Group 2A: IMRT to Tissue Expander (and participating in sub-study)

Protocol Activity	Screening	Treatment		End of Treatment/ Withdrawal	Post-Treatment Follow-Up *After IMRT completion*			
Study Week(s)/ Months	0-4 weeks	Day 1[f]	2-4 weeks	2-4 weeks	Approximately 4-8 months[i]	12-18 months	18 months	30 months
Visit Window	before IMRT	during IMRT	during IMRT	after completion of IMRT	3-10 weeks after exchange surgery	± 6mos	± 2mos	± 2mos
Evaluation by Radiation Oncologist[a]					X		X	X
Evaluation by Plastic Surgeon[a]					X[b]		X[c]	X[c]
MRI at the MSKCC main campus[d]					X		X	X
Breast-Q© Questionnaire					X		X	X
CBC	X		X					
IMRT		X	X					
Pregnancy Test[j]	X							
^{13}N-NH_3 PET/CT[e]	X					X		
Strain Echocardiogram[g]	X			X				
Flow-mediated dilatation (FMD)	X			X				
Cardiac Biomarkers[g]	X			X				
Cardiopulmonary Exercise Testing (CPET)[g]	X			X				
FACT-B and FACIT Questionnaires [g,h]	X			X				

a) Evaluation includes assessment of capsular contracture and cosmesis
b) May occur at any time point between the exchange surgery and 10 weeks after exchange surgery.
c) Follow-up clinical evaluations by the plastic surgeon can be from the completion of RT or the date of exchange surgery. This will ensure that patients are seen routinely as per standard care and will ease the schedule to accommodate changes in scheduled appointments.
d) The MRI is an optional assessment but highly recommended
e) ^{13}N-NH_3 PET/CT for subset of 10 patients who agreed to participate. Baseline occurs during radiation simulation. Follow-up scan occurs 12-18 months (± 6 months) after the completion of IMRT.
f) Patients will be fully registered prior to start of Radiation Treatment (refer to section 15.0)
g) **Group 2A:** In addition to the evaluations described above in Group 2, n=10 patients will undergo these evaluations for the assessment of early subclinical toxicity at these timepoints.
h) FACT-B and FACIT questionnaires can be found in Appendices 6 and 7, respectively.
i) The optimal time of exchange surgery will be determined by the treating plastic surgeon. The window is roughly 4-8 months after the completion of radiation therapy.
j) Pregnancy Test: Serum pregnancy is required 14 days prior to RT. A urine pregnancy test is also accepted (if performed, must be done at set-up).

Group 2B: Mastectomy and no RT (participating in sub-study)

Protocol Activity		
Study Week(s)/ Months	**4-8 weeks**	**15-20 weeks**
Visit Window	after mastectomy	after mastectomy
Strain Echocardiogram	X	X
Flow-mediated dilatation (FMD)	X	X
Cardiac Biomarkers	X	X
Cardiopulmonary Exercise Testing (CPET)	X	X
FACT-B and FACIT Questionnaires[a]	X	X

a) FACT-B and FACIT questionnaires can be found in Appendices 6 and 7, respectively.

11.0 TOXICITIES/SIDE EFFECTS

11.1 IMRT

Potential acute side effects of IMRT are identical to those associated with radiation delivered with conventional 3D techniques. These include mild-moderate erythema, hyperpigmentation, moist desquamation of the chest wall, fatigue, radiation pneumonitis, predisposition for developing a chestwall skin infection, and/or changes in blood count (<3 and will scored according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0). Additionally, CBC will be measured at specified time points as per standard care. For pre-menopausal women, the first CBC may be consolidated with the pre-study pregnancy test.

Capsular contracture and cosmesis will be graded by the Baker scoring system and Breast-Q© questionnaires at time points specified for Group 1 and Group 2.

At any time following completion of radiation, implant failure can be assessed by surgical intervention requiring implant removal or replacement.

Lactating and pregnant women will be excluded because of potential teratogenic effects of radiotherapy that may be harmful to the developing fetus or nursing infant.

11.2 Breast MRI

Side effects of breast MRI include claustrophobia. Gadolinium contrast will be utilized in MRI and in CT simulation, provided the patient is not allergic. Side effects of the injection of Gadolinium include temporary pain, bleeding, and bruising at the injection site. The risk of anaphylactic reaction with gadolinium is small, and a physician will be present for evaluation as per standard care. Patients with tissue expanders or any other ferrous-containing substance within or on the body will not be allowed to undergo MRI due to interaction of the metal port within the expanders with the magnet.

