Pilot Study of Multi-Beam Intensity-Modulated Radiation Therapy for Node-Positive Breast Cancer Patients Requiring Treatment of the Internal Mammary Lymph Nodes MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

Principal Investigator/Department:	Simon Powell, M.D.	Radiation Oncology
Co-Principal Investigator(s)/Department:	Beryl McCormick, M.D.	Radiation Oncology
Investigator(s)/Department:	Ase Ballangrud-Popovic, Ph.D. Ellen Yorke, Ph.D. Andrew Jackson, Ph.D. Zhigang Zhang, Ph.D. Kathryn Beal, M.D. Boris Mueller, M.D. Borys Mychalczak, M.D. Daphna Gelblum, M.D. Lior Braunstein, M.D. Atif Khan, M.D. Carla Hajj, M.D. Marsha Reyngold, M.D. Chiaojung Jillian Tsai, M.D. Melissa Remis Zinovoy, M.D. Richard Gewanter, M.D. Oren Cahlon, M.D. Annemarie F. Shepherd, M.D. John Cuaron, M.D. Daniel Gorovets, MD Justin Mann, MD Dhwani Parikh, MD Linda Chen, MD Jung (Julie) Kang, MD Quincey LaPlant, MD Narek Shaverdian, MD David Guttman, MD Ariel Marciscano, MD Yao Yu, MD Michael Bernstein, MD Christopher Barker, MD Erin Gillespie, MD Carol Milazzo, NP Adriana Olivo, RN Janice Terlizzi, NP Dierde Bracken, APN Eileen Jackson, NP Ilana Genin, APN Janine (Cleary) Davis, NP Janet Cogswell, RN Jennifer Howgate-Klingaman, RN Lisa Sarmasti, RN Megan Stasi, RN	] Medical Physics Medical Physics Medical Physics Epidemiology & Biostatistics Radiation Oncology Nursing Nursing Nursing Nursing Nursing Nursing Nursing Nursing Nursing

	Ofer Maimran, RN	Nursing
	Geri Arnell, RN	Nursing
	Raylene Langish, RN	Nursing
	Nicole Heinz, RN	Nursing
	Jessica Marchisotto, RN	Nursing
	Irene Kelly, RN	Nursing
	Gloria Wasilewski, RN	Nursing
	Sherie Mar-Chaim, RN	Nursing
	Maureen Kennedy, RN	Nursing
		Nursing
		Nursing
Consenting Professional(s)/Department:	Simon Powell, M.D.	Radiation Oncology
	Beryl McCormick, MD	Radiation Oncology
	Annemarie F Shepherd, M.D.	Radiation Oncology
	Oren Cahlon, M.D.	Radiation Oncology
	John Cuaron, M.D.	Radiation Oncology
	Kathryn Beal, M.D.	Radiation Oncology
	Boris Mueller, M.D.	Radiation Oncology
	Borys Mychalczak, M.D.	Radiation Oncology
	Daphna Gelblum, M.D.	Radiation Oncology
	Lior Braunstein, M.D.	Radiation Oncology
	Atif Khan, M.D.	Radiation Oncology
	Carla Hajj, M.D,	Radiation Oncology
	Marsha Reyngold, M.D.	Radiation Oncology
	Chiaojung Jillian Tsai, M.D.	Radiation Oncology
	Melissa Remis Zinovoy, M.D.	Radiation Oncology
	Richard Gewanter, M.D.	Radiation Oncology
	Daniel Gorovets, MD	Radiation Oncology
	Justin Mann, MD	Radiation Oncology
	Dhwani Parikh, MD	Radiation Oncology
	Linda Chen, MD	Radiation Oncology
	Jung (Julie) Kang, MD	Radiation Oncology
	Quincey LaPlant, MD	Radiation Oncology
	Narek Shaverdian, MD	Radiation Oncology
	David Guttman, MD	Radiation Oncology
	Ariel Marciscano, MD	Radiation Oncology
	Yao Yu, MD	Radiation Oncology
	Michael Bernstein, MD	Radiation Oncology
	Christopher Barker, MD	Radiation Oncology
	Erin Gillespie, MD	Radiation Oncology

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Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10065

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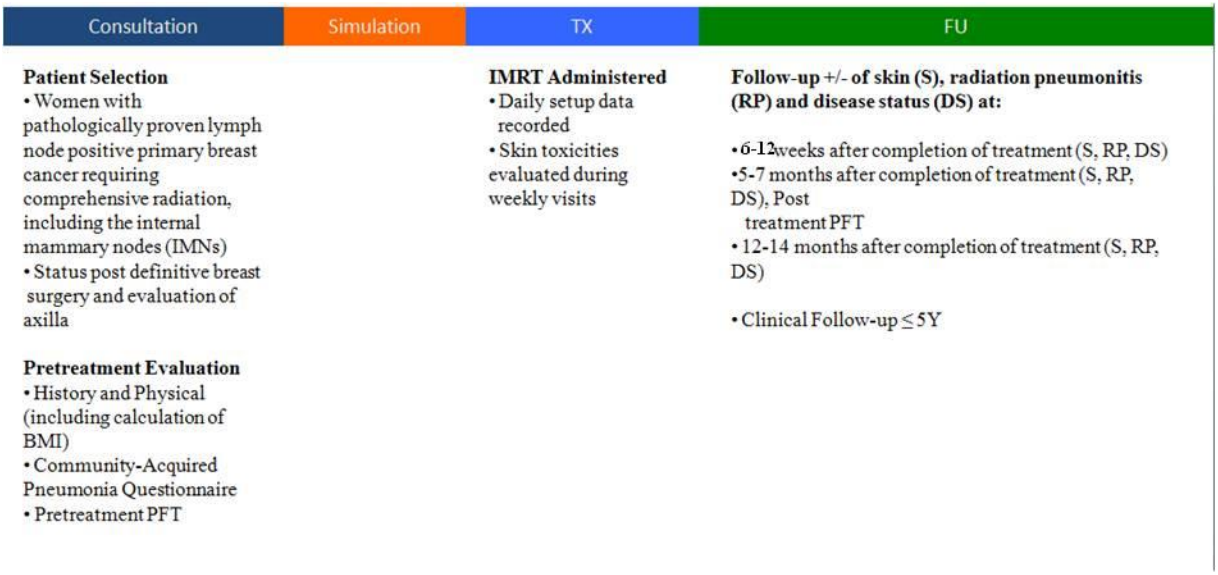
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

We propose a single-arm feasibility study utilizing multi-beam intensity-modulated radiation therapy (IMRT) in the adjuvant treatment of the breast and regional lymph nodes of women with node-positive breast cancer who require coverage of the internal mammary lymph nodes. Daily three-dimensional (3D) set-up verification will be performed prior to radiation treatment. The primary objective is to assess feasibility of multi-beam IMRT (feasibility is defined in detail below). Secondary objectives are to evaluate acute and late toxicities and locoregional recurrence associated with this treatment.



