University of Pennsylvania

A FEASIBILITY AND PHASE II TRIAL OF ACCELERATED PARTIAL BREAST IRRADIATION USING PROTON THERAPY FOR WOMEN WITH STAGE 0-IIA BREAST CANCER

Principal Investigator: *Gary Freedman, MD*
Radiation Oncology
Hospital of the University of Pennsylvania
PCAM/ TRC4 West
3400 Civic Center Blvd
215-615-6767
Gary.freedman@pennmedicine.upenn.edu

Sub-Investigator: *Neil Taunk, MD*
Radiation Oncology
Hospital of the University of Pennsylvania
PCAM/ TRC4 West
3400 Civic Center Blvd
215-615-6767
Taunk@pennmedicine.upenn.edu

Collaborators: *Julia Tchou, MD*
Kevin Fox, MD
Angele DeMichele, MD
Angela Bradbury, MD
Susan Domchek, MD
Amy Clark, MD
Rosemarie Mick, MS

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CONFIDENTIAL

Table of Contents

LIST OF ABBREVIATIONS

APBI: Accelerated Partial Breast Irradiation
BCT: Breast-Conserving Therapy
BCTOS: Breast Cancer Treatment Outcomes Scale
EBRT: external beam radiotherapy
Gy: Gray
CGE: Cobalt Gray Equivalent
LET: Linear Energy Transfer
RBE: Relative Biologic Effectiveness
RT: Radiation Therapy
SOBP: Spread Out Bragg Peak
OER: Oxygen Enhancement Ratio

Study Summary

Title	*A feasibility and phase II trial of accelerated partial breast irradiation using proton therapy for women with stage 0, I, and II breast cancer.*
Short Title	*Proton Radiotherapy for APBI in Early Stage Breast Cancer*
Protocol Number	*UPCC# 04113; IRB# 817359*
Phase	*Feasibility/Phase II*
Methodology	*Open*
Study Duration	*8 years*
Study Center(s)	*University of Pennsylvania*
Objectives	1. *The primary objectives are to determine feasibility and the acute toxicity profile of accelerated partial breast radiation using protons.* 2. *Additional objectives of late toxicities, cosmesis, and clinical efficacy are evaluated in these patients on the phase II portion of the trial.*
Number of Subjects	*12 patients are included in the feasibility study* *45 additional patients are enrolled in the phase II study*
Diagnosis and Main Inclusion Criteria	*Stage IA- IIA breast cancer and Stage 0 DCIS*

1 Introduction

1.1 Breast Conservation

Breast conserving therapy (BCT) has been conclusively shown in multiple randomized controlled trials to provide outcomes that equal to mastectomy in terms of disease-free and overall survival (1, 2). There may also be for most women improved quality of life from organ preservation. On this basis the NCI has designated BCT as an equal alternative option for treatment for the majority of women with early stage invasive breast cancer (3).

Despite the demonstrated equivalence in survival and potential for improved quality of life for women treated with BCT, mastectomy rates remain high (4, 5). The causes of the apparent underuse of BCT are likely multifactorial. One significant barrier to the more widespread application of BCT may be the inconvenience associated with breast radiotherapy which traditionally has been administered over a period of 5-7 weeks. The inconvenience associated with a 5-7 week course of RT may also be a contributing factor to the substantial problem of omission of RT in women who undergo breast-conserving surgery but nevertheless fail to complete a course of breast RT (6, 7).

1.2 Whole Breast Hypo-fractionation

In recent years, research efforts have focused on expanding access to RT and decreasing cost by decreasing the length of time required to complete the course of treatment. One approach has been increasing fraction size for daily radiation and reducing the total number of treatments. This approach, called whole-breast hypofractionation, continues to make the target for radiation the whole-breast.

Investigators from Canada and the Great Britain have conducted studies of hypofractionated radiotherapy, in which irradiation of the whole breast is accomplished in a shorter period of time (3-5 weeks) by increasing the fraction size and decreasing the total number of fractions (8-10). In each of these studies, the goal was to deliver a hypofractionated dose schedule that is biologically equivalent to the standard fractionation breast dose of 50 Gy in 25 fractions of 2 Gy. With 5-10 year follow-up of these studies, there has been similar in-breast local control between the hypofractionated and standard fractionated arms. These studies have also reported equal cosmetic and quality of life outcomes.

Whether these results of whole-breast hypofractionation improve the utilization of BCT, or the utilization of postoperative radiation after lumpectomy, remains to be seen. However, the shortening of treatment length to 3-5 weeks from 6-7 weeks may not be the limit of our ability to shorten treatment time. And in many women with small, favorable breast cancers, the question still remains whether the whole breast needs to be the target for irradiation. While there was good rationale for replacing one whole breast treatment (mastectomy) with another (whole breast radiation), a significant number of women may have more limited disease that could be treated by a more targeted approach to only a small portion of the breast.

1.3 APBI

Another promising approach to shortening the course of radiation length has been to reduce the target volume from the whole breast to a limited volume of tissue surrounding the lumpectomy cavity alone. The use of radiation therapy limited to the region of the tumor bed, or partial breast irradiation, is currently a subject of great interest to the international community of breast cancer surgeons and radiation oncologists. The rationale for APBI arose from the observation that the vast majority of local recurrences in women with biologically favorable breast cancers appear to be confined to the tumor bed (11-14). Partial breast irradiation is usually delivered with hypofractionation, or use of greater than a standard 1.8 - 2 Gy fraction sizes per day, to shorten overall treatment time. This combination gives rise to the term accelerated partial breast irradiation (APBI).

ABPI has many potential benefits to patients and providers of breast cancer treatment. APBI is intended to improve the convenience of radiation therapy as a part of breast conservation by reducing the treatment time required to 5 days. The advantages also include greater convenience for patients, increased utilization of existing radiation resources, and the potential for reduced cost. APBI could also increase the overall utilization of breast conservation and postoperative radiation in eligible women who might otherwise choose mastectomy or lumpectomy without radiation rather than undergo a long course of radiation. Because APBI limits radiation to the region of the primary tumor alone with a small margin, and omits radiation to other quadrants of the breast, there is also the theoretical potential for salvage of in-breast local recurrences by repeat use of lumpectomy and APBI (particularly for recurrences away from the area of previous high dose APBI). This last possibility is the subject of an ongoing RTOG trial.

The major techniques of APBI can be divided into external beam radiation therapy or delivery of radiation through sources placed inside temporary internal catheters (brachytherapy). There are advantages and disadvantages to each method.

- The method with the longest duration of follow up is interstitial breast brachytherapy. This method uses interstitial catheters placed in the breast either at the time of lumpectomy or at a later date. Despite providing excellent coverage of the tumor bed with a reasonably homogeneous dose distribution, interstitial breast brachytherapy has never been widely adopted because it is time-consuming, invasive, and requires a highly skilled operator. This also may be restricted if there is small breast size, difficult lumpectomy cavity geometry or narrow balloon distance from the skin. The catheter protrudes form the breast for the entire course of treatment, and therefore may cause discomfort, inconvenience to the patient, and possible infection.
- To address these shortcomings, the MammoSite catheter, a single lumen HDR brachytherapy catheter housed within a saline-inflated balloon, was developed. The FDA approved the device in May 2002 and it rapidly supplanted interstitial-catheter based breast brachytherapy. Since that time a number of other non-interstitial brachytherapy catheters have been developed which attempt to improve upon the original MammoSite catheter in a number of ways. The Contura and MammoSite ML catheters employ multiple channels that allow for reduction in dose to the skin and/or chest wall by adjusting the dwell times in each channel. The Savi catheter uses a cage-structure rather than a saline filled balloon; its purported advantage is that it more closely resembles interstitial brachytherapy and that it eliminates the problem occasionally encountered

with balloon-based systems of non-conformance of breast tissues to the surface of the balloon.

- As a result of the aforementioned drawbacks of catheter-based brachytherapy, an alternative method of delivering APBI has been with 3D-conformal external beam radiotherapy (3D-CRT). This technique typically utilized 3-5 photon and/or electron fields that converge on the tumor bed. In the ongoing RTOG randomized trial of WBI versus APBI, approximately 2/3 of patients randomized to receive APBI have in fact been treated with the 3D-CRT approach. External beam radiation has the obvious advantage of being non-invasive, flexible to cover unusual geometry of the lumpectomy cavity, and may treat a wide rim of normal tissue at risk for microscopic disease around the lumpectomy cavity. The chief disadvantage with photon external beam radiation is the higher relative dose given to other quadrants of the breast compared to the highly conformal and localized dose possible with internal radiation sources or proton beam radiation.