11.3 PET Myocardial Perfusion Scan

Temporary side effects of the vasodilator administration include dyspnea, headache, dizziness, nausea and chest or abdominal discomfort. Rare but serious side effects include fatal arrhythmia and

myocardial infarction. Placement of the angiocatheter for the radiotracer /vasodilator injection may result in temporary pain, bleeding or bruising at the injection site. There is no expected toxicity related to the ^{13}N-NH_3 injection.

11.4 Cardiopulmonary Exercise Testing

In appropriately selected patients , graded exercise testing carries a finite risk of adverse cardiovascular event with <1/100,000 in well individuals and 1/10,000 in clinical populations.

11.5 Strain Echocardiogram

Echocardiography is a common test that is performed in patients for cardiac assessment. No radiation is involved with this test and no anticipated side effects are expected.

11.6 Flow-Mediated Dilatation/Ultrasound of the Brachial Artery

The patient will be monitored throughout the testing period for reactions to the prolonged cuff inflation such as arm pain and numbness. These reactions are not unexpected, and should last only seconds. Suprasystolic pressure will be adjusted for patient comfort. There are no expected adverse events from the ultrasound of the brachial artery.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

For Group 1, at 12 and 24 months (± 2 months) and for Group 2, at 18 and 30 months (± 2 months) following IMRT, the patient will undergo clinical examination to assess treatment efficacy as well as cosmesis and degree of capsular contracture. The treating radiation oncologist and plastic surgeon will evaluate the patients at these pre-determined time points. However, assessment for the primary endpoint, implant failure, may occur at any time between the end of IMRT to the end of the study follow-up period for each group.

The incidence of capsular contracture and minor revisional surgeries will also be assessed. Breast-Q© questionnaires will be used to assess patient-rated cosmesis. Post-treatment MRI studies will be correlated with clinical assessments of capsular contracture to determine the specificity and sensitivity of this diagnostic study as a tool to follow implant patients who were treated with radiation. The quantification of post-radiation changes in the implant and overlying capsule will be descriptive and formulate the basis for future studies.

The rationale for our follow-up period is based on data from our center assessing implant failure rates in patients treated with conventional RT at MSKCC. Given that the bulk of events occurred within the first 2 years after radiation, we believe that 24-30 months of follow-up after radiation is sufficient to capture the proposed endpoints of the study. These data are consistent with other reports in the literature in which approximately 92% of contractures occur within the first 12 months of surgery[50].

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient desires to quit participation in the study or is found to be ineligible for the protocol as designated in the section on Criteria for Subject Eligibility (i.e. a change in diagnosis), the patient will be removed from the study.

If at any time the patient develops progressive disease that warrants a change in the radiation treatment plan (planned dose, fractionation, technique, volume), they will be withdrawn from the study and treated with the alternative therapy.

14.0 BIOSTATISTICS

14.1 Statistical Plan for Assessment

14.1.1 Implant Failure

The primary objective of this study is to assess for the reduction of implant failure associated with multi-beam IMRT, compared to our published historical implant failure rates associated with conventional radiation techniques. The primary endpoint is incidence of implant failure by the end of the study period (24 months post-IMRT for Group 1, and 30 months post-IMRT for Group 2).

Our published data and recent findings in the literature suggested that the implant failure rate (implants that are removed or replaced by another reconstruction) was 20% at 24 months post-IMRT for group 1 [20] and 30% at 30 months post-IMRT for group 2 [51]. Assuming that 1/3 of the patients we will enroll are going to be in group 1 and the remaining 2/3 will be in group 2, we set up the hypotheses that an implant failure rate of 26% or more is considered unacceptable while 16% or less is considered acceptable. Since the endpoint cannot be measured until 2 years after the treatment, we will utilize a one-stage design. We will test the hypothesis using a binomial test based on a cohort of 100 patients. We insist that at minimum 34 of them will be enrolled in group 1 and at minimum 66 will be in group 2, and we will combine them for the primary objective. We will claim that multi-beam IMRT significantly reduces the implant failure rate if no more than 20 patients have an implant failure after IMRT within 24 months of the treatment for patients in group 1 or within 30 months after IMRT in group 2. For this decision rule, we have a type I error (i.e., claiming multi-beam IMRT promising while it is not) rate less than 0.10 and a type II error (i.e., claiming multi-beam IMRT not promising while it actually is) rate less than 0.15.

Because there is no reason why local control or lung or other toxicities would be impacted secondary to treatment with multi-beam IMRT instead of conventional treatment, an early stopping rule in order to detect early recurrences was not deemed necessary.