2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objective

To assess the feasibility of adjuvant radiation therapy via multi-beam IMRT using daily 3D position verification in patients with node-positive breast cancer who require coverage of the internal mammary lymph nodes. Infeasibility is defined in Section 12.0.

2.2 Secondary Objectives

The endpoints in these objectives are descriptive and will form the basis for designing future studies. In keeping with the feasibility nature of this study, endpoints will be observed at least through 5-7 months following the completion of radiation therapy. The Common Terminology Criteria for Adverse Events (CTCAE version 3.0) will be used for grading toxicities (see Appendix 1; the complete toxicity grading system is available for review at http://ctep.cancer.gov).

- To evaluate the rate and severity of both acute and late cutaneous toxicity
- To evaluate the rate and severity of late subcutaneous fibrosis
- To evaluate the rate and severity of radiation pneumonitis (RP)
- To evaluate local-regional control rates
- To evaluate patient set-up reproducibility in breast cancer patients treated with multi-beam IMRT

3.0 BACKGROUND AND RATIONALE

3.1 Comprehensive Radiation Therapy for Breast Cancer Patients Requiring Treatment of the Internal Mammary Lymph Nodes

Treatment of the internal mammary lymph nodes (IMNs) in locally advanced breast cancer patients is controversial and technically challenging from a radiation point of view. The 2008 NCCN Practice Guidelines recommend consideration of radiation therapy to the IMNs for patients with node-positive breast cancer after mastectomy or breast-conserving surgery (1). Although the internal mammary node chain is a first-echelon nodal drainage site in breast cancer, the importance of its treatment is much debated, as there are concerns about the potential added cardiac and pulmonary toxicity from irradiation of the IMNs and there are several negative (but underpowered) trials testing the value of surgical removal of the IMNs(2-5).

Nearly 30% of locally advanced breast cancer patients who receive adjuvant radiation therapy as part of their management at Memorial Sloan-Kettering Cancer Center (MSKCC) are treated with comprehensive radiation therapy to any residual breast tissue, the chest wall, and regional lymph nodes, which include the axillary, internal mammary, and supraclavicular nodes. Comprehensive radiation therapy positively impacts disease-free survival and contributes to gains in overall survival (6-9). The most recent meta-analysis from the Early Breast Cancer Trialists' Collaborative Group showed that adjuvant radiation therapy reduced 5-year local recurrence risk from 23% to 6% and improved 15-year breast cancer mortality from 54.7% to 60.1% in node positive patients treated with mastectomy and lymph node dissection (10). Inspection of the one-year data for lymph-node positive patients who receive either breast conservation surgery plus radiation or mastectomy plus axillary clearance plus radiation demonstrated a local-regional recurrence of around 2%. The EBCTCG meta-analysis showed that for every for local-regional recurrence prevented at 5 years, an additional survivor at 15 years was gained. This demonstration of the significance relationship between local control and long-term survival and the fact that treatment of the internal mammary lymph nodes were included in 24 out of the 25 postmastectomy radiation therapy studies included in the meta-analysis has led to a rebirth of interest in IMN treatment in patients with advanced breast cancer.

There are several indications for comprehensive radiation to the breast, chest wall, and internal mammary lymph nodes, including the presence of stage T4 disease, ≥4 involved axillary lymph nodes, inadequate axillary sampling, or positive surgical margins (11). Comprehensive radiation therapy is sometimes also recommended in patients with less than T4 disease or with 1-3 positive axillary lymph nodes in consideration with other patient- and tumor-specific risk factors (7-9), such as involved regional lymph nodes before or after neoadjuvant chemotherapy, high clinical stage of disease, premenopausal status, and presence of lymphovascular space invasion (12-14).

A course of comprehensive radiation therapy traditionally consists of a series of daily radiation-therapy treatments delivered to residual breast tissue, chest wall, axillary, supraclavicular, and internal mammary lymph node regions. Generally, between 1.8 Gy and 2.0 Gy are delivered to these regions five days per week to a total dose of 50 Gy to 50.4 Gy, resulting in a five- to six-week course of therapy. The chest wall and/or residual breast tissue is typically treated with a pair of radiation fields oriented 180 degrees apart from each other that are tangential to the chest wall. The superior axilla and supraclavicular regions are typically treated with a single slightly oblique anterior field. The internal mammary region may be included within the chest wall fields or via a separate field. Comprehensive radiation therapy usually occurs after the completion of all cytotoxic chemotherapy.

3.2 Toxicities of Comprehensive Radiation Therapy

3.2.1 Acute Toxicities

The toxicity of comprehensive radiation therapy has been well described (15). Acute toxicity is defined as those effects that occur during a course of radiation therapy or within 90 days of its completion. Essentially all patients experience skin erythema, which may progress to desquamation in a fraction of patients. A mild pharyngitis is rarely seen. Fatigue can develop in up to 40% of patients. Acute side effects generally resolve within several weeks of the completion of radiation therapy and only rarely cause a treatment interruption. Acute toxicities to the skin and pharynx are typically graded using the CTCAE version 3. Relevant sections of the CTCAE are included in Appendix 1.

3.2.2 Late Toxicities

Surrounding adjacent organs may receive a radiation dose during radiation treatment. In breast cancer, normal tissues at risk for complications due to radiation exposure mostly include the irradiated skin, lung, and heart.

3.2.2a Cardiac Toxicity

Pierce's report that compares various standard techniques of comprehensive radiation therapy provides an excellent review of some of the standard techniques currently utilized (16). Figure 1 illustrates a typical medial tangent field that is treating the breast, chest wall, internal mammary lymph nodes, and the lower axilla. Figure 2 shows a typical supraclavicular field that also treats the supraclavicular lymph nodes and upper axilla.

Depending on her individual anatomy, a patient with left-sided breast cancer requiring coverage of the internal mammary lymph nodes may have a portion of the heart exposed to radiation beams (Figure 3), as the internal mammary lymph nodes lie in the 1st to 3rd intercostal spaces, directly above the heart. Meta-analysis and registry studies have shown an increase in ischemic heart disease in patients who received adjuvant radiation, in particular for left-sided breast cancers (17-18). However, these reviews included older studies where outmoded radiation delivery techniques and large fraction sizes were utilized, resulting in high doses of radiation to the heart. In contrast, the Danish 82b and 82c studies have not shown any increase in ischemic heart deaths in the irradiated group at 12 years (19).