1.4 Problems with Current External Beam APBI Techniques

Despite its increasing popularity, concerns have been raised about the potential short and long-term toxicity of the 3D-CRT approach to ABPI. Although the photon beams do indeed converge on the tumor bed, they enter and exit through substantial volumes of normal breast tissue. The result is that a large volume of breast tissue receives low to moderate doses of radiation and the volume of breast tissue receiving the prescription dose is considerably in excess of the planning target volume (PTV).

On RTOG 04-13, a randomized trial of whole-breast versus partial breast irradiation, the normal tissue constraints allowed up to 60% of the whole breast reference volume to receive 50% of the prescription dose and up to 35% of the whole breast to receive up 100% of the prescription dose. Despite utilizing these constraints, a trial conducted at the University of Michigan of APBI using IMRT and respiratory motion control had to be terminated early when 7/34 patients developed new unacceptable cosmesis at a median follow-up of 2.5 years (15). Investigators at Tufts University and Brown also found high rates of soft tissue toxicity when following these parameters for external beam photon APBI (16).

In addition to treating large volumes of normal breast tissue, the 3D-CRT method may also result in significant exposure of the ipsilateral lung, or in patients with left-sided breast cancer the heart. Patients treated on a phase II trial of ABPI at Harvard experienced a higher than expected rate of radiation pneumonitis (17).

1.5 ASTRO Consensus Statement on APBI

Clinical experience with APBI has so far resulted in low local recurrence rates, although the length of follow-up in most studies is short (18-22). These favorable outcomes have been achieved using careful clinicopathologic selection factors that usually include small, unifocal cancers, nonlubular, and without an extensive intraductal component. The degree to which age or adverse pathologic features such as extensive intraductal component, lobular carcinoma in situ, or basal-like molecular profile will influence local control are unknown.

A consensus group by ASTRO has published recommendations regarding APBI outside of a clinical trial (23). A most suitable group was considered women age ≥ 60 years, with no known BRCA mutation, T1 (≤ 2 cm size), > 2 mm margins, lymphovascular space invasion not present, ER positive, unicentric, invasive ductal or other favorable histology, extensive intraductal component not present, and lymph nodes negative for metastases. Other patients with less favorable features were either considered cautionary or unsuitable outside of a clinical trial. Similar patient and tumor-related characteristics were used to define a low risk subgroup of patients who could be good candidates for APBI by the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (Polgar et al 2009) but the age parameter was defined as > 50 years.

Our trial originally excluded lobular histology for two reasons: one that there was relatively little data on outcomes for invasive lobular with partial breast radiation, and two because the ASTRO consensus placed this histology in the category of cautionary outside of a clinical trial (likely due to that relative lack of data). There have since been published 2 randomized trials from Europe showing 5-year non-inferiority to partial breast compared to whole breast radiation. The GEC-ESTRO trial had a patient make-up of approximately 10-13% lobular, the Florence Italy trial about 10-15% lobular or mixed ductal and lobular. There were no differences seen by histology in those 2 randomized trials.

1.6 Rationale for Protons

The goal of radiation therapy is to deposit most of the dose to the target while minimizing the dose delivered to the surrounding normal tissues. Conventional photon radiotherapy deposits its dose along the entire beam path to the tumor or target volume as well as beyond the depth of the target. Techniques to minimize the dose to surrounding tissues such as using multiple beam angles and modulating the intensity of the radiation delivered through each beam have been utilized; however, these techniques still entail both an entrance dose to normal tissue as it penetrates to reach a tumor at depth in tissue, and an exit dose as it exits the body in a straight path beyond the tumor. Proton radiotherapy differs from photon radiotherapy in that most of the energy is deposited at a specific depth known as the Bragg peak. The dose immediately beyond the Bragg peak is essentially zero, which allows tissues on the posterior side of the tumor to be spared. The clinical application of protons provides an improvement over photons in the ability to deliver a high-dose-volume to any configuration within an anatomical site while maintaining lower doses to surrounding normal tissues, resulting in decreased short- and long-term morbidity, due to the unique Bragg Peak phenomenon of the dose distribution of protons. Theoretically, this should ease the current limitation of normal tissue tolerance as a dose-limiting factor, particularly for larger tumors, as well as allow greater dose to be delivered to the tumor/target volume.

Protons have a similar biologic effect to photons against tumors. The biological effect of radiation is dependent on its linear energy transfer (LET). LET is defined as the rate of energy transferred by ionizing radiation per unit path length. To compare different types of radiation, we use the relative biologic effectiveness (RBE), which is defined as the ratio of the dose of particle radiation to the dose of 60Co radiation producing the same biological endpoint. Standard photon radiation therapy has a RBE of 1.0; the RBE of protons is thought to be between

1.05 to 1.25 (24-26). A recent review of in vivo and in vitro experiments concluded that RBE varies with dose or dose per fraction and increases with an increasing depth in the spread out Bragg Peak (SOBP) and is most significant at the distal edge of the SOBP. Overall though, based on the data to date, an average RBE of approximately 1.1 in the entrance of the SOBP is reasonable to assume (27). The clinical advantage of proton beam radiotherapy over standard photon radiation results from the more favorable dose distributions achievable with its particular physical properties as previously described. The advantage of protons has been demonstrated for medulloblastoma and prostate cancer, and comparative treatment planning using protons versus photons has shown a clear advantage to protons in terms of dose distribution (28-33).

Proton therapy, due to its unique dosimetric characteristics, may offer women who are candidates for APBI the convenience and noninvasiveness of 3D-CRT combined with the superior conformality of brachytherapy. Because protons deposit dose at a finite range that depends on the energy of the beam, the exit dose seen with protons is dramatically reduced compared with photon therapy. A reduction in exit dose would be expected to significantly reduce the volume of normal breast tissue receiving the prescription dose and to dramatically reduce exit dose to the underlying heart and/or lung.

The group from Massachusetts General Hospital and Harvard has reported their intial dosimetric experience with proton APBI (34) and dosimetric comparison studies with protons versus photon APBI (35).

- In their first study (34), from March 2004 to June 2005, 25 patients with tumors < or =2 cm and negative axillary nodes were treated with proton APBI. The prescribed dose was 32 Cobalt Gray Equivalents (CGE) in 4 CGE fractions given twice daily. One to three fields were used to provide adequate planning target volume (PTV) coverage and dose homogeneity. Excellent target coverage and dose homogeneity were obtained in all patients with one to three proton beams. The median volume of nontarget breast tissue receiving 50% of the prescribed dose was 23%. Median volumes of ipsilateral lung receiving 20 CGE, 10 CGE, and 5 CGE were 0%, 1%, and 2%, respectively and contralateral lung and heart received essentially no radiation dose.
- In their second study (35), twenty-four patients with fully excised, stage I breast cancer treated with proton APBI had treatment plans generated comparing them to mixed-modality, photon-electron APBI. Proton APBI reduced the volume of nontarget breast tissue receiving 50% of the prescribed dose by an average of 36%. Proton APBI significantly reduced the volume of irradiated nontarget breast tissue, including ipsilateral lung, contralateral lung, and heart.

Moon et al. (36) reported a dosimetric study comparing four different methods of APBI in 30 patients. Proton beam APBI was superior to tomotherapy, intensity modulated radiation, and 3D conformal radiation in dose to breast tissue outside of the planning target volume. Protons also resulted in lowest ipsilateral lung dose and heart dose.

1.7 Clinical experience with Protons and APBI

The group from Mass General has reported their initial clinical experience (37) using proton beam radiation for APBI. 20 patients with Stage I breast cancer were treated with proton APBI

in a Phase I/II clinical trial. With a median follow-up of 12 months, no recurrent disease was detected. There was an unexpectedly high rate of acute skin toxicity: moderate to severe skin color changes developed in 79% of patients at 3 to 4 weeks and moderate to severe moist desquamation in 22% of patients at 6 to 8 weeks. Despite the severity of the acute skin toxicity observed in the trial, late effects appeared to be modest with only 3 patients developing telangiectasias, 3 patients reporting rib tenderness, and one patient developing a rib fracture. Nor did the severity of the acute skin toxicity appear to portend adverse cosmetic outcomes. With a median follow-up of 12 months (range 8-22 months), global breast cosmesis was judged by physicians to be good or excellent in 89% and 100% of cases at 6 months and 12 months, respectively. Patients rated global breast cosmesis as good or excellent in 100% of cases at 6 and 12 months. At last follow-up, 95% of patients reported total satisfaction with proton APBI.