We expect to accrue 3-4 patients per month. Thus, the trial should be completed within 3 years. Efforts will be made to follow-up every patient for at least 24 months (Group 1) or 30 months (Group 2). Since patients may drop off (for reasons unrelated to toxicity) or be lost to follow-up, we will enroll a total of 130 patients. However, only the first 100 patients (subject to the restriction that at minimum 34 are in group 1 and at minimum 66 are in group 2) who have been followed for at least 24/36 months from IMRT will be analyzed towards the primary objective. Only patients who are irradiated to a tissue expander or permanent implant will be counted in the analysis of the primary objective (i.e. patients in the cardiac substudies who do not receive IMRT to the tissue expander or implant will not be included in the analysis of the primary objective).

14.1.2 Capsular Contracture

For the secondary objectives, the incidence of moderate and severe capsular contracture will be examined using proportions of patients who developed Baker grade <II and ≥II capsular contracture, respectively, at 12 or 18 months and 24 or 30 months after IMRT was administered. Incidence of minor revisional surgeries by plastic surgeon will be evaluated by proportions too. Again, the rates (proportions) will be compared across the two groups.

To evaluate cosmesis, the Breast-Q© will be utilized in these assessments and will be presented descriptively, giving summary statistics for changes in the Breast-Q© scores over time.

Post-treatment MRI outcome is defined as a continuous variable. We will examine the correlation between the 12-month MRI and 12-month Baker score (<II vs ≥II in Group 1 and between the 18-month MRI and 18-month Baker'score in Group 2. The correlation will be assessed by Wilcoxon rank sum tests. We will also examine the sensitivity and specificity of MRI by using Baker score as the gold standard. All patients enrolled will be used for the analysis of secondary objectives if they provided eligible measurements. Analyses for secondary objectives will be done separately for the two groups.

14.1.3 ^{13}N-NH$_3$ PET/CT Feasibility Endpoint

We will assess the feasibility of performing ^{13}N-NH$_3$ PET studies in breast cancer patients undergoing IMRT within the RT simulation session. This involves delivering the dose on time (taking into account the short half life of ^{13}N-NH$_3$), performing all scans successfully, and most importantly, having the patient tolerate all imaging sessions while in the treatment position.

For each patient, if even one out of the two planned studies are unable to generate doses for the heart segments, this patient will be considered as a —failure‖ towards the endpoint of feasibility. The approach will be declared feasible if we are able to obtain doses for all 17 segments of heart in at least 7 out of 10 patients. Should a patient drop out before they receive their follow-up scan, they will be replaced by another patient, unless the first scan was already a —failure‖. We expect n=10 patients, but have budgeted enough scans for 12 patients, in the event a patient gets lost to follow-up/dies and cannot have the second scan, or declines the second scan. However, the decision rule is built by using the first 10 evaluable patients. This decision rule has the following probabilities of declaring success/feasibility.

True feasibility rate	0.85	0.80	0.70	0.60	0.50	0.45
Prob. of declaring feasible	95%	88%	65%	38%	17%	10%

We will further assess feasibility by correlating pre and post-IMRT measures of MBF/CFR with corresponding RT dose delivered to the ventricular myocardium on a global regional and segmental basis. The post-RT studies will help determine the incidence of MBF/CFR changes following radiation as determined by ^{13}N-NH$_3$ PET imaging.

We will measure the correlation between the changes in flow and flow reserve and the dose level in 17 pairs (17 segments per PET data and 17 doses delivered by IMRT). Data will be visually examined first in order to choose the most appropriate correlation coefficient (e.g., Pearson or Spearman or Kendall's Tau, etc., though at this stage we expect that the nonparametric Spearman correlation coefficient will be used). Each patient will thus provide a correlation coefficient. The 10 correlation coefficients for 10 patients in the study will be summarized and descriptive statistics will be computed.

14.1.4 Early Subclinical Cardiotoxicity, Fatigue and QoL Endpoints

Each patient will provide baseline testing results after surgery and/or before the start of RT. We will preliminarily assess the correlation between receipt of IMRT and cardiotoxicities as measured by CPET, strain echocardiogram, cardiac blood markers, FMD and QOL questionnaires in 20 patients using Wilcoxon rank sum test (for continuous measures) and Fisher exact test (for categorical measures). Among the 20 patients whose data will be counted towards the analysis of these exploratory endpoints, 10 of them are in the control group of patients who do not receive IMRT (Group 2B). The data from these 10 patients in the control arm will only be utilized to study the exploratory objective and will not be/cannot be used to assess the primary endpoint, which is implant failure following IMRT. The data from the 10 patients in the experimental arm (Group 2A), however, will be used in the analysis of the primary endpoint since these 10 patients will have received IMRT.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

There is no randomization.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinating the activities of the protocol study team.

The data collected for this study will be entered into a secure database (Clinical Research Database– CRDB). Source documentation will be available to support the computerized patient record.