After computed tomography (CT)-based radiation treatment planning was developed, the relationship between radiation dose, volume of heart irradiated, and cardiac outcomes could be more closely evaluated. It has generally been established that the risk of cardiovascular disease increases with increasing mean heart dose. Doses in excess of 40 Gy to small volumes of the heart are felt by some authors to increase a patient's risk of cardiovascular disease and may lead to increased cardiac events (20). Doses of 25 Gy have been shown to induce temporary perfusion defects (21). There is emerging data that doses to specific parts of the heart, such as the coronary arteries, may be more important in predicting cardiac outcomes (22-24). Pericarditis is a very rare late toxicity, occurring in <1% of patients (25).

3.2.2b Pulmonary Toxicity

When irradiating just the breast/chest wall and supraclavicular and axillary lymph nodes, between 20% and 50% of the ipsilateral lung will receive in excess of 20 Gy, a dose which may reduce the functional capacity of that volume of tissue (26). When attempting to cover the internal mammary lymph nodes with tangent beams, it is possible that an even greater amount of ipsilateral lung with receive in excess

of 20 Gy. Exposure of lung to ionizing radiation may cause RP, which is characterized by cough, shortness of breath, and low-grade fevers. A chest x-ray may show no findings or an infiltrate corresponding to the irradiated lung volume. The presence of such an infiltrate in the absence of symptoms is neither diagnostic nor predictive of RP. The influence of treatment factors in the development of RP is unclear; however, the dose of radiation to a given volume of lung seems to play a key role. RP typically occurs between 1 and 4 months following the completion of a course of radiation therapy and, depending on the severity of symptoms, is treated with corticosteroids or observation. Conditions such as infection, cardiovascular disease, other pulmonary disease, and tumor metastasis must be considered, as RP is a diagnosis of exclusion. Thus, the diagnosis of RP is typically made by considering the presenting symptoms and their timing relative to radiation therapy, evaluating the patient for any other medical conditions, and obtaining radiographic imaging of the lungs.

RP is currently scored according to CTCAE version 3. This scale characterizes the severity of RP via five categories from grade 1 (asymptomatic with radiographic findings only) to grade 5 (death from pulmonary complications of treatment). This scale is useful in populations of patients with lung cancer because they experience RP at a clinically relevant frequency. However, in breast cancer, this scale represents a very coarse metric, as it is unlikely that a large proportion of patients will experience greater than grade 2 toxicity. The incidence of RP in breast cancer patients receiving comprehensive radiation therapy is typically quoted at around 5% (27). However, this number is likely an underestimate of the actual incidence of RP, because most studies determine the incidence of RP retrospectively and only capture patients who were hospitalized or medicated as having RP.

Recent developments in chemotherapy may also impact rates of RP in patients who receive multimodality care. Cooperative group trials CALGB 9344, BCIRG 001, and PACS 01 have shown an improvement in disease-free survival and overall survival with the addition of a taxane (docetaxel or paclitaxel) to the systemic therapy of patients with advanced breast cancer (28). Many of these patients will also receive comprehensive radiation therapy. Since the publication of these trials, particularly CALGB 9344, an increasing number of patients with breast cancer have been receiving a taxane as part of their systemic therapy (29). Delivery of a taxane either concurrently or in close temporal proximity to comprehensive radiation may increase the risk of RP. Taghian et al.(30) found an incidence of 14.6% in this group and a CALGB trial(31) studying concurrent administration of paclitaxel and radiation was stopped after 25% of patients developed grade 2 or 3 toxicity.

The incidence of RP as reported by several recent series that utilized both modern chemotherapy and radiation therapy techniques are summarized below. The majority of these reports have used the Radiation Therapy Oncology Group (RTOG) acute lung morbidity scoring system to describe the severity of RP:

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
RTOG ACUTE LUNG MORBIDITY SCORING CRITERIA	No Change	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents/dyspnea with minimal exertion	Severe cough, no response to narcotic antitussives or dyspnea at rest/clinical or radiological evidence of acute pneumonitis/ intermittent O_2 or steroids may be required	Respiratory insufficiency/ continuous oxygen or assisted ventilation	Fatal

The following retrospective studies report on incidences of RP after adjuvant radiation for breast cancer. It is important to note that only two of the series (30, 32) included patients who required internal mammary lymph nodes. Voduc reported a 2% incidence of grade 2-3 RP using the RTOG scale in a group of 77 women with breast cancer treated at the British Columbia Cancer Agency (BCCA)(33). No grade 4 or 5 events occurred. All patients had lymph node–positive disease with negative estrogen receptor expression and underwent surgery, adjuvant doxorubicin/cyclophosphamide for four cycles followed by four cycles of paclitaxel (AC,T) followed by radiation therapy. This study represents a patient population who were treated with the systemic regimen that most of these patients in the proposed study will receive. Yu and Buchholz reported the MD Anderson Cancer Center (MDACC) incidence of RP in a Phase III study comparing neoadjuvant four cycles of paclitaxel followed by four cycles of 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) versus eight cycles of FAC. Of 524 patients treated in the study, 189 also received radiation therapy (34). RP was scored using the RTOG scale. Clinically evident pneumonitis was observed in 5% of the paclitaxel-FAC group and 4.5% of the FAC-only group (difference not significant). Only two patients of 189 required steroids, one other required narcotics, and none were hospitalized. Taghian et al. from the Massachusetts General Hospital (MGH) reported RP rates in 41 breast cancer patients treated with mastectomy and axillary lymph node dissection followed by four cycles of adjuvant doxorubicin/cyclophosphamide followed by four cycles of paclitaxel (30). Radiation therapy to the chest wall and regional lymphatics were given concurrently with paclitaxel in 21 patients and sequentially in the remainder. In contrast to the BCCA and MDACC experiences, an incidence of 14.6% (6 of 41 patients) grade 2-3 RP using the RTOG scale was observed at the MGH regardless of the sequencing. Five of the events were grade 3 and no grade 4-5 events occurred. Lind et al reviewed Duke's experience with RP in a cohort of breast cancer patients treated with breast-only radiation therapy versus comprehensive radiation therapy (32). In 319 patients who received radiation to the breast alone the RP rate was 0.9%. When comprehensive radiation therapy was employed, the RP incidence increased to 4.1% (12 of 294 patients). All 12 patients were treated with oral corticosteroids. There were neither hospitalizations nor deaths from pneumonitis, which means that the incidence of 4.1% may be regarded as the incidence of RTOG grade 3 events. The Duke report predated the widespread use of taxane chemotherapy, but AC chemotherapy or cyclophosphamide, methotrexate, and 5- fluorouracil was given to 42% of the group, which resulted in a RP rate of 3.8%. Beal and McCormick reported a small series of 38 node-positive breast cancer patients treated with surgery, adjuvant (AC, T), followed by comprehensive radiation therapy at MSKCC (35). No cases of RP were seen in this group after a median follow-up of 28 months. However, none of the patients in this study required irradiation of the internal mammary lymph nodes.

Summary of Retrospective Studies Reporting RP After Breast RT:

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

In order to assess the feasibility endpoint in the proposed study, we are most interested in capturing incidences of RP that requires corticosteroids or hospitalization (RTOG grade 3-5). However, no series

reported any fatalities or grade 4 events from RP after breast RT, so serious pneumonitis in this population appears to be limited to RTOG grade 3 events. The weighted average for grade 3 RP in these series using the RTOG scale is around 3.3%. Again, not all of the reported series included patients who required internal mammary lymph node radiation.

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

As discussed above, the CTCAE is a coarse tool to measure RP in women with breast cancer. While we will grade any RP event using the CTCAE, we will also use a patient questionnaire to evaluate pulmonary symptoms. Unfortunately, a validated questionnaire for radiation-induced pneumonitis does not exist. Infectious pneumonia is the main item to be excluded when RP is being considered, and a validated questionnaire *does* exist for the evaluation of the severity of community acquired pneumonia (CAP) (36). The questionnaire focuses on the presence of dyspnea, severity of dyspnea, presence of cough, and general health and generates a “CAP score.” In view of the similarity in symptoms between RP and CAP, we have elected to use CAP scores which are derived from an eight-item questionnaire in order to assess for the presence of RP (See Appendix 3). This questionnaire can likely be completed by patients in less than five minutes. Moussaoui (36) studied CAP scores in a cohort of patients participating in an antibiotic study and found high internal consistency (Cronbach alpha = 0.87) and high test-retest reproducibility (intraclass correlation coefficient = 0.83). It has been found to be simple, reliable, valid, and highly responsive. As there is such a high degree of overlap between the symptoms of RP and CAP, we propose to use CAP scores measured before and after radiation therapy as a measure of the incidence of RP.

Pulmonary function tests (PFTs) are a broad range of tests that measure how effectively the lungs inhale, exhale, and transfer oxygen to the blood. PFTs may show a decrease in values by six months following the completion of comprehensive radiation therapy (37). Changes in pulmonary function tests before and after comprehensive radiation therapy correlate with changes in pulmonary perfusion (38). The magnitude of these changes has also been correlated with the severity of pneumonitis in a cohort of breast cancer patients treated with aggressive combination chemotherapy and radiation therapy (39). In this study, we will obtain PFTs before and once after radiation therapy, at 5-7 months following the completion of treatment (CoT).

3.3 Rationale for Current Study

As detailed above in Section 3.2.2, treatment of the internal mammary lymph nodes, which lie in the first three intercostal spaces directly above the heart, often poses a technical challenge to radiation oncologists when attempting to optimize nodal coverage while minimizing dose to the heart and lungs. Dosimetric studies have demonstrated that the currently available radiation treatment techniques to

cover the internal mammary chain can result in both variable cardiac doses and coverage of the nodes(16, 40). In the current era, where systemic agents with known cardiotoxic effects such as anthracycline-based chemotherapy and Trastuzumab are frequently utilized (41-42), minimization of radiation dose to the heart while adequately covering the internal mammary lymph nodes becomes a particularly important therapeutic goal.

Our rationale for utilizing multi-beam IMRT in the adjuvant treatment of breast cancer patients requiring radiation to the breast and regional lymph nodes (including the IMNs) is to minimize high radiation doses to the heart and lung, while maintaining optimal coverage of the breast and lymph nodes. Minimization of doses to these structures while adequately covering structures at risk could subsequently lead to decreased rates of side effects such as radiation pneumonitis and late cardiac toxicities without compromising the efficacy of adjuvant radiation therapy for breast cancer.

Currently, breast cancer patients requiring IMN treatment at Memorial Sloan-Kettering Cancer Center's Department of Radiation Oncology are treated with a "simplified" IMRT approach utilizing 3-4 conventional beams. Given the few number of beams utilized, this approach can be regarded as similar to "conventional" radiation techniques used for the treatment of breast cancer, but is a more technologically sophisticated treatment than what is considered "traditional" 3D radiation. Although efficacious and with a favorable safety profile, simplified IMRT in select patients can result in high radiation doses to normal structures such as lung and heart. In Figure 4a and 4b, two radiation plans devised for a patient with a right-sided breast cancer requiring comprehensive radiation treatment to the chest wall and regional lymph nodes (including the IMNs) is shown. A standard simplified IMRT technique utilizing two beams is compared to the multi-beam IMRT technique proposed in this protocol. Due to the decreased amount of lung exposed to the high dose radiation resulting from the standard simplified IMRT technique, the patient was ultimately treated with the multi-beam IMRT plan. The more conformal coverage of the chest wall with the multi-beam IMRT technique, compared to the standard technique, is also demonstrated.

Over the past year, a few important treatment trends have impacted the way radiation is delivered for breast cancer patients in our department and have helped us identify particular patient populations with unfavorable anatomy who may especially benefit from the multi-beam IMRT technique. The number of patients with locally advanced breast cancer requiring coverage of the internal mammary lymph nodes between 11/2008 and11/2009 has tripled in our department, compared to the prior year. This trend can be attributed to the larger volume of patients with locally advanced breast cancer seen in our department, the enhanced use of PET and MRI to detect internal mammary lymph node metastases, and the unresolved clinical question of whether or not treatment of the internal mammary lymph nodes may improve survival in locally advanced breast cancer.

Secondly, the proportion of patients who received immediate reconstruction after mastectomy with an ipsilateral implant has increased considerably over the past 4 years. The presence of an implant or temporary expander often poses technical challenges in delivering a homogenous dose to the chest wall secondary to the sharp slope of the implant on the chest wall, compared to a flat chest wall. In addition, the number of patients who underwent contralateral prophylactic mastectomy (CPM) simultaneously in addition to ipsilateral mastectomy has also dramatically increased in our department over the past year. Reconstruction with bilateral permanent implants frequently follows bilateral mastectomies and is the most common form of immediate reconstruction offered to bilateral mastectomy patients at MSKCC. We have simulated 60 patients with bilateral implants since 2008 to the present time (11/09), compared to 49 patients in a three-year time period between 2004 and 2007.

This increase in the number of bilateral implant reconstructions parallels both national trends in increased use of CPM over the past decade(43), as well as trends here at MSKCC. A retrospective study of CPM utilization at MSKCC demonstrated that the rate of CPM paralleled the use of MRI and increased from 7% to 25% between 1997 and 2005 (abstract presented by King et al at SABCS 2009). The presence of an implant/temporary expander can be problematic when planning radiation treatments to the chest wall and regional lymph nodes. Optimizing beam angles such that the target structures are covered, while avoiding the contralateral implant, lung, and heart is technically challenging. These patients could therefore potentially benefit from multi-beam IMRT.

This protocol proposes to investigate an alternate mode of delivering IMRT using *multiple* beams (6-12 beams, therefore referred to as "multi-beam" IMRT) and verification of patient setup with daily imaging. Although more complex to plan and deliver, this method has been shown to significantly reduce radiation dose to the lung and heart in various dosimetric studies by several groups who have investigated this approach in order to improve the therapeutic ratio. IMRT is an advanced method for planning and delivering external radiation therapy where each beam delivers multiple intensity levels rather than one uniform intensity level to the planning target. This is achieved by changing the beam aperture during the "beam-on" time. 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. A multi-beam IMRT technique (typically 6-12 beams equally spread over the chest wall) differs from the simplified IMRT treatment technique (typically 3-4 beams) currently used for comprehensive breast and nodal radiation therapy at MSKCC. Simplified IMRT 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. Krueger reported a planning study of multi-beam IMRT versus conventional radiation therapy (44). This group found improved radiation homogeneity in the chest wall and improved nodal coverage with multi-beam IMRT. The maximum dose to the ipsilateral lung was significantly reduced with multi-beam IMRT, but the contralateral breast and lung had a slightly larger volume exposed to a very low dose of radiation. Cho compared a variety of different methods of conventional comprehensive radiation therapy with multi-beam IMRT in 19 patients with left-sided, upper-inner quadrant breast cancers in which internal mammary lymph nodes were also targeted (45). Multi-beam IMRT yielded the best combination of uniform dose to breast and internal mammary lymph nodes with a low dose to the lung and heart. A preliminary dosimetric study was performed on five patients with breast cancer at Washington University in whom tomotherapy plans were generated using the same CT scan obtained for the conventional radiation therapy plan (46). All patients were actually treated with the conventional radiation therapy technique. Their results demonstrated that tomotherapy has the potential to decrease the volume of lung treated to a dose greater than 20 Gy. The mean percentage of ipsilateral lung that received ≥20 Gy (V20) was 32.2% with conventional radiation delivery and 16.8% with tomotherapy (paired t-test, $p = 0.017$). This has the potential to lower the rate of RP, as data suggests that 20 Gy may represent a threshold dose for the development of RP (26). In all of these planning studies, conventional techniques, not multi-beam IMRT, were used to deliver the actual radiation therapy. Dosimetric studies have also shown an improvement in coverage of the target tissue by eliminating high- and low-dose regions commonly seen in the junction region between the tangent beams and the anterior oblique beam of conventional techniques. The trade-off from this approach is that a larger volume of lung will receive a low dose of radiation from the multi-beam IMRT technique. Figure 5 and Figure 6 show simplified IMRT (typically performed at MSKCC) and multi-beam IMRT axial and sagittal dose distributions generated from MSKCC planning studies in a patient with bilateral implants, the presence of which can pose technical

challenges with conventional radiation techniques. The multi-beam IMRT distributions are notable for the lack of high-dose regions in the heart. The fraction of lung exposed to high doses was also less with multi-beam IMRT. However, greater regions of low dose to the lung are noted with multi-beam IMRT. Figure 7 demonstrates the dose-volume histograms for a simplified IMRT and multi-beam IMRT plan on the same patient. In this case, actual radiation treatment was delivered with the simplified IMRT plan.

Breast cancer radiation oncologists have been concerned about implementing multi-beam IMRT because of the large geometric margins that need to be applied to target volumes. These margins are needed to ensure that target tissue is irradiated despite variations in interfraction patient position. Therefore, it is critical to be able to deliver the multi-beam IMRT plan to the intended target volume in a consistent, accurate fashion. 3D imaging of the target volume allows the opportunity to visualize the accuracy of a patient's setup prior to the delivery of radiation treatment. Currently, our department is equipped with the Varian Trilogy™ and 2100EX Systems, which are linear accelerators capable of delivering state-of-the-art IMRT. In addition, an FDA-approved method of providing accurate patient set-up positioning, AlignRT (Vision RT, London, UK), which is a commercially available 3D-surface imaging system (47-49), is available in our department on our Varian Trilogy machine. One Trilogy and two 2100EX linear accelerators with on-board kilovoltage (KV) imagers also exist. The on-board imagers available on three of our treatment machines allow for acquisition of two orthogonal KV images that can be used for accurate patient positioning. The acquired images will be compared to digitally reconstructed radiographs from the planning CT and shifts will be determined either by aligning bony anatomy or by aligning clips, if clips have been left in the lumpectomy cavity. Both of these technologies provide the ability to minimize day-to-day position variability (50-51).

The merit of treating patients requiring internal mammary lymph node radiation with multi-beam IMRT therefore lies in its potential to provide improved coverage of the nodal target sites while simultaneously minimizing lung and heart toxicities. Decreasing dose to these normal structures can potentially reduce the incidence of late cardiac side effects and radiation pneumonitis. Patients with left-sided breast cancers, obese body habitus, and bilateral implants may particularly benefit from the enhanced conformality of the multi-beam IMRT technique, as delivery of radiation with the standard technique can be technically challenging.

In view of these preliminary results from the aforementioned dosimetric studies documenting decreased dose to the lung and heart as well as an expanded patient population at MSKCC in whom this technique may be beneficial, we propose to conduct a feasibility study of delivering adjuvant comprehensive radiation therapy via multi-beam IMRT with daily set-up position verified using either of the two available setup techniques mentioned above. In addition to feasibility, we will evaluate the rates of local-regional recurrence and RP.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a Phase I single-arm feasibility study of multi-beam IMRT with daily set-up verification in the treatment of women with node-positive breast cancer who will receive radiation to the breast/chest wall and regional lymph nodes, including the internal mammary lymph nodes.

4.2 Intervention

IMRT with multiple beams will be utilized to treat the breast or chest wall and axillary, supraclavicular and internal mammary lymph nodes. Treatment will be delivered once a day, 5 days a week for approximately 5 weeks. Daily set-up error will be checked prior to the delivery of every treatment.

Prior to beginning treatment with multi-beam IMRT, patients will be status post partial mastectomy or mastectomy with an assessment of axillary lymph node status. Axillary assessment may be any combination of sentinel lymph node biopsy or axillary lymph node dissection.