The group from Loma Linda University Medical Center has reported the results of a phase II trial of proton beam APBI (38). Eligible patients included women with invasive breast cancer, nonlobular histology, size $\leq$ 3 cm, negative margins $\geq$ 2 mm, and negative axillary lymph nodes. Extensive in-situ ductal carcinoma was excluded. 40 Gy was given in 10 fractions over 2 weeks. 50 patients were enrolled. With a median follow-up of 48 months there were no local recurrences and one new breast primary in an adjacent quadrant more than 5 years after treatment. Acute toxicities were limited to mild grade 1 radiation dermatitis in 26 patients and grade 2 in 4 patients. Late skin toxicities included 3 grade 1 telangiectasias. There were no posttreatment infections or ulcerations and no cases of fat necrosis, rib fractures, radiation pneumonitis, or cardiac events. Ninety percent of patients rated their cosmetic result as good or excellent (54% excellent, 36% good) with the remaining ten percent fair.

The severity of the acute skin toxicity observed in the phase I/II trial from Harvard was likely the result of the treatment techniques used in that study. Patients were treated with only 1-3 fields, with the vast majority (84%) of the patients receiving treatment with only 1 or 2 fields. Furthermore, in patients treated with 2-3 fields, only one field was treated per fraction. In the Loma Linda study, 2 to 3 proton beam ports were used to treat patients, with at least 2 fields treated daily. Care was taken to minimize the volume of skin encompassed by the 90% isodose.

In the original Loma Linda partial breast experience with protons cited in the protocol, the fractionation used was 10 fractions over a 2-week course. While twice daily is the most common scheduled used for partial breast, allowing once daily fractionation could improve study enrollment by improving convenience for some patients unable/unwilling to wait in the department for a second treatment 6 hours apart each day.

In an effort to reduce the risk of skin toxicity observed in the Harvard study, investigators from MDACC developed a modified proton beam treatment approach employing 3-4 passive scattering beams that are individualized based on patient-specific anatomy and target location (39). In a planning study they generated comparative proton and photon APBI plans for 11 patients. The proton plans employed beam arrangement described above. The 3DCRT plans used 3-5 coplanar and noncoplanar beams. The target dose and specified normal tissue constraints followed the NSABP B-39/RTOG 0413 protocol. In contrast to phase I-II trial of APBI using proton therapy conducted at Harvard, in which doses to the skin were considerably higher with protons than photons and consequently high rates of acute skin toxicity were

observed, the MDACC planning study revealed that the dose to the skin was significantly reduced for protons compared with photons. Protons reduced the average V10, V30, V50, and V75 for breast skin by 47.3%, 39.9%, 27.8%, and 18.9% respectively; the V90 for breast skin was comparable for protons and photons. As expected, the dose to normal breast tissue, lung, and heart were also reduced with protons compared with photons. Treatment with protons resulted in absolute reductions in the V100, V90, V75, V50, and V20 for normal breast tissue of 3.4%, 8.6%, 11.8%, 17.9%, and 23.6%, respectively. The proton plan also significantly reduced the dose to the heart and lung. Analysis of the impact of range uncertainty and patient set-up uncertainty (including respiratory motion) revealed that the proton plans remained robust in the face of these uncertainties.

Although recent planning studies such as the one from MDACC described above have demonstrated the dosimetric advantages of protons beam ABPI over photon beam APBI with regard to sparing of normal tissues including the skin, clinical experience with proton beam APBI remains limited.

2 Study Objectives

The current protocol proposes to use proton beam radiation (which is approved by the U.S. Food and Drug Administration) for the adjuvant treatment of women with stage 0 DCIS or stage IA-IIA invasive breast cancer who have undergone breast-conserving surgery. The purpose is to establish the feasibility, efficacy, and safety of proton beam therapy for APBI.

2.1 Primary Objective

The primary objectives are to determine feasibility and the acute toxicity profile of accelerated partial breast radiation using protons.

2.2 Secondary Objectives

The secondary objectives of this study are to assess the late toxicities, cosmesis, and clinical efficacy of accelerated partial breast radiation using protons.

3 Subject Selection and Withdrawal

3.1 Inclusion Criteria

- Histologically confirmed diagnosis of invasive or non-invasive breast cancer.
- Invasive ductal, lobular, medullary, papillary, colloid (mucinous) or tubular histologies.
- AJCC T1 or T2; N0 or N1mic; Stage IA-IIA breast cancer or AJCC TIS (Stage 0) ductal carcinoma in situ without invasion
- Gross disease must be unifocal with pathologic (invasive and/or DCIS) tumor size 3 cm or less. (Patients with microscopic multifocality are eligible as long as total pathological size is 3 cm or less).
- Estrogen and/or progesterone receptor positive invasive breast cancer. DCIS stage 0 does not require receptor testing.

- No evidence of distant metastatic disease as documented by history and physical examination (radiographic staging only to be performed as indicated by symptoms or physical findings.)
- Patients must have an ECOG Performance Status of 0, 1 or 2
- Age ≥ 50.
- Patients must be able to provide informed consent.
- Patients must have undergone breast-conserving surgery
- All tumors (invasive and non-invasive disease) must be excised with a minimum margin width of ≥ 2 mm. Re-excision of surgical margins is permitted. Focally close (<2 mm) or positive (tumor cells at the inked edge of the specimen) margins determined to be at an anatomic boundary of resection by the surgeon, such as posterior fascia for posterior margins or skin for anterior margins, are also acceptable.
- Patients with invasive breast cancer must be node-negative (N0) or have only microscopic disease (≤2mm) in the nodes (N1mi). Patients with Stage IA – IIA are required to have axillary staging but it will not be done for patients with Stage 0 DCIS. Options for axillary staging include:
    1. Negative sentinel lymph node biopsy (SLNB)
    2. Level I-II axillary lymph node dissection (ALND) (6 or more nodes removed).
    3. Positive SLNB followed by completion ALND (6 or more nodes removed).
- Patients presenting with abnormal microcalcifications on a screening mammogram must have radiographically confirmed excision of the suspicious microcalcifications, either by specimen radiograph or post-biopsy mammograms.
- The patient must be enrolled on the study within 60 days following the last surgery for breast cancer (lumpectomy, re-excision of margins, or axillary staging procedure).
- The target lumpectomy cavity must be clearly delineated and the target lumpectomy cavity/whole breast reference volume must be ≤ 30% based on the postoperative/pre-enrollment CT scan.
- Patients must have imaging (mammogram or breast MRI) of both breasts, unless opposite breast absent, within 6 months of diagnosis of their breast cancer.CBC/differential obtained within 6 months prior to registration on study, with adequate bone marrow function defined as follows: Absolute neutrophil count (ANC) ≥ 1,800 cells/mm3; Platelets ≥ 75,000 cells/mm3; Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable).
- Patients with synchronous bilateral breast cancers who will be treated with radiotherapy to each breast are eligible, provided such treatment can be performed in a manner that avoids overlap between treatment fields. Both sides may be treated with APBI if the pathologic eligibility criteria are met for both tumors, or only one side may be treated with APBI if the criteria are met for only one tumor.
- Patients with a history of prior breast cancer in the opposite breast are eligible as long as treatment can be performed without overlapping any prior RT fields.
- Patients with a history of prior breast cancer in the ipsilateral breast treated with lumpectomy alone (no RT) are eligible as long as the other entry criteria for this study are met.
- Patients with a history of non-breast malignancies are eligible as long as they have not received prior radiotherapy to the thoracic region, and have a greater than 2 year interval without evidence of recurrence.

- Women of childbearing potential must be non-pregnant and non-lactating and willing to exercise an effective form of birth control during radiation therapy (e.g. oral contraceptive, IUD, condoms or other barrier methods etc.). Hysterectomy or menopause must be clinically documented.
- Patient must provide study-specific informed consent prior to study entry

3.2 Exclusion Criteria

- Male breast cancer
- T2 (>3cm), T3, T4, Node positive (other than N1mi), or M1 disease
- Multifocal primary tumor.
- Clear delineation of the extent of the lumpectomy cavity is not possible.
- Prior or simultaneous malignancies within the past two years (other than carcinoma in situ of the cervix, CIS of the colon, melanoma in situ, thyroid cancer, and basal cell or squamous cell carcinoma of the skin).
- Any non-axillary sentinel node(s) positive. (Note that intramammary nodes are staged as axillary nodes).
- Patients who have had a positive SLNB but decline completion ALND are not eligible.
- Patients treated with neoadjuvant chemotherapy are not eligible.
- Palpable or radiographically suspicious ipsilateral or contralateral axillary, supraclavicular, infraclavicular, or internal mammary nodes, unless there is histological confirmation that these nodes are negative for tumor.
- Suspicious microcalcifications, densities, or palpable abnormalities (in the inpsilateral or contralateral breast) unless these were biopsied and found to be benign.
- Proven multicentric carcinoma (invasive cancer or DCIS) in more than one quadrant or two or more breast cancers not resectable through a single lumpectomy incision.
- Paget's disease of the nipple.
- Surgical margins that cannot be microscopically assessed or are positive at pathological evaluation. A focally positive margin determined to be at an anatomic boundary of resection by the surgeon, such as posterior fascia for posterior margins and skin for anterior margins, is also acceptable. If surgical margins are rendered free of disease by re-excision, the patient is eligible.
- Breast implants. (Patients who have implants removed are eligible).
- Prior ipsilateral breast or thoracic radiation for any condition.
- Collagen vascular disease, specifically dermatomyositis with a CPK level above normal or with an active skin rash, systemic lupus erythematosis, or scleroderma.
- Pregnant women, women planning to become pregnant and women that are nursing.
- Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements.
- Actively being treated on any other therapeutic research study.

3.3 Subject Recruitment and Screening

Subjects will be recruited from the Surgical, Radiation, and Medical Oncology practices at the Hospital of the University of Pennsylvania and from Network Sites of the University of

Pennsylvania Department of Radiation Oncology. The treating radiation oncologist will determine if the patient is a potential research candidate and has the capacity to consent. The treating radiation oncologist will approach and inform the patient about the study, thereby initiating the informed consent process. If the patient expresses interest in the study, the treating radiation oncologist will contact a qualified member of the research team in the Radiation Oncology department at the University of Pennsylvania and request availability for enrollment. Should slots be available, a qualified member of the research team will continue the formal consent process. This person will explain the requirements of the study and provide a copy of the Informed Consent Form. The person obtaining consent will state the volunteer nature of research and advise the subject to take sufficient time to discuss the study before making her decision to sign the informed consent document. If a decision to participate is made, the informed consent form is signed after which screening procedures will be performed. Patient eligibility will be evaluated based upon the criteria outlined in Section 3.1 and Section 3.2. After eligibility is established, a subject study number will be issued. Eligibility is confirmed with the study investigator. All members of the research team will have successfully completed patient oriented research training. **Subjects will receive all treatment in the Radiation Oncology Clinic of the University of Pennsylvania.** Subjects will not be paid for participating in the study. All medical costs will be the responsibility of the subjects and/or their insurers. Cost of living expenses will be the responsibility of the subjects.

At the Hospital of the University of Pennsylvania, we currently treat approximately 150 cases of stage 0-II breast cancer per year with radiation as a part of BCT. We anticipate that with the availability of proton radiotherapy, these numbers may increase. We estimate an annual accrual of 10-12 subjects per year. Following its approval by the IRB, this protocol will be listed on our website. Physicians within the Penn Radiation Oncology Network sites and our referring physicians will also be informed about the availability of this study.

3.3.1 Inclusion of Minorities

The University of Pennsylvania Cancer Center reports that minorities accounted for 14% of all patients (adult and pediatric) enrolled on therapeutic clinical trials. Furthermore, it is estimated that approximately 30% of cancer patients admitted to the Hospital of the University of Pennsylvania are minorities (Source: University of Pennsylvania Cancer Center Grant).

The University of Pennsylvania Cancer Center has developed a number of minority outreach strategies. These include development of relationships with local community organizations, presentations or distribution of materials to local groups regarding trials, advertisements in minority newspapers and magazines, and presentations to professional organizations. If under-accrual of minority subjects is determined to be a problem, we will employ these methods to improve accrual.

3.3.2 Vulnerable Populations

Children, pregnant women, fetuses, neonates or prisoners are not included in this research study.

3.4 Early Withdrawal of Subjects

3.4.1 When and How to Withdraw Subjects

- Recurrent or Progressive Disease: Subjects who have clinical or radiologic evidence of recurrent disease will undergo an evaluation to document the nature of the abnormality. If recurrent or progressive cancer is diagnosed, the subject will be considered off study at that time but all efforts will be made to follow patients for survival for as long as the patient chooses to be clinically followed.

- At the discretion of the Principal Investigator: Subjects may be withdrawn at any time during the study if the PI believes it is in the subject's best interest. In this event, the reasons for withdrawal will be documented.

- Treatment is interrupted for reasons of treatment-related toxicity for more than 5 days.

- Subject Participation: Refusal to continue treatment, follow-up, comply with the protocol or withdrawal of consent. In this event, the reasons for withdrawal will be documented.

- Any grade 4 toxicity thought to be definitely or probably caused by the treatment

Once the subject has discontinued treatment, the primary reason for discontinuing treatment must be clearly documented in the subject's records and on the CRF. The investigator will assess each subject for response at the time of withdrawal.

Every effort will be made to follow subjects off study for toxicity and survival. Acute toxicities will be assessed for 60 days from the last date of treatment. Survival will be followed for a minimum of 5 years.

4 Radiation Therapy

4.1 Treatment Planning, Imaging and Localization Requirements

All subjects will be immobilized on an angled breast board in the supine position. Patients may be positioned with alpha cradle casts, adjustable breast boards, wing boards, vac-loc, or other methods of immobilization at the discretion of the treating physician. All immobilization devices will be located outside of the treatment beam. Arms should be in an up position in order to eliminate CT scan artifacts from the humerus and be located outside of the treatment beam.

4.1.1 Radio-opaque markers may be placed on external landmarks at the time of CT for radiation planning at the direction of the treating physician.

4.1.2 A treatment planning 4DCT and /or breathold and free breathing scans in the treatment position will be required to define the clinical target volumes (CTV, iCTV) and planning target volumes (PTV). This CT must be post-lumpectomy. The CT should extend cephalad to start at or above the mandible and extend sufficiently caudally (or inferiorly) to the

inframammary fold to encompass the entire lung volume. A CT scan image thickness of ≤ 0.3cm should be employed or as specified by the Proton Scanning Protocol. All CTs scans (freebreathing, 4D and breatholding) employed for dose calculation during the treatment planning process should be acquired without contrast. All scans which require contrast to define gross target volume (GTV) and clinical target volume (CTV) have to be acquiered after the planning CT was obtained. All CT scans should be acquired with the subject in the same position and using the same immobilization device as for treatment. Treatment planning will be done using a 3D based CT treatment planning system. All tissues to be irradiated must be included in the CT scan. Based on the 4DCT evaluation an active motion management should be employed for target motion > 1cm for passive scattering proton techniques or as indicated by the planning protocol for pencil beam scanning techniques. Treatment planning will be performed on the average CT data set or breathold CT data set.

4.1.3 External skin localizing marks, which may include permanent tattoos, are recommended for radiation daily localization and set-up accuracy.

4.2 Target Contouring

Target contouring follows the general guidliness enclosed bellow for breathold based delivery. For 4DCT all target structures will be derived based on the target motion during the breathing cycle (inhale, exhale phase) on the average CT.

4.2.1 The Gross Tumor Volume (GTV) is defined as the boolean volumetric combination of the seroma (radiographic abnormality seen in the breast corresponding with fluid and/or scar tissue in the lumpectomy cavity) and surgical clips (or other fiducial markers) as determined from CT, MRI, and other relevant clinical information.

4.2.2 The Clinical Target Volume (CTV) is defined as the GTV with a margin of 15 mm to account for microscopic disease extension of disease. However, the CTV will be limited to 5 mm from the skin surface and limited posteriorly at the boundary of the breast tissue extent at the pectoral muscle (chest wall and pectoralis muscles are not to be included).

4.2.3 The Planning Target Volume (PTV), defined as a uniform 5 mm expansion around the CTV, will provide a margin the CTV to compensate for set-up variability and target volume motion due to respiration.

4.2.4 The Evaluation Planning Target Volume (PTV_Eval) is equivalent to the PTV but excludes any part of the PTV that extends outside the patient, the first 5 mm of tissue under the skin surface, and any part of the PTV that extends beyond the posterior edge of the breast tissue (i.e., chest wall, pectoralis muscles, and lung are excluded). Clinical Target Volume (CTVinhale) is defined as the GTV inhale plus areas that are conside**red t**o contain potential microscopic disease on the inhale phase CT data set.

4.2.5 Clinical Target Volume (CTVexhale) is defined as the GTVexhale plus areas that are conside**red t**o contain potential microscopic disease on the exhale CT data set.

4.2.6 Imaged based CTV(iCTV) will be determined on the average CT data set as a boolean of the CTVinhale and CTVexhale of the target on the average CT data set. Alternatively it can be derived based on the 4D analysis of target motion or can be manually edited by the treating physician on the average CT data set based on the 4DCT data sets available.

4.2.7 The Planning Target Volume (PTV), defined as a uniform 5 mm expansion around the iCTV, will provide a margin the CTV to compensate for set-up variability and possible changes in target volume motion due to changes in respiration pattern.

4.3 Normal Structures

4.3.1 The dosimetrist will define two structures: Skin-2 (2 mm thick surface) and Skin-PTV (all PTVs subtracted from the surface contour). Skin-PTV is the normal tissue structure that is all tissue other than what is contoured as something else.

4.3.2 Organ at risk volume (OAR) is contoured as visualized on the planning CT or MR scan. Planning organ at risk volume (PAR) is the OAR volume expanded for setup uncertainty or organ motion. The physician will contour the OAR. The dosimetrist will create the PAR by expanding the OAR by 2-3 mm, depending on the situation.

4.3.3 The following normal structures will be contoured: skin, ipsilateral and contralateral whole breast reference volumes, thyroid, lung (right/left), heart and spinal cord.

4.4 Dose fractionation and specification

4.4.1 A total dose of 38.5 Gy (RBE) will be prescribed to the ICRU reference point (usually isocenter). Two fractions, each of 3.85 GY (RBE) separated by at least 6 hours, will be administered on 5 treatment days (over a period of 5 to 10 days) for a total of 10 fractions**.** A fractionation schedule of 3.85 Gy once a day for 10 fractions over 2-3 weeks is also permitted.

4.5 Treatment Planning

4.5.1 The dose will be prescribed to the ICRU reference point (usually the isocenter) to be consistent with the ongoing RTOG 04-13 study.

4.5.2 Dose constraints for PTV_Eval: 95% of the prescription dose should cover at least 95% of the PTV_Eval.

4.5.3 Dose Constraints for normal tissues:

- *Uninvolved normal breast*: Less than 60% of the whole breast reference volume should receive ≥ 50% of the prescribed dose and < 35% of the whole breast reference volume should receive the prescribed dose.
- *Contralateral breast*: The contralateral breast reference volume, contoured using the same methods described for the ipsilateral breast reference volume, should receive < 3% of the prescribed dose to any point.
- *Ipsilateral lung*: < 15% of the lung can receive 30% of the prescribed dose.
- *Contralateral lung*: < 15% of the lung can receive 5% of the prescribed dose.

- *Heart (right-sided lesions)*: < 5% of the heart should receive 5% of the prescribed dose.
- *Heart (left-sided lesions)*: The volume of the heart receiving 5% of the prescribed dose (V5) should be less than the 40%.
- *Thyroid*: maximum point dose of 3% of the prescribed dose.

4.5.4 At least two fields should be employed for each treatment delivery. Preferably different sets of beam pairs should be employed for BID treatments in order to avoid skin toxicity.Plans should be carried out based on the departmental protocol.

4.5.5. Target coverage should be reviewed beam-by-beam based on the PTVeval, CTV, iCTV DVH indicators in order to ensure the robustness of the plan. Beam parameters should not be altered to reduce apparent "hot" or "cold" spots, or to increase conformality. The above criteria can be altered by the treating Physician in consultation with Physics.

4.6 Treatment Duration

Proton radiation therapy will, in most instances, be completed within 2 weeks of the start of treatment. This may be extended if subjects require a break from treatment. Criteria for break would include any **Grade 3 or** G**rade 4** toxicity. All subjects experiencing **Grade 4** toxicity will be taken off study. Further treatment plans will be decided at the discretion of their treating physician.

4.7 External Beam Equipment and Beam Delivery

Protons: A 230 MeV proton beam will be used. Treatments will be administered in the Roberts Proton Therapy Center at the University of Pennsylvania. All charged particle treatment will be given with the patient in the appropriate immobilization device and aligned based on the departmental protocol.

Film or digital images will be taken prior to the initial treatment to verify the position of the patient and the aperture and as appropriate. A radiation oncologist will check the first film on all fields. A radiation therapist will check subsequent films taken before treatment.

All set-up films will be permanently filed for each subject.

4.8 Quality Assurance

4.1. Conventional portal filming
Daily portal films, and/or daily online radiographic imaging will be performed during therapy.

4.2. Video surface image guidance
Video surface image guidance will be used in all patients. Video surface mapping will be conducted with the AlignRT system (Varian Medical Systems, Palo Alto, CA). This system

employs dually mounted cameras that capture external surface anatomy. The data is used to generate 3D topographic mapping of the patient surface anatomy in the treatment set-up position. A region of interest, in this case the breast, can be used to reposition the patient or make shifts in couch position to improve daily set-up accuracy.

5 Systemic Therapy

5.1. Chemotherapy

Patients enrolled in this study will receive systemic therapy as deemed appropriate by their medical oncologist. If chemotherapy is recommended it will be given after radiotherapy but not concurrently. The interval between the RT and chemotherapy should be at least 2 weeks.

5.2 Endocrine Therapy

If endocrine therapy is recommended it may be initiated before, during, or after RT at the discretion of the patient's treating physicians.

6 Study Procedures

6.1 Prior to study entry

- History and Physical including breast exam and ECOG performance status.
- Breast MRI and/or Mammogram (or mammogram of right and left breast done at separate times) within six months of diagnosis.
- Negative post post-excision mammogram for patients with malignancy-associated calcifications after lumpectomy
- CBC within 6 months of study entry.
- AJCC TNM Staging.
- Serum Pregnancy test if applicable before radiation simulation.
- A treatment planning CT scan of the ipsilateral breast in the treatment position is required to define the clinical target volumes (CTV) and planning target volumes (PTV) for radiation. This should be done between 14 and 60 days after surgery.

6.2 Pre-treatment

- Patient reported health-related quality of life will be assessed using the Breast Cancer Treatment Outcomes Scale (BCTOS) (See Appendix for Scale)
- Physician reported Harvard cosmetic assessment (Excellent, Good, Fair, Poor)

6.3 Weekly During Treatment

- History and Physical including breast exam and ECOG performance status
- Physician toxicity assessment

6.4 Approximately one month after completion of radiation therapy, approximately 6 months after completion of RT, and then every approximately 6 months for 5 years' post-treatment

- History and Physical including breast exam and ECOG performance status
- Physician toxicity assessment
- Patient reported BCTOS
- Physician reported cosmetic assessment

Study Procedures

	Eligibility	Pre-treatment	Weekly	Months 1	Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60
Tests and Observations					
History and PE	X		X	X	X
ECOG performance status	X		X	X	X
Biopsy	X				
Pathology review	X				
ER/PR determination for invasive breast cancer	X				
Mammogram	X				Month 6 then annually
Laboratory					
CBC	X				
Pregnancy Test	X				
Toxicity Assessment			X	X	X
Patient-reported BCTOS		X		X	X
Physician cosmetic assessment		X		X	X

6.5 Post-treatment Evaluation and follow-up

- Patients will be treated and followed 1 month after completion of radiation treatment to determine feasibility and safety (acute toxicity).
- All subjects will be evaluated by a radiation oncologist 1 month after completion of RT. Additional time points at 6 months after completion of RT and every 6 months thereafter for a total of 5 years' post-treatment can be evaluated alternatively by surgery or medical oncology.
- For all follow-up time points, there is a window of +/- 2 months.
- Each follow-up examination will consist of interval history and physical examination including a breast exam and ECOG performance status and toxicity assessment.
- A bilateral mammogram will be obtained at month 6 and then annually.

6.5.1 Recurrence

- **Local failure** is defined as biopsy-proven recurrent breast cancer within 5 years from completion of radiation in the treated breast.
- **Nodal Failure** is defined as clinical evidence of recurrence by physical examination, CT or PET scan with or without biopsy proven disease in the regional axillary, supraclavicular, or internal mammary lymph nodes.
- **Distant failure** is defined as clinical evidence of recurrence by physical examination, CT or PET scan with or without biopsy proven disease beyond local or regional nodal sites.
- **Overall Survival** is defined as survival time between study registration until death or censored at date of last follow-up for patients still alive.

7 Statistical Plan

7.0 Statistical Plan

This is a study of accelerated partial breast irradiation (APBI) using proton therapy for patients with favorable Stage 0, I or II breast cancer. The trial will be conducted in two phases: first, a feasibility study and then, a phase II study. Since proton therapy is a new treatment modality at PENN, the first proton trial conducted in each cancer site (and here proton is prescribed on an accelerated treatment schedule) will be a feasibility study, in order to gain experience on both the logistics of proton planning, dosimetry, scheduling, and delivery, as well as patient safety issues.

7.1 Feasibility Study

7.1.1 Design

A total of 12 patients will be enrolled. The total dose of 38.5 CGE will be given in 10 fractions. The regimen is intended to be completed in 5 treatment days. A fractionation schedule of 3.85 Gy once a day for 10 fractions over 2-3 weeks is also permitted. Patients undergo 2 fractions per day, a minimum of 6 hours apart. Twelve patients will be enrolled and followed for a minimum of 30 days after the completion of radiotherapy to score acute toxicity. This shortened follow-up period is appropriate for an accelerated treatment schedule in which treatment may be completed in 5 days. Thirty days of observation from the end or radiotherapy will be required in all 12 patients prior to commencing the phase II study. Patients enrolled in the feasibility study will continue to be followed beyond 30 days post-radiation, since they contribute to primary and secondary endpoints of the phase II study.

7.1.2 Objectives.

The primary objectives are to determine feasibility and the acute toxicity profile of accelerated partial breast radiation using protons. Additional objectives, such as late toxicities, cosmesis, and clinical efficacy are evaluated in these patients on the phase II portion of the trial.

7.1.3 Endpoints

Primary Endpoints

Feasibility will be based on multiple radiation planning and treatment parameters. Should a patient experience one of the following events, treatment will be deemed infeasible:

a) Patient cannot be given treatment because anatomy is such that a dosimetrically satisfactory treatment plan cannot be devised. For example, the dosimetry is unsatisfactory if < 95% of the target volume is covered by 95% of the dose.
b) Patient is unable to tolerate more than 20% of treatments using proton radiotherapy (i.e., >2 of the 10 fractions). This can be for any reason, including the inability to set the patient up within acceptable limits of tolerance, or the patient is unable to tolerate treatment position or immobilization for duration of treatment. Thus, up to 20% (i.e., 2 of the 10 fractions) of treatments could be delivered using photons.
c) Patient is unable to complete all treatment within 5 days of the estimated date of treatment completion or requires a treatment break of $\geq$ than 5 days.
d) No more than 20% of patients experience an acute toxicity, as defined below.

Acute toxicity is defined as any grade 3 or higher hematologic or non-hematologic toxicity, including skin changes, as graded by the NCI CTC Version 5.0, observed **within 30 days from the end of radiotherapy**, which is probably or definitely related to proton therapy.

Secondary Endpoints

Late toxicity is defined as any grade 3 or higher hematologic or non-hematologic toxicity which occurs more than 30 days after end of therapy. Late toxicities will be graded according to the CTC Version 5.0. Special attention will be paid to fibrosis and cosmesis. The time frame for late toxicity is open-ended because late toxicities have been known to occur a year or more after therapy. Follow-up for late toxicity will cease when a patient experiences disease progression since 2nd line therapies may then be initiated.

Cosmesis will be scored using the Harvard scoring system (scale = excellent, good, fair, poor) and CTC Version 5.0. In addition, cosmesis will be scored by the cosmesis and breast pain subscales of the Breast Cancer Treatment Outcomes Scale (BCTOS) instrument.

Clinical Efficacy. Time to local failure will be defined as the time from the start of radiation therapy to local failure. Overall survival will be defined from the time from the start of radiation therapy to death due to any cause or last patient follow-up. These outcomes will likely be summarized during the phase II study.

7.1.4 Rules for Early Termination for Feasibility and Acute Toxicity.

Bayesian probability calculations will be employed to define rules of early termination for feasibility and safety. The tables below indicate termination rules after groups of 3 patients have been treated, although the Bayesian probability of an event may be calculated at any time during the trial. Hundreds of patients

with certain types of cancer have undergone radiation therapy with protons. Thus, we will assume a modest amount of "prior" feasibility and safety data for proton for our Bayesian calculations.

Feasibility

We will assume a beta (5,1) prior, which is information equivalent to feasibility established in 5 of 6 treated patients. A feasibility rate ≥90% is considered acceptable. If the number of patients in whom proton is deemed feasible is less than or equal to the number in the table below then termination will be considered as it is highly unlikely that the feasibility rate is >90%, as noted by the Bayesian posterior probabilities.

Bayesian Rule for Feasibility				
Patients treated	3	6	9	12
Patients in whom proton is feasible	1	4	6	9
Posterior Prob[feasibility rate >90%]	0.04	0.09	0.04	0.08
Action	Terminate enrollment			

Acute Toxicity

Acute toxicity with accelerated partial breast radiotherapy with photons is quite low, although skin toxicity is fairly common. Proton therapy is expected to spare normal tissues; therefore, a rate of Grade 3 or higher acute toxicity observed **within 30 days from the end of radiotherapy**, including skin changes, which is probably or definitely related to proton therapy of ≤20% is considered acceptable. We will assume a beta (1,5) prior, which is information equivalent to Grade 3 or higher acute toxicity in one of 6 treated patients. If the number of patients with Grade 3 or higher acute toxicity is greater than or equal to the number in the table below, then termination will be considered, because it is likely that the toxicity rate is >20%, as noted by the Bayesian posterior probabilities.

Bayesian Rule for Acute Toxicity including skin changes				
Patients treated	3	6	9	12
Patients who experience acute toxicity	2	2	3	4
Posterior Prob [acute toxicity rate >20%]	0.80	0.62	0.70	0.76
Action	Terminate enrollment			

7.1.5 Statistical Analyses.

Feasibility: The posterior probability that this feasibility rate is 90% will be calculated. The feasibility rate and exact 90% CI will also be computed. The reasons why patients were not feasible will be tabulated.

Acute toxicity: All toxicities observed within 30 days from end of therapy will be graded by CTC Version 5.0 and tabulated. The posterior probability that this acute toxicity rate is 20% will be calculated.

Late toxicity: All toxicities observed later than 30 days from end of therapy will be graded by the CTC Version 5.0 and tabulated.

Cosmesis will be scored using the Harvard scoring system and CTC Version 5.0. BCTOS will be scored every 6 months and fold changes over time will be described and plotted.

Clinical efficacy: Local control (time to local failure) and overall survival will be estimated by the Kaplan-Meier method. It is likely that these time-to-event outcomes will be summarized after completion of the phase II study.

Estimation of Event Rates: The table below displays the 90% exact binomial confidence intervals based on 12 patients treated.

No. of Events	%	90% exact CI	No. of Events	%	90% exact CI
0	0.0	17.5*	7	58.3	31.5 , 81.9
1	8.3	.43 , 33.9	8	66.7	39.1 , 87.7
2	16.7	3.0 , 43.8	9	75.0	47.2 , 92.8
3	25.0	7.2 , 52.7	10	83.3	56.1 , 97.0
4	33.3	12.3 , 60.9	11	91.7	66.1 , 99.6
5	41.7	18.1 , 68.5	12	100.0	82.5*
6	50.0	24.5 , 75.5	* 90% 1-sided CI		

7.2 PHASE II STUDY.

7.2.1 Design and Objectives.

Once feasibility and safety are established, then the phase II portion of the study will commence. A total of 57 patients will be enrolled; 12 patients are included from the feasibility study and 45 additional patients are enrolled in the phase II study. The two primary objectives are: to determine whether the rate of Grade 3+ acute toxicity is $\leq$20% and whether the rate of maintained excellent to good cosmesis is $\geq$85% at 2 years post-XRT. Only patients with excellent or good cosmesis at baseline contribute to this analysis.

7.2.2 Endpoints.

Acute Toxicity, as defined in Section 7.1.3
Cosmesis, as scored by the Harvard scale, CTC Version 5.0 and BCTOS scoring systems.
Late Toxicity, Local control and overall survival, as defined in Section 7.1.3

7.2.3 Rules for Early Termination for Acute Toxicity.

A primary objective is to assess the rate of acute toxicity which will be tested by chi-square test at the end of the phase II study. But since accelerated partial breast radiotherapy with photons is a novel intensive treatment course, we have decided to continue Bayesian monitoring of acute toxicity throughout the course of the phase II study. Assuming a beta (1,5) prior, if the number of patients with Grade 3 or higher acute toxicity is greater than or equal to the number in the table below, then termination will be considered, because it is likely that the toxicity rate is >20%, as noted by the Bayesian posterior probabilities.

Bayesian Rule for Acute Toxicity including skin changes				
Patients treated	20	30	40	50
Patients who experience acute toxicity	6	8	10	12
Posterior Prob [acute toxicity rate >20%]	0.89	0.85	0.82	0.79
Action	Terminate enrollment			

7.2.4 Statistical Analyses.

The following are standard methods for data analysis which will be employed. Graphical analyses will include scatter plots, box plots, mean (±SE) plots and histograms. The distribution of continuous variables will be characterized with mean, median, standard deviation and range, while the distribution of categorical variables will be described with frequency, percentage and 95% CI. Toxicities will be categorized as acute or late and will be graded and tabled by toxicity type. The Grade 3+ acute toxicity rate and confidence interval will be calculated and a one sample chi-square test will be performed. The rate of excellent to good cosmesis at 2 years post-XRT and confidence interval will be calculated and a one sample chi-square test will be performed. Time to local failure and overall survival will be estimated by the Kaplan-Meier method.

7.3 SAMPLE SIZE/POWER

Acute toxicity. A total of 57 patients will be enrolled and will contribute to the hypothesis test of the acute toxicity rate. Since these are favorable risk patients, no loss to follow-up by 30 days post-XRT is expected. With 57 patients, there is 90% power for a chi-square test at a 1-sided 10% significance level, to test the null hypothesis that the acute toxicity rate is ≥ 35% (clearly unacceptable) versus the alternative hypothesis that the acute toxicity rate is ≤ 20%. This analysis will be performed when 57 patients have 30 day post-XRT data.

Cosmesis at 2 years. The rate of excellent to good cosmesis on the Harvard scale will be scored at 2 years post-XRT. We anticipate that 3 patients will enroll on the study with fair cosmesis at baseline and they will be excluded from this endpoint. In addition, we anticipate that another 4 patients will be lost or have progressive disease before 2 years and who are not scored as fair or poor cosmesis (i.e., considered a failure) at a time point prior to 2 years and they will be excluded from this endpoint. Thus 50 patients will contribute to the analysis of whether excellent to good cosmesis is maintained at 2 years post-XRT. With 50 patients, there is 90% power for a chi-square test at a 1-sided 10% significance level, to test the null hypothesis that the cosmesis rate is ≤ 70% (clearly unacceptable) versus the alternative hypothesis that the cosmesis rate is ≥ 85%.

7.4 TRIAL DURATION.

A total of 57 patients will be enrolled. With an expected monthly accrual of 2 patients, this study will enroll for approximately 2.5 years and the total duration of the study is approximately 4.5 years, in order to follow patients for 2 year cosmesis.

8 Safety and Adverse Events

The principal and secondary investigators will be responsible for detecting, documenting and reporting all events that meet the definition of an AE or SAE as defined in this protocol.

8.1Definitions

Adverse Event

An ***adverse event*** (AE) is any unfavorable and unintended sign, symptom, illness/disease (new or exacerbated) or experience that develops or worsens in severity temporally associated with the use of the proton APBI and is considered by the investigator to be definitely or probably related to the treatment. Intercurrent illnesses or injuries should be

regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a Serious Adverse Event (SAE)
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

AEs Not to Include:

- Medical or surgical procedures (e.g. endoscopy, appendectormy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (elective and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuation of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen in grade or severity.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Grade 1 adverse events that are not in the following categories: fatigue, skin, breast, ribs, heart, and lungs.

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***Serious Adverse Event*** is any medical occurance that at any dose:

- fatal
- life-threatening

Note: (the subject was at risk of death at the time of the event, not events that hypothetically might have caused death if it were more severe)

- hospitalization or prolongs hospital stay (hospitalization signifies in general, the subject has been detained [at least an overnight stay] at the hospital or emergency department for observation/treatment that would not have been appropriate in a physician's office or outpatient setting).

Note: Hospitalization for elective treatment, diagnostic purposes or a pre-existing condition that did not worsen from baseline in not considered an AE or SAE. Hospitalization/prolonged hospitalization to allow for study efficacy assessment is not an SAE.

- results in persistent or significant disability or incapacity

Note: A substantial disruption of a person's ability to conduct normal life functions. Not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***adverse events (AEs)*** *per protocol definition.*

Clinical Laboratory and Other Safety Assessments

Any abnormal laboratory test result (.e.g. hematology, clinical chemistry, urinalysis) or other safety assessment (e.g. ECGs, radiological scans, vital signs), including those that worsen from baseline and are felt to be **clinically significant** in the medical and scientific judgement of the investigator are to be recorded as AE or SAEs if they meet the definition of an AE, as defined above. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be recorded as AEs or reported as SAEs.

The investigator will exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. This assessment will be documented on the lab report or in a timely clinic/progress note.

Disease Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event that is part of the natural course of the disease (e.g. disease progression) does not need to be reported as an SAE. Progression of the subject's cancer will be clearly recorded in the clinic/progress note. Death due to progressive disease is not an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject or if the investigator considers that there was a causal relationship between the investigational agent/treatment/device and the disease progression, then this must be reported as an SAE. Any new cancer must be reported as an SAE.

Preexisting Condition

A preexisting condition is one that is present at the start of the study, prior to administration or exposure to any protocol agents/treatments/devices. A preexisting condition should be recorded as Medical History and becomes an adverse event if the frequency, intensity, or the character of the condition worsens during the study period as defined by the protocol.

Radiation Effect

Radiation side effects are typically divided into those that occur acutely (during radiation and up to 1 month after radiation) and those that occur later (>1 month post-radiation).

Common acute radiation side effects include fatigue and radiation dermatitis. The potential late effects of APBI using proton therapy include fibrosis of breast tissue adversely affecting cosmesis and/or causing breast pain, rib fractures, pulmonary fibrosis, and radiation-induced heart disease. Another rare but serious late side effect is the development of second tumors. It is hoped that proton radiation will substantially reduce both acute and late side effects by reducing the amount of normal tissue that is irradiated.

For acute and late radiation effects CTCAE 5.0 will be employed.

Assessment of Causality

The investigator must assess the relationship between the investigation aspect of the protocol and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational aspect of the protocol should be considered and investigated.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

8.2 Assessing and Recording Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning, examination and review of clinical documentation (e.g. lab reports, radiology reports). Information on all adverse events, as defined by the protocol, should be recorded immediately in the source document and also on the adverse event Case Report Form (CRF). It is preferred that events are recorded by diagnosis (where applicable) instead of through signs/symptoms/test results. For example, shortness of breath, chest pain and nausea may have been confirmed as a myocardial infarct through lab test and an ECG, therefore, "MI" or "myocardial infarct" or "heart attack" should be recorded instead of all of the signs/symptoms.

All adverse events meeting the protocol definition, occurring during the study period must be recorded. Full documentation of an event includes start/stop dates, event, grade, expectedness, attribution and outcome. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

All Adverse and Serious Adverse Events will be assessed using NCI Common Terminology Criteria for Adverse Events version 5 (CTCAE 5.0). Expectedness will be captured for all adverse events

8.3Reporting of Serious Adverse Events

8.3.1 Adverse Event Reporting Period

The study period during which Adverse Events must be collected and Serious Adverse Events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. This protocol will begin assessment of AEs and SAEs following the first dose/treatment with any experimental aspect of the protocol. Therefore, only treatment emergent events will be evaluated. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

8.3.2 IRB Notification by Investigator

All events meeting the Penn IRB SOP for Unanticipated Events posing risks to subjects or others will be reported to the IRB as follows:

The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process
Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

If the adverse event involved death as unforeseen and indicates participants or others are at increased risk of harm, report in three days.

Any adverse event that represents a serious unexpected problem that is rare in absence to drug exposure (agranulocytosis, hepatic necrosis, or Stevens-Johnson syndrome).

Withdrawal from marketing for safety of a drug, device, or biologic used in a research protocol.

Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.

Event that requires prompt reporting to the sponsor (*where applicable*).

Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.

Violation, meaning an accidental or unintentional change to the IRB approved protocol that placed one or more participants at increased risk, or has the potential to occur again.

Breach of confidentiality.(*must also be reported to the institutional Office of Research Compliance and Integrity).*

Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.

8.3.3 Data and Safety Monitoring Committee (DSMC) Notification by Investigator

On-Site subjects (this includes any subjects enrolled at other sites on an in-house study)
All grade 3 or higher events within ten days of knowledge
All unexpected deaths within 24 hours of knowledge
All others deaths within 30 days of knowledge

8.3.4 FDA Notification by Sponsor

Not applicable

8.4Stopping Rules

See section 7.2

8.5Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.5.1 Institutional Data and Safety Monitoring Committee

The Abramson Cancer Data and Safety Monitoring Committee is charged with the responsibility of reviewing all SAEs, deviations, Medical/Safety Monitoring reports for all cancer based protocols conducted at the University of Pennsylvania. The DSMC reviews these document and data on a monthly basis and makes recommendation necessary to ensure subject safety and study integrity. Additionally, the DSMC monitors and audits the progress and conduct of all cancer based studies in accordance with their NCI approved Institutional Data and Safety Monitoring Plan.

Protocol Deviations/Exceptions
Occasionally, the investigator may need to deviate from the approved protocol.
Exception

A one time, intentional action or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, advance documented IRB and DSMC approval is required.

• For in-house studies with a Medical Monitor or Safety Monitoring Committee (not DSMB), approval must be obtained from the Medical Monitor or Safety Monitoring Committee prior to submitting your exception request to the DSMC.

Upon receipt of a deviation request, the DSMC (or only the Chair as appropriate) will review the request within 24 hours and notify the PI of the Committee's decision. The DSMC may request additional information to assist with the determination. The IRB will be copied on all exception decisions made by the DSMC.

Deviation
A one time, unintentional action or process that departs from the IRB and CTSRMC approved study protocol, involving one incident and identified retrospectively, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints) or compromises the safety and welfare of the subjects, the deviation must be reported to the CTSRMC within five business days and the IRB within ten business days.

Examples of Exceptions/Deviations that must be submitted (not meant to be inclusive)
May/can/have affects/affected subject safety. So, a subject missing a visit is not an issue unless a critical/important treatment or procedure was missed and must have been done at that specific time.
• Violate eligibility
• Dose adjustment
• Stopping criteria
• Affect sample size (adding more subjects, decreasing number of subjects, changing the number of subject in a specific arm/cohort)

Other deviations should be explained in a memo to file or on a deviation log. Upon receipt of a deviation request, the DSMC (or only the Chair as appropriate) will review the report and notify

the PI of the Committee's assessment of the impact of the deviation. The DSMC may request additional information to assist with the assessment. The IRB will be copied on all exception decisions made by the DSMC if the Committee believes the deviation affects subject safety or study integrity. The DSMC may also request the DOCM conduct follow-up compliance activities to address issues revealed by the deviation report.

All deviations from the study protocol will be handled as follows:

Eligibility- Deviations from established eligibility criteria will not be allowed. If the investigator believes that a subject would truly benefit from the protocol therapy and there are no other viable options, then the protocol should be amended to reflect the change in restrictions. There may be situations where the deviation from eligibility may not warrant a study amendment (e.g. a necessary test/procedure being a few days outside of the eligibility window, subject taking a concomitant medication within recent timeframe etc.). These deviations must still be reviewed and approved in advance of enrolling the subject.

The IRB must be notified of the planned deviation and a copy of all applicable amended study documents must be sent to the IRB. The planned deviation must also be submitted to the DSMC for evaluation. The DSMC does not approve deviations but rather provides and unbiased assessment of the appropriateness of the request. Both committees must be given sufficient time to review the request, gather additional information as necessary and make a decision.

Other Reportable- Deviations that affect the protocol treatment administration (i.e. dose administered, route/method of administration etc.), dose adjustment schema, stopping rules, modification to follow-up, removal of safety assessments/follow-up visits, accrual goal or any deviation that may affect the study outcome analysis or study integrity must be approved by the IRB and reviewed by the DSMC.

Non-Reportable- During the course of a study, there may be times when deviations are outside of the control of the investigator (i.e. subject not showing up for a study visit, lab errors, subject confusion etc.). These type of deviations are not reportable (unless they occur at a level that impacts any of the reportable categories) but must be documented in a timely manner to show the impact of the deviation and corrective/follow-up actions that were taken. Documentation can be in the clinic/progress notes or note/memo to file. Notes/memos should be signed and dated.

Reporting Deviations/Exceptions
Reports to the IRB and DSMC will be done via HS-ERA and the DSMC website www.ctsrmc.org, respectively.

9Data Handling and Record Keeping

9.1Confidentiality

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

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

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

9.1.1Unintentional Disclosure:

Upon discovering that PHI may have been or has been disclosed to anyone not specified in the HIPAA disclosure consent, the investigator will report the disclosure to the Institutional Officer in the Office of Research Compliance and Integrity. The report should contain details about the type of data disclosed and the extent of the disclosure (number of subjects, who received it etc.).

9.2Source Documents

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

9.3Case Report Forms

Electronic case report forms will be developed and completed in Velos in lieu of paper case report forms.

9.4Records Retention

Federally Funded Research or Non-IND/IDE Research (*for applicable studies*):
The DHHS regulation (45 CFR 46.115) states that records relating to research conducted or supported by any Federal department or agency shall be retained for at least 3 years after completion of the research.

The FDA regulation (21 CFR 56.115) is virtually identical; it also states that IRB records must be retained for at least 3 years after completion of the research for these same types of studies.

Records for this study will be maintained in a secure location with access limited to the investigators and the study specific research team for 3 years from the date of full study terminations. If necessary, after the first year of termination, records may be moved to an off-site secure storage facility.

Research Conducted Under an IND (*for applicable studies*):
Clinical Trials with a Food and Drug Administration (FDA) Investigational New Drug Application (IND) must additionally comply with 21 CFR 312.57 and 21 CFR 312.62. These regulations apply to investigational drug records, investigator financial interest records, and patient case histories. Both regulations require that the sponsor retain records and reports for 2 years after a marketing application is approved for the drug. If an application is not approved for the drug, the investigator retains records and reports until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified.

Records for this study will be maintained in a secure location with access limited to the investigators and the study specific research team for 2 years per 21 CFR 312.57 and 21 CFR 312.62 . If necessary, after the first year of termination, records may be moved to an off-site secure storage facility.

Research Conducted Under an IDE (*for applicable studies*):
An investigator shall maintain the records during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a pre-market approval application or a notice of completion of a product development protocol.

Records for this study will be maintained in a secure location with access limited to the investigators and the study specific research team for 2 years as specified above. If necessary, after the first year of termination, records may be moved to an off-site secure storage facility.

HIPAA Retention Period (45 CFR164.530(j):
Protected Health Information (PHI) Research Requests (HIPAA1-008): Records documenting research requests, privacy board review or privacy officer expedited review, background material, and acceptance or denial of request. Retain 6 years after research completed.

Protected Health Information Disclosure Records (HIPAA1-009): Documenting the release of PHI, including **both authorized and unauthorized** releases. Should include the date of release, to whom the information was released, and the circumstances of the release. Retain 6 years after research completed.

Maintenance of HIPAA records is independent of the regulations for clinical study records. All records of PHI research requests and any type of release will maintained for 6 years after the research is fully terminated.

10Study Monitoring, Auditing, and Inspecting

10.1Study Monitoring Plan

The study PI is responsible for ensuring the ongoing quality and integrity of the research study. In addition, this study will monitored or audited in accordance with Abramson Cancer Center's NCI approved Institutional Data and Safety Monitoring Plan.

Auditing and Inspecting
The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

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

11Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be maintained in the study specific Regulatory Binder which contains "Essential Study Documents". In addition, NCI requires all cancer based studies to have an independent scientific review. This protocol must be reviewed and fully approved by the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) prior to enrolling any subjects. Documentation of CTSRMC approval must also be maintained in the study specific Regulatory Binder.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment X for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed and dated by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the

conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

13 Publication Plan

The results of this study will be published in the peer reviewed literature.

14 References

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15 Attachments

This section should contain all pertinent documents associated with the management of the study. The following list examples of potential attachments:

- *Sample Consent Form*
- *BCTOS*

The Breast Cancer Treatment Outcome Scale (BCTOS)

We are interested in your evaluation of your physical appearance and functioning since your breast surgery. Please rate the following items on this four-point scale, according to your evaluation at this point in time. (Note: If you have had bilateral surgery, complete the items with regard to the difference between the right and left side.)

1 = no difference between treated and untreated breast and area
2 = slight difference between treated and untreated breast and area
3 = moderate difference between treated and untreated breast and area
4 = large difference between treated and untreated breast and area

___ 1. Breast size
___ 2. Breast texture (hardening)
___ 3. Arm heaviness
___ 4. Nipple appearance
___ 5. Shoulder movement
___ 6. Arm movement
___ 7. Breast pain
___ 8. Ability to lift objects
___ 9. Fit of shirt sleeve
___ 10. Breast tenderness
___ 11. Shoulder stiffness
___ 12. Breast shape
___ 13. Breast elevation (how high the breast is)
___ 14. Scar tissue
___ 15. Shoulder pain
___ 16. Arm pain
___ 17. Arm swelling
___ 18. Breast swelling
___ 19. Arm stiffness
___ 20. Fit of bra
___ 21. Breast sensitivity
___ 22. Fit of clothing