16.1 Data Collection

The following data forms (found in the regulatory binder) and appendices (found on ProtocolWeb) will be completed and entered into CRDB at specified time points according to the tables below:

Groups 1, 2, 2A:

Time Points:	Data Forms / Appendices:	To Be Completed By:
Baseline (Pre-Treatment)	• Minimal Data Set in CRDB (within 2 weeks of registration)	RSA
	• Data form 1: Patient Information	RSA
	• Appendix 3: Dose Parameters	Dosimetrist
3-10 Weeks Post-Exchange Surgery **AND** Follow-up	• Appendix 4a or 4b: Breast-Q Questionnaire	Patient
	• Dataform 3a: Evaluation of Capsular Contracture & Cosmesis by Radiation Oncologist	Radiation Oncologist
	• Dataform 3b: Evaluation of Capsular Contracture & Cosmesis by Plastic Surgeon	Plastic Surgeon
	• Data form 4: MRI Assessment	Radiologist

Groups 2A & 2B:

Time Points:	Data Forms / Appendices:	To Be Completed By:
Baseline: 0-4 Weeks Pre-RT (Group 2A) **OR** 4-8 Weeks Post-Mastectomy (Group 2B)	• Appendix 10: CPET Form	Exercise Physiologist
	• Appendix 11: CPET Recording Sheet	Exercise Physiologist
Follow-up: 2-4 Weeks Post-RT (Group 2A) **OR** 15-20 Weeks Post-Mastectomy (Group 2B)	• Appendix 12: FMD Form	Exercise Physiologist
	• FACIT and FACT-B Questionnaires	Patient

16.2 Quality Assurance

Regular registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits may be conducted by the study team, at a minimum of once per year, more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at MSKCC were approved by the NCI in September 2001. The plans address the new policies set forth by the NCI in the document entitled ―Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials‖, which can be found at http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC DSM Plans can be found on the MSKCC Intranet at http://mskweb2.mskcc.org/irb/index.htm. There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place

for quality assurance (e.g. protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board. During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (eg, NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

Inclusion of Women and Minorities: MSKCC has filed forms HHS 441 (civil rights), HHS (handicapped individual), 639-A (sex discrimination), and 680 (age discrimination); we also take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. Only female patients will be accepted into the protocol. The proposed study population is as described in Section 6.0.

Exclusion of Lactating or Pregnant Women: Children have been excluded from this study. Thus, the relevance of this treatment to the pediatric population has not been established. Lactating and pregnant women are also excluded because of potential teratogenic effects of radiotherapy that may be harmful to the developing fetus or nursing infant.

Benefits: It is not known whether this treatment will affect the overall survival or local control of the patients.

Costs: The patient will be responsible for the costs of standard medical care including CT simulation. Patients will not be billed for the cost of the MRIs or ^{13}N-NH_3 PET scans.

Incentives: No incentives will be offered to patients/subjects for participation in the study.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study.

Incidental Clinically Significant Findings: Unlike clinical MRI exams, research images collected in this study may be of insufficient quality to yield any diagnostic information. Also, the investigational images are not immediately reviewed by radiologists. For these reasons, incidental findings may not be identifiable, or they may not be identified until long after the research MR exam is performed (in cases where the image production is delayed).

If an incidental clinically significant finding is detected on the research MRI sequences, the investigators and the PIs will propose an appropriate diagnostic imaging plan for such a finding. If a diagnostic MRI is already performed along with the research MRI, the incidental clinically significant finding will be

documented in the clinical MRI report and this will be communicated with the referring physician as per institutional guidelines. If the incidental clinically significant finding is detected only on the research MRI, such as in volunteers undergoing only research MRIs, then the finding and options for an appropriate diagnostic imaging plan will be discussed with the subject, and the discussion will be documented in our research file. In addition, the Institutional Review Board will be notified if this occurs.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

  The PI's signature and the date it was signed are required on the completed report.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in

the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.
6. An option for eligible participants to indicate their voluntary participation in the PET/CT sub-cohort (thereby including this portion of the study in their overall written consent).

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix 1 – Baker Classification System

Appendix 2 – Planning Target Volume Contouring Guidelines

Appendix 3 – IMRT Dose Parameters

Appendix 4 – Breast-Q©'s Reconstruction Module

Appendix 5 – Exercise Physiology Guidelines

Appendix 6 – FACT-B Questionnaire

Appendix 7 – FACIT-fatigue Questionnaire

Appendix 8 – Baseline Scheduling Phone Call Template

Appendix 9 – Baseline Appointment Reminder Phone Call

Appendix 10 – Cardiopulmonary Exercise Test Form

Appendix 11 – CPET Recording Sheet

Appendix 12 – FMD Recording Form

Appendix 13 – Borg Scale