Concurrent cytotoxic chemotherapy is not allowed in this study. Concurrent biologic therapy with radiation therapy is allowed. We anticipate that concurrent trastuzumab will be the most frequent example of concurrent biologic therapy. Antiestrogen hormonal therapy (eg, Tamoxifen or aromatase inhibitors) may be administered concurrently with radiation therapy.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.0.1 Two techniques that allow verification of setup accuracy are currently available in the Department of Radiation Oncology:

1) AlignRT employs three ceiling-mounted 3D camera units to produce high-resolution and accurate 3D surface data referenced to the treatment isocenter. At each treatment fraction, the system images the current patient position instantaneously. AlignRT® is able to gate its image capture so that 3D data are acquired at a reproducible point in the breathing cycle. 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.

2) An orthogonal pair of KV images allows optimal visualization of bony anatomy as well as clips in the lumpectomy cavity or axilla. One Trilogy and two 2100EX linear accelerators with on-board KV imagers are available in the department.

5.0.2 BreastQ questionnaire

The BreastQ questionnaires have been developed by the MSKCC Department of Surgery. For patients who received a mastectomy with or without reconstruction, the questionnaire will be administered at baseline and 5-7 months after treatment (Appendix 6). Below is information about the questionnaire validation process:

The conceptual model and item list were developed from patient interviews (n=48), focus groups (n=18), expert panels and literature review. A conceptual model for the impact of breast surgery was developed with scales that examine: (1) psychosocial well-being, (2) physical well-being, (3) sexual well-being, (4) satisfaction with breasts, (5) satisfaction with overall outcome and (6) satisfaction with care. The process of item generation led to a separate module for each surgery type: 1) breast augmentation, 2) reduction, 3) reconstruction and 4) mastectomy without reconstruction. Each module has a pre and postoperative version with all preoperative items repeated in the postoperative questionnaires. . The preliminary questionnaire was pilot tested with cognitive debriefing interviews

(n=47) and further modified. Field-testing was preformed at 5 centers in the US and Canada (total n=1950, test-retest n=491, response rate 72%). 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. Cronbach's alphas for all 18 scales (3 modules with 6 scales) ranged from 0.87 to 0.98. Test-retest reliability, as measured by intraclass correlation coefficients, ranged from 0.85 to 0.98. 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.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. Female gender
2. Age ≥18 years
3. An invasive primary breast cancer of any histology arising from breast parenchyma
4. Patient must be status post mastectomy or partial mastectomy with an assessment of axillary nodes via sentinel lymph node biopsy and/or axillary lymph node dissection
5. Pathologic confirmation of metastatic disease in at least one regional lymph node. Regional lymph nodes are defined as the ipsilateral axillary lymph nodes, ipsilateral supraclavicular lymph nodes, and ipsilateral internal mammary lymph nodes. Thus, any T stage is allowed as long as the N stage is ≥1 and M stage is 0.
6. Patient signed study-specific consent form.

6.2 Subject Exclusion Criteria

1. Patients with distant metastasis.
2. Patients who are pregnant or breastfeeding.
3. Patients with psychiatric or addictive disorders that would preclude obtaining informed consent.
4. Time between initial diagnosis of breast cancer and start of radiation therapy exceeds 13 months.
5. Estimated life expectancy judged to be less than one year by patient's treating radiation oncologist.
6. Prior radiation therapy to the ipsilateral or contralateral breast or thorax.
7. Primary breast cancer is a lymphoma or sarcoma histology.
8. Patients with a history of non-skin malignancy <5 years prior to the diagnosis of breast cancer.
9. Patients requiring radiation to the bilateral breasts

7.0 RECRUITMENT PLAN (Limited Waiver of Authorization)

This study will be available to all patients seen at MSKCC who meet the eligibility criteria. MSKCC is a large referral center for breast cancer. In addition, the study will be placed on the MSKCC Website as well as available at the MSKCC satellite centers to maximize patient recruitment. 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, s/he 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, we 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).

We estimate that between 130 and 150 eligible patients are treated in the Department of Radiation Oncology per year. On average, 15-20 eligible patients are under treatment at any moment. This provides a large pool of patients who could be eligible for this study. We estimate that, on average, there will be room for approximately five to ten breast cancer patients on our treatment machines, leading to treating 30-60 breast cancer patients per year. Considering these estimates, we predict that we will meet our accrual goal of 100 evaluable patients within two years. Patients will be considered evaluable when they have completed their 5-7 month follow-up and PFT. Patients that have been registered but have withdrawn from the study prior to completing their 5-7 month follow-up and PFT will not be evaluable for the study. Since there may be patients enrolled on study who are later found to be inevaluable, our maximum target accrual is 120 patients. However, if we are able to accrue 100 evaluable patients before we reach the maximum target accrual, we will close the study to accrual.

8.0 PRETREATMENT EVALUATION

All of the following pretreatment evaluations should be completed within 45 days of the start of radiation therapy:

- Assessment of weight and height for calculation of BMI
- Completion of the CAP questionnaire
- Completion of the BreastQ (if patient received mastectomy +/- reconstruction)
- PFTs
- Serum pregnancy test (for women of childbearing potential)

- Attestation that an acceptable radiotherapy treatment plan has been generated. Guidelines defining a dosimetrically "acceptable" radiation plan are described in Section 9.3 and 9.4. The treating radiation oncologist must confirm whether an acceptable multi-beam IMRT plan was generated or not by signing the patient's treatment plan. If an acceptable plan cannot be generated then the patient is scored as a failure for feasibility purposes and is no longer in this study
- Mammogram (any time prior to treatment. Only applicable for patients with intact breasts)
- History and physical exam in Radiation Oncology (no more than 120 days prior to the start of radiation therapy)

9.0 TREATMENT/INTERVENTION PLAN

9.1 Simulation

These simulation procedures generally represent our standard simulation procedures for comprehensive radiation therapy.

9.1.1 In order to develop a conformal treatment plan, all patients will undergo a CT simulation. IV contrast is not necessary for simulation.

9.1.2 All patients will undergo simulation in the treatment position with both upper extremities extended above their head using an Alpha Cradle (Alpha Cradle, Smithers Medical Products, North Canton, OH) or slant board immobilization.

9.1.3 The medial, lateral, superior, and inferior borders of any residual breast tissue and chest wall on the patient's skin will be marked prior to simulation scanning.

9.1.4 Patients will be scanned from the base of skull through 5 cm below the clinically marked inferior port edge.

9.2 Virtual Simulation

9.2.1 The CT scan will be exported to a commercial virtual simulation software package. Normal structure and treatment volume contours will be delineated.

9.2.2 The following structures will be contoured with name allocation exactly as written in protocol. Standard contouring techniques in virtual simulation will be used to define these structures:

1. "Heart"
2. "The Planning Target Volume" (PTV)
3. "Contralateral breast"
4. "Thyroid"
5. "Right Lung"
6. "Left Lung"
7. "Humerus"
8. "Cord"

The PTV is defined as any residual breast tissue, chest wall, ipsilateral axillary lymph nodes, ipsilateral supraclavicular lymph nodes, ipsilateral infraclavicular lymph nodes, ipsilateral interpectoral lymph nodes, and ipsilateral internal mammary lymph nodes. Anatomic guidelines for defining these

boundaries have been extensively described by Dijkema et al(52). Several figures and a description of nodal boundary guidelines are included in Appendices 4 and 5.

9.3 Radiation Dose, Fractionation, Energy, and Parameters

9.3.1 The image and contour data will be exported to the treatment-planning system as appropriate where treatment planning and multi-beam IMRT optimization will occur. Optimization will be guided by the target tissue coverage and normal tissue avoidance parameters described below. All dose constraints must be within 2% of the given value.

9.3.2 The prescribed dose for all patients will be 5000 cGy in 25 fractions. 95% of the PTV will be prescribed to receive ≥95% of the prescription dose. The maximum allowed heterogeneity will be limited to less than 5% of the PTV receiving greater than 110% of the prescription dose. Photons with energy of 6 MV will be used.

9.3.3 The following normal tissue limits will be used to optimize treatment planning. These limits were derived from a preliminary dosimetric study utilizing multi-beam IMRT treatment planning for comprehensive breast and nodal RT performed at Washington University(46).

Ipsilateral Lung V20	≤30%
Ipsilateral Lung mean dose	≤2200 cGy
Contralateral Lung V20	≤8%
Heart V25	≤25%
Heart mean dose	≤2000 cGy
Heart maximum dose	≤5300 cGy

9.3.4 The number of gantry angles used for the multi-beam IMRT plan will be optimized for each patient but will generally range between six and twelve beams. The multi-beam IMRT plans will be delivered using dynamic multileaf collimators.

9.3.5 Some patients will receive a boost to part of the residual breast tissue. The decision to employ a boost will be made by the treating physician based on patient-specific criteria. The boost will be delivered sequentially, following multi-beam IMRT to the breast and regional lymph nodes.

9.4 Treatment Plan Evaluation

The treatment plan will be evaluated by the treating physician prior to treatment in order to ensure that all treatment parameters have been met. Isodose curves and dose volume histograms (DVH) will be analyzed. Evaluation criteria will include:

1. Isodose curves:

   a. The 95% isodose line must generally conform to the PTV with visually acceptable target volume coverage and visually acceptable critical structure avoidance.
   b. The 110% isodose line must not include any critical structure volumes.

2. Dose-Volume Histogram (DVH):

a. The maximum allowed heterogeneity will be limited to less than 5% of the PTV receiving greater than 110% of the prescription dose.
b. PTV DVH must meet all prescription parameters.
c. Critical structure DVHs should meet constraint parameters (described in Section 9.3.3).

If a dosimetrically acceptable multi-field plan cannot be generated for an individual patient, she will be treated with our conventional technique of simplified IMRT.

9.5 Radiation Therapy Daily Treatments and Quality Assurance

9.5.1 Patients will receive external beam treatment once a day, 5 days a week for approximately 5 weeks. All missed radiation treatment visits will be made up. Daily set-up error will be minimized by the aforementioned clinically approved and commercially available patient setup techniques: AlignRT or KV imaging with orthogonal pair films will be performed. Generally, standard skin alignment marks are initially used to position patients. To increase accuracy of treatment delivery, AlignRT or KV films are subsequently taken. The patient is then shifted into the proper position and treatment is delivered.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Tests and Observation	Pre-Treatment	During IMRT	Completion of IMRT (COT)[4]	6-12 weeks after CoT	5-7 mo after CoT	Follow up [1]
History	X[2]			X	X	X
Physical	X[2]	X[5]	X	X	X	X
(Feasible Plan Generated/Delivered	X					
Daily Setup Data			X			
PFTs	X				X	
BMI	X					
Mammogram[3]	X					X
Clinical Assessment of Acute Skin Toxicity		X[5]	X	X		
Late Subcutaneous Fibrosis					X	X
Late Cutaneous Toxicity					X	X

Clinical Assessment of RP				X	X	X
RP CAP Questionnaire	X			X	X	X
BreastQ Questionnaire (for mastectomy patients)	X				X	
Pregnancy test (if relevant)	X					

[1]Patients will be seen at 12-14 months following the CoT and then every 6-8 months for up to 5 years of follow up.
[2]Done within 120 days of RT start
[3]Mammogram at baseline and then annually or more often if clinically indicated (only applicable for lumpectomy patients). The annual mammogram will be based on the patient's last follow up mammogram (+/- 1 month window). For patients found to have distant metastasis after treatment, annual mammograms will no longer be required.
[4] Done ±10 days of the last radiation treatment (CoT)
[5] Done at least two times during radiation treatment including the CoT timepoint

10.1 Evaluations During Treatment

All patients will undergo an interview and physical examination a minimum of two times during radiation treatment. The maximum toxicities graded by CTCAE will be submitted to the Research Study Assistant at the Completion of IMRT Treatment (CoT). CoT is defined as within ten days of the last radiation treatment.

10.2 Evaluations After Treatment

Patients will have follow-up visits with physical examinations at 6-12 weeks, 5-7 months, and 12-14 months following the completion of radiation therapy. PFTs will be repeated at 5-7 months following CoT. Mammograms will be obtained annually (for patients with intact breasts) or more frequently if clinically indicated. The annual mammogram will be based on the patient's last follow up mammogram with a +/- 1 month window. For patients found to have distant metastasis after treatment, annual mammograms will no longer be required.

More frequent follow-up visits are at the discretion of the treating physician. After the follow-up visit that occurs 12-14 months after CoT, patients will be seen at a minimum of every 6-8 months until 5 years of follow up after CoT. The patient will be asked to complete the CAP questionnaire at each follow up visit when she sees the radiation oncologist.

Patients who cannot make their follow-up appointments have the option of conducting these visits over the phone. Visit requirements that cannot be assessed by phone will be eliminated for these visits. However, the 5-7 month PFT must be completed.

10.4 Evaluations of Early and Late Toxicity

The CTCAE version 3.0 scale will be used. The portions of the CTCAE relevant to this study are available in Appendix 1. The grading scale for other toxicities that are not appropriately measured by CTCAE is available in Appendix 2.

11.0 TOXICITIES/SIDE EFFECTS

Patients will be assessed for toxicities related to radiation treatment. Potential acute side effects include skin reactions, erythema, edema, hyperpigmentation, desquamation, fatigue, and/or RP. The incidences of these side effects with conventional radiation techniques to the breast and lymph nodes are described in Section 3.2.1.

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.

Patients will be assessed for late toxicities (>3 months post radiation) as described in Section 3.2.2, including skin toxicity and/or RP. Toxicities will be scored according to the CTCAE, version 3.0 criteria.

No side effects are expected to result from the daily imaging used for target localization.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Assessment of Primary Objective

The study will be deemed infeasible if greater than 10% of enrolled patients in each group have at least one of the following outcomes:

a. Treatment cannot be administered to 10 patients because a dosimetrically satisfactory treatment plan could not be devised secondary to her anatomy. Before radiation therapy begins the treating radiation oncologist must document whether the treatment plan is dosimetrically satisfactory.

b. By the time the patient has completed the 5-7 month follow-up, the patient develops CTCAE version 3.0 grade ≥3 RP or any ≥grade 4 toxicities related to treatment.

12.2 Assessment of Secondary Objectives

Various metrics will be gathered at the following times: Pre-treatment (defined as within 45 days prior to the start of radiation treatment, excluding the History and Physical and mammogram), completion of therapy (done ± 10 days of the last radiation treatment), 6-12 weeks following CoT, 5-7 months following CoT, and 12-14 months following CoT. These metrics are described below.

a. To evaluate the rate and severity of both acute and late cutaneous toxicity

The radiation oncologist will score cutaneous toxicity at the end of treatment (±10 days of the last radiation treatment) and at 6-12 weeks following CoT. Late cutaneous toxicity will be scored at 5-7 months and 12-14 months following CoT, utilizing the CTCAE version 3.0 grading system. Some of these toxicities are not appropriately measured by the CTCAE and a more suitable scale is attached in Appendix 2.

b. To evaluate the rate and severity of late subcutaneous fibrosis

The radiation oncologist will score late subcutaneous fibrosis at 5-7 months and 12-14 months following CoT, utilizing the CTCAE version 3.0 grading system. Some of these toxicities are not appropriately measured by the CTCAE and a more suitable scale is attached in Appendix 2.

c. To evaluate the rate and severity of RP.

RP rates will be assessed by CTCAE version 3.0 grading system at 6-12 weeks, 5-7 months and at 12-14 months following CoT. We will also administer the CAP questionnaire pretreatment, at 6-12 weeks, 5-7 months and at 12-14 months following CoT. PFTs will be obtained at pretreatment and 5-7 months following CoT.

d. To evaluate local-regional control rates

Locoregional recurrence is defined as tumor in the ipsilateral breast/chest wall and/or ipsilateral regional lymph nodes (axillary, supraclavicular or internal mammary). Time to local recurrence will be calculated from the date of the completion of radiation treatment to the date of the biopsy proving recurrence or the first CT, PET, or MRI scan demonstrating recurrence. Kaplan-Meier methods will be used to assess local-regional control.

e. To evaluate patient set-up reproducibility in breast cancer patients treated with multi-beam IMRT using daily 3D position verification.

Standard skin marks for positioning patients for external beam radiation therapy will be applied during the simulation process. These marks will be used by radiation therapists to initially position patients in the treatment unit. AlignRT or KV imaging with orthogonal films will then be taken and used to accurately position the patient for treatment. The difference in initial set up and final set up will be recorded in mm on a daily basis. Basic descriptive statistics will be tabulated after the CoT.

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 the patient will be removed from the study.

14.0 BIOSTATISTICS

The purpose of this pilot study is to assess the feasibility of utilizing multi-beam IMRT in the adjuvant treatment of the breast and regional lymph nodes of women with node-positive breast cancer requiring coverage of the internal mammary lymph nodes. Infeasibility is defined in Section 12.1 in detail. A feasibility rate of at least 90% is required, ie, treatment can be successfully planned and delivered for at least 90% of the patients.

For this study, we require 100 evaluable patients for analysis of the primary endpoint. We define a patient who is evaluable for analysis as one who has completed their 5-7 month follow-up and 5-7 month PFT. A patient is inevaluable for analysis if he or she is not able to complete the 5-7 month follow-up and 5-7 month PFT. According to our experience, since there may be patients enrolled on study who are later found to be inevaluable, our maximum target accrual is 120 patients. However, if we are able to accrue 100 evaluable patients before we reach the maximum target accrual, we will close the study to accrual.

The multi-beam IMRT method is considered feasible if the treatment plan can be attempted for at least 90 patients among the 100 patients to be treated and evaluated. With this rule, the probability of considering the multi-beam IMRT feasible is 99%, 58%, 10% and 0.6% if the true feasibility rate is 0.95, 0.90, 0.85 and 0.80, respectively. An exact 95% confidence interval for the feasibility rate will also be

computed using the binomial distribution. With the sample size of 100 patients, and assuming for example the observed feasibility rate is 90%, the resulting confidence interval will be (84%, 95%).

For the secondary objectives, we will use descriptive summary for most endpoints and apply appropriate tests when necessary. Specifically, the demographic and clinical characteristics of the sample will be summarized by descriptive statistics. The number and reasons of infeasible patients will be tabulated.

1) The incidences of acute and late cutaneous toxicity and its 95% confidence intervals will be calculated.

2) The incidences of acute and late subcutaneous fibrosis and its 95% confidence intervals will be calculated.

3) The incidences of acute and late RP and its 95% confidence intervals will be calculated.

4) The local-regional recurrence rate associated with using multi-beam IMRT will be estimated using the Kaplan-Meier product limit method. If competing risks are present in the data (eg, patients may die without any recurrence), we will modify the analysis plan to accommodate the competing risks.

5) To evaluate patient set-up reproducibility in breast cancer patients treated with multi-beam IMRT using daily 3D position verification, the difference in initial set up and final set up will be recorded in mm on a daily basis. Basic descriptive statistics will be tabulated at the CoT.

Because the Grade 4 toxicity rate is expected to be very low, safety is not a major issue for this study. Therefore a stopping rule is not needed here.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. 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. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

This is not a randomized study.

16.0 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC 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. Standardized Case Report Forms (CRFs) that meet the requirements for MSKCC data reporting have been generated for this study.

16.1 Quality Assurance

Weekly 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 two times per year, more frequently if indicated.

16.2 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 (eg, 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.

Incentives: No incentives will be offered to patients/subjects for participation in the study. Patients may be eligible for other investigational studies.

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.

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.

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgement, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols:

The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

17.2.1

Because this is not an Industry or Cooperative group protocol, the SAE reporting information is the same as in 17.2.

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.

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.

19.0 REFERENCES

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20.0 APPENDICES

Appendix 1 – Toxicity CTCAE version 3.0

Appendix 2 – Grading Scale for Other Toxicities

Appendix 3 – CAP score calculation scheme

Appendix 4 – Planning Target Volume Contouring Guidelines

Appendix 5 – Figures

Appendix 6 – Breast Q Questionnaire Mastectomy

Appendix 7 – Breast Q Questionnaire Reconstruction