Evaluation of Single Fraction High-gradient Partial Breast Irradiation as the Sole Method of Radiation Therapy for Low-risk Stage 0 and I Breast Carcinoma

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Protocol Revision History

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Amendment #1	**04/01/2014**
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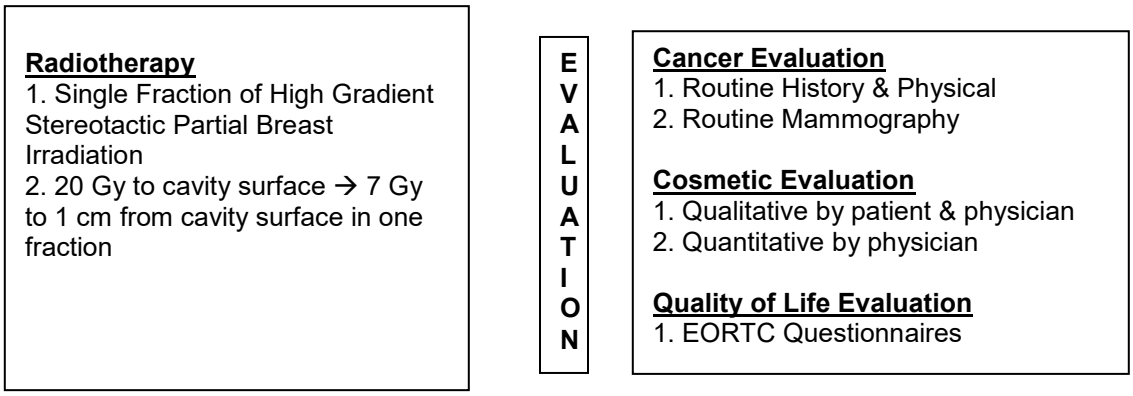
SCHEMA

Study Summary
This is a phase I/II study which will evaluate the complication rates, local control, cosmetic results, and quality of life of single fraction high gradient partial breast irradiation (HG-PBI) when used as the sole method of radiation therapy for patients with pathologic stage 0 (≤ 2 *cm)* or I carcinoma of the breast treated with partial mastectomy with histologically assessed negative surgical margins. Time to event parameters that will be collected are IBTR, mastectomy-free survival, regional recurrence rate, distant disease free survival, and overall survival.



Systemic Therapy
Cytotoxic chemotherapy, hormonal, or biologic therapies are not to be started until at least 4 weeks after radiation therapy.

Eligibility *(see Section 3.0 for details)*
- Ductal carcinoma in situ *(lesions* ≤ 2 *cm)*
- Invasive ductal, lobular, medullary, papillary, colloid (mucinous), tubular histologies, or mixed histologies *(lesions* ≤ 2 *cm)* that are estrogen or progesterone receptor positive and do not exhibit HER2/neu gene amplification
- Stages TisN0M0 or T1N0M0
- Postmenopausal
- Age ≥ 50 years
- No prior ipsilateral breast cancer
- No neoadjuvant systemic therapy
- Negative surgical margins after partial mastectomy
- No systemic lupus erythematosis, scleroderma, or dermatomyositis
- Time interval from final definitive breast surgical procedure to HG-PBI less than 8 weeks
- Signed study-specific consent form

Required Sample Size
50 evaluable patients, with target accrual of 55 patients (expected drop-out rate = 10%)

Glossary of Abbreviations

3D-CRT	Three dimensional treatment planning
AE	Adverse event
AJCC	American Joint Committee on Cancer
APBI	Accelerated partial breast irradiation
ATC	Advanced Technology Consortium
BCT	Breast conserving therapy
BID	Bis in die (twice a day)
BRA	Breast Retraction Assessment
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical target volume
DCIS	Ductal carcinoma in situ
DOB	Date of birth
DSM	Data and safety monitoring
DVH	Dose volume histogram
EORTC	European Organization for Research and Treatment of Cancer
HDR	High dose rate
HG-PBI	High gradient partial breast irradiation
HRPO	Human Research Protection Office
IBTR	Ipsilateral breast tumor recurrence
IMRT	Intensity modulated radiation therapy
IRB	Institutional review board
LCIS	Lobular carcinoma in situ
NCI	National Cancer Institute
NSABP	National Surgical Adjuvant Breast and Bowel Project
OHRP	Office for Human Research Protections
PTV	Planned treatment volume
QA	Quality assurance
QASMC	Quality Assurance and Safety Monitoring Committee
QOL	Quality of Life
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event
SBRT	Stereotactic body radiotherapy
SCC	Siteman Cancer Center
TARGIT	Targeted intraoperative radiotherapy
UPN	Unique patient number
WBI	Whole breast irradiation

Table of Contents

1.0 INTRODUCTION

1.1 Introduction to Accelerated Partial Breast Irradiation

Prospective, randomized, controlled trials have established that breast conservation therapy (BCT), consisting of partial mastectomy and adjuvant radiation therapy, offers equivalent disease control in women with Stage I and II breast cancer as compared to mastectomy, and it offers significantly superior disease control when compared to partial mastectomy alone [1-3]. BCT offers patients better cosmetic outcomes with less emotional trauma than mastectomy [4]. In the setting of ductal carcinoma *in situ*, adjuvant radiation therapy has been shown to increase local control when delivered as a part of breast conservation surgery [5-7].

The standard method for administering breast irradiation as a part of BCT is whole breast irradiation (WBI), where the entire breast is treated with external beam radiation delivered in five daily fractions per week for several weeks, often followed by a boost to the partial mastectomy site. Typical whole breast doses range from 40-50 Gy and boost doses range from 10-16 Gy. WBI can present a host of challenges for patients involving work schedules, commuting time, transportation expenses, and difficulties with mobility. Previous studies have suggested that some women may decline breast conservation therapy due to the time commitment required to complete therapy, and some women may simply elect to forgo the radiation therapy component resulting in suboptimal care [8-10].

Accelerated partial breast irradiation (APBI) techniques were developed in part to improve breast conserving surgery rates and compliance with adjuvant radiation therapy. APBI challenges the paradigm that the entire breast should be subjected to adjuvant radiation therapy by treating a volume of breast tissue around the partial mastectomy site. APBI is based on both pathologic [11] and empiric [12] data that demonstrates that the greatest site for an ipsilateral breast tumor recurrence (IBTR) is near the partial mastectomy surgical bed in patients who are at an overall low risk for multicentric foci of disease. As most commonly practiced, APBI delivers a total dose of 34 Gy in 10 BID fractions over five treatment days via high dose rate (HDR) brachytherapy. APBI began by using multicatheter interstitial brachytherapy with early reports from a number of others, including the Oschner Clinic, [13] William Beaumont Hospital[14], and the Radiation Therapy Oncology Group (RTOG) 95-17[15] trial which all described excellent outcomes. Unfortunately, multicatheter interstitial implants proved technically challenging and never achieved widespread popularity. This led a number of companies to develop intracavity brachytherapy applicators such as the Mammosite (Hololgic, Bedford, MA), Contura (Bard Biopsy Systems, Tempe, AZ), and SAVI (Cianna Medical, Aliso Viejo, CA). Although there are a number of technical differences between these devices, they are all inserted into the partial mastectomy cavity and serve as applicators for HDR brachytherapy. The largest series of intracavitary APBI is the Mammosite registry trial that reports a less than 4% five-year IBTR[16].

To avoid the attendant risks of pain, bleeding, and infection that are associated with intracavity APBI applicator placement, investigators have developed external beam methods of treating a limited breast volume. External beam APBI uses three dimensional treatment planning (3D-CRT) to develop a complex, patient-specific beam arrangement to treat the target volume to a dose of 38.5 Gy in 10 BID fractions over five treatment days. Typically, three to six beams are used and there is the occasional need for intensity modulated beams. 3D-CRT has been studied by the RTOG 0319 trial [17] and by institutions such as the William Beaumont Hospital [18], with low IBTR in both publications. In general 3D-CRT avoids the applicator placement issues of intracavitary APBI

at the expense of greater radiation exposure to breast tissue, chest wall, lungs, and, for left sided cancers, heart.

At Washington University, multicatheter interstitial brachytherapy represents our earliest APBI technique and was practiced from 2002-2009. We have completed a phase I/II trial of multicatheter APBI that was designed to quantify five year IBTR with a narrow 95% confidence interval (HRPO# 03-1205). We have demonstrated low IBTR[19] while maintaining excellent cosmetic results[20] with low toxicity[21]. Since then, we have initiated both intracavitary and external beam APBI programs. We have completed a dose escalation study utilizing 3D-CRT APBI (HRPO# 05-1053). At present we offer APBI or WBI therapy as treatment options for early-stage breast cancer in appropriately selected patients. An exhaustive list of APBI studies using a variety of techniques is reported in Smith et al [22].

1.2 Targeted Intraoperative Radiotherapy (TARGIT)

APBI minimizes the irradiated volume and shortens the treatment time for adjuvant radiation therapy all while maintaining low IBTR. The ultimate extrapolation of APBI is to reduce the fractionation to one and the treatment time to several minutes after partial mastectomy. TARGIT is such a method. Although TARGIT will be described for the necessary context, it is important to note from the outset that this proposed clinical trial involves *replicating* the TARGIT radiation dose distribution but does *not* use the TARGIT device or involve delivering radiation dose intraoperatively. Adjuvant radiation in the TARGIT method is generated from the Intrabeam device (Carl Zeiss, Oberkochen, Germany). This FDA-approved device provides a point source of low energy x-rays (50 kV maximum) at the tip of a 3.2 mm diameter tube that is placed at the center of a spherical applicator (Figure 1). After a standard partial mastectomy an appropriate applicator is selected and placed in the tumor bed. The Intrabeam device is switched on for 20-35 minutes which typically delivers a surface dose of 20 Gy that attenuates to 5-7 Gy at 1 cm depth. If necessary the underlying chest wall and/or the skin can be protected by radiopaque tungsten-filled polyurethane caps.

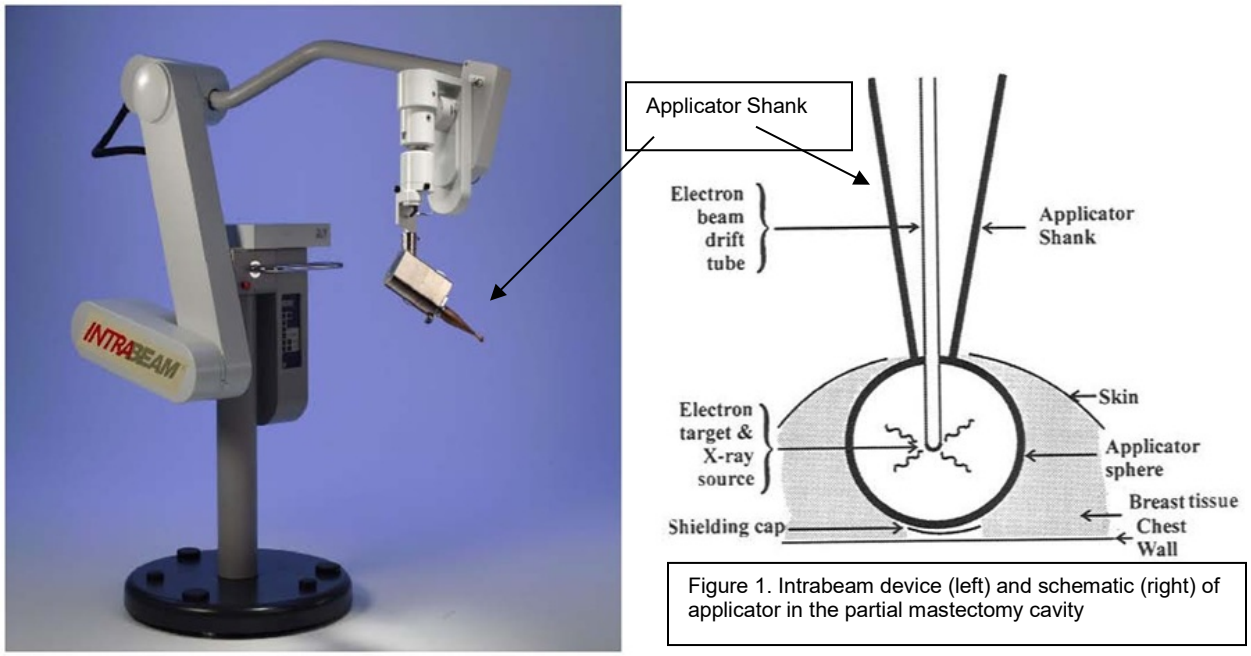
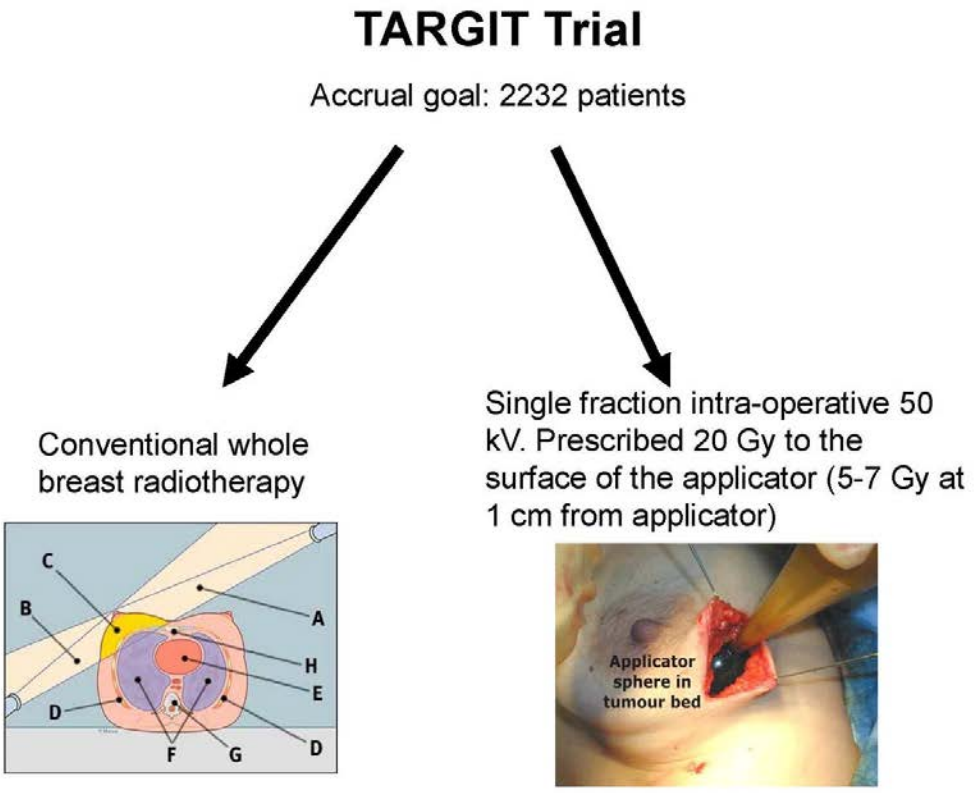


Figure 1. Intrabeam device (left) and schematic (right) of applicator in the partial mastectomy cavity

The safety and tolerability of the TARGIT was evaluated in a pilot study of 25 breast cancer patients[23] where it was used to replace the boost component of whole breast radiation therapy. There were no major complications and no IBTR at 24 months. This was followed by a larger phase II study of 301 patients who again received TARGIT as a boost followed by whole breast radiation therapy[24]. The five year IBTR was 2.6% and complications remained acceptable. The finding that the TARGIT method was feasible along with the separate, coincident development of APBI methods led to the design of a prospective, randomized, non-inferiority phase III trial that compared standard whole breast radiation therapy with TARGIT-alone APBI (Figure 2).

Eligible patients included women at least 45 years of age with unifocal invasive breast cancers suitable for surgical resection via partial mastectomy. The control arm received conventional whole breast radiotherapy of 40-56 Gy with or without a boost of 10-16 Gy. This study has completed planned accrual and is in follow-up [25]. Median age was 63 years, 86% of tumors were ≤ 2 cm, 83% of patients had node negative disease, and 90% of patients had estrogen receptor-positive disease. Early results showed a 4-year IBTR of 1.2% in the control arm and 0.95% in the TARGIT arm. In the TARGIT arm the infection rate was 1.8% and 3.3% had skin breakdown or delayed wound healing. Further publications from this study are planned when the median follow-up is greater.

Figure 2. TARGIT-A Trial Schema



The major shortcoming of the TARGIT approach is the need to administer radiation therapy before the true pathologic extent of disease is known. In the TARGIT-A study, 15% of patients in the TARGIT arm had unexpected pathologic findings that resulted in them requiring an additional 25

treatments of daily external beam radiation therapy to achieve the desired outcome, negating the positive benefit intended of receiving a solitary treatment. Some patients in the TARGIT-A study did have TARGIT treatment as a separate procedure several weeks after the initial partial mastectomy. While this approach avoids the risk of unexpected pathologic findings, it does require a reopening in the partial mastectomy incision, and extensive manipulation of breast tissue after some healing has occurred negating some of the benefits of a single treatment. Finally TARGIT involves considerable expense as it requires purchase of dedicated equipment that has few other uses.

1.3 Single Fraction High Gradient APBI (HG-PBI)

The proposed clinical trial arose from discussion regarding the numerous merits of TARGIT treatment along with its significant limitations. Clearly a single treatment that is well tolerated and effective has enormous appeal. It has the potential to minimize the impact of local breast cancer treatment on the lives of thousands of women each year. And yet the fact that TARGIT is insufficient treatment due to a margin issue, lymph node metastasis, or some other pathologic finding in at least 15% of patients (and the frequency is likely to be greater in clinical practice than it was in a clinical trial) is clearly unsatisfying. A review of the radiation dose distributions generated in TARGIT demonstrates that they are very similar to those achieved by stereotactic body radiosurgery (SBRT). SBRT is a relative recent method of delivering highly conformal radiation dose distributions via external beam radiation therapy; it is commonly used in the radiotherapeutic management of small tumors in the lung, liver, and vertebral bodies[26]. In SBRT, typically patients receive one to five radiation treatments. SBRT utilizes special patient immobilization devices and requires image guided radiation therapy, but it has become well established in most large radiation oncology clinics.

As a preliminary work, we examined the radiation therapy CT data sets of several patients who were treated with 3D-CRT APBI. We sought to determine the feasibility of generating dosimetrically acceptable plans with external beam. Our main dosimetric goal was to deliver 7 Gy to an irregular surface 1 cm away from the surgical cavity while achieving a dose of at least 15 Gy but no more than 20 Gy at the cavity surface. We sought to limit the skin dose to less than 5 Gy and minimize low dose exposure to the surrounding breast tissue and to the nearby chest, lung, and heart. These plans which included IMRT plans using the flattening filter free mode on TrueBeam (Varian Medical Systems Inc., Palo Alto, CA) as well as Smart Arc (Philips, Amersterdam, NL) plans, showed good conformality and coverage with minimal exposure to normal tissue. An example of a 5 field IMRT plan is shown in Figure 3a and 3b below.

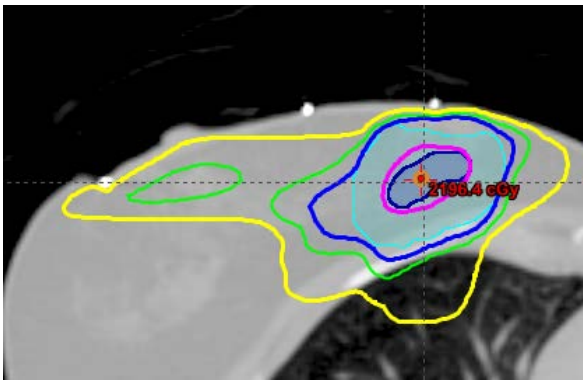
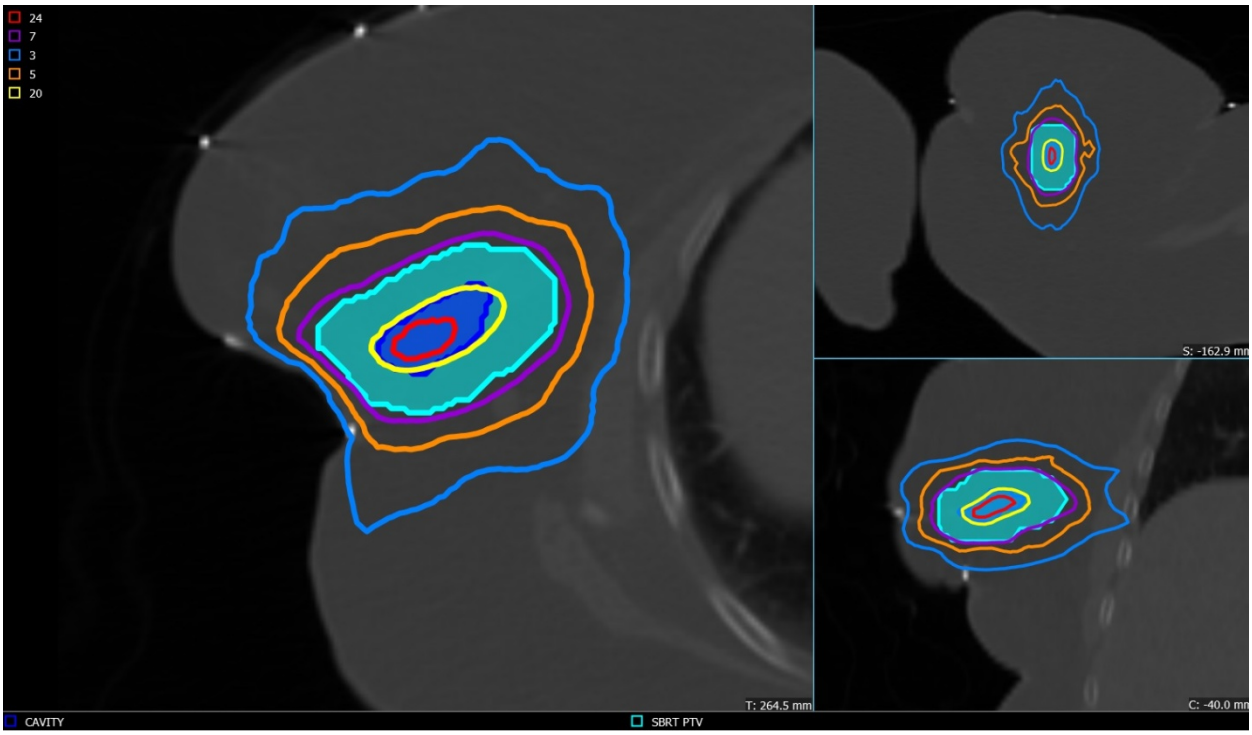


Figure 3a (Left): Isodose distribution for a 5 field IMRT plan using the 10 MV flattening filter free mode from TrueBeam. The dark blue target is the surgical bed with a prescription Dose of 20 Gy (Magenta line). The cyan target is a 1cm expansion of the surgical bed which is expected to be covered by 7 Gy (shown in blue). Dose to the lungs should be less than 5Gy (green line). The yellow line represents the 3 Gy isodose.

Figure 3b (below): Isodose distribution for a SmartArc Plan on a different patient. Again the dark blue target is the surgical bed while the cyan is a 1 cm expansion.



We have demonstrated that it is feasible to generate these plans in several patients who received conventional APBI (Table 1). This dose distribution has been shown to be well tolerated and effective in the TARGIT studies. We believe that this will also be the case when external beam radiation therapy is used. Our proposed approach allows us to avoid administering radiation before the pathologic extent of disease is known and without the purchase of specialized intraoperative radiation equipment. If successful this has the potential to revolutionize partial breast irradiation by allowing it to take place at many radiation oncology centers with minimal specialized equipment beyond that available with modern linear accelerators. Our first step is this proposed single institution phase I/II study designed primarily to evaluate the tolerance of this approach which we are choosing to call Single Fraction High Gradient APBI (HG-PBI).

Table 1. HG-PBI parameters averaged over 9 patients		
Skin structure is from skin to skin-3 mm in the region of the target		
PTV Cavity		
V20 (Rx)	93.77	%
V19 (95% Rx)	97.87	%
Min	16.622	Gy
Max	26.828	Gy
Mean	23.1	Gy
PTV + 1 cm		
V7 (Rx)	97.448	%
V6.65 (95% Rx)	97.962	%
Min	4.482	Gy
Max	26.828	Gy
Mean	14.972	Gy
Contralateral Lung		
Max	1.824	Gy
V5	0	%
Ipsilateral Lung		
Lung_Ipsi_DMax_Gy	6.164	Gy
Lung_Ipsi_V5Gy_%	2.05	%
Heart		
Heart_V5Gy_%	0.268	%
Skin		
Max	8.7575	Gy
V7	0.9425	cc
V5	4.185	cc
V3	14.6975	cc

1.4 Cosmetic Analysis in BCT

The cosmetic result after BCT is an important outcome. Unfortunately, there is no standard method for cosmetic evaluation. Harris described a four category qualitative scoring system whereby cosmesis was classified as excellent, good, fair, or poor.[27] Although this method provided for easy patient assessment of their own cosmesis, Pezner demonstrated that consensus between observers could only be attained if the four categories were reduced to excellent/good versus fair/poor.[28] Aaronson expanded the Harris scale to include global cosmetic result, appearance of the surgical scar, breast size, breast shape, nipple position, shape of the areola, and skin color as categories to be evaluated by the Harris rating system.[29] (See Appendix I) Whelan *et* al recently reported the cosmetic results in BCT using Aaronson's scale in the setting of a large phase III National Cancer Institute of Canada trial testing two radiotherapy fractionation schedules.[30] At five years, 76-77% of patients had an excellent or good cosmetic outcome. A more quantitative cosmetic assessment is the Breast Retraction Assessment (BRA) originally proposed by Pezner[31] (See Appendix III). This tool attempts to quantify the retraction in the treated breast versus the contralateral, untreated breast. The European Organization for Research and Treatment of Cancer (EORTC) has published a validation study of the Aaronson scale and the BRA using 731 patients with Stage I or II breast cancer involved in a much larger trial.[32, 33] The investigators describe moderate intraobserver agreement for the qualitative scoring system with a simple Kappa of 0.42 and a fair interobserver agreement with a multiple Kappa of 0.27. The BRA had a mean value of 30 mm with an intraobserver deviation from average of 2.3 mm (7.7%) and an interobserver deviation from the mean of 2.6 mm (8.7%). The BRA and the qualitative score were significantly correlated; however, some treatment sequelae such as scars or skin changes were best measured

qualitatively. This study will use both the Aaronson qualitative cosmetic assessment method used in the EORTC trial and the quantitative BRA for cosmetic evaluation.

1.5 Quality of Life Analysis in Breast Cancer

Quality of Life (QoL) has emerged as an important endpoint in therapeutic clinical trials. This has been particularly true in the study of diseases that have excellent overall survival and/or equivalent alternative therapies. Measures of QoL have evolved from qualitative descriptions such as performance status assigned by medical professionals to more quantitative data obtained from questionnaires filled out by patients. The EORTC Study Group on QoL has developed and validated a general cancer QoL questionnaire with several site-specific modules. The general cancer QoL questionnaire (QLQ-C30 shown in Appendix VI) contains thirty questions that assess the impact of disease and treatment on the daily life of cancer patients and is optimally used in conjunction with the appropriate disease site module.[34] The QLQ-C30 is scored using algorithms developed by the EORTC.[35] Groenvold reported high agreement between the QLQ-C30 and observer rating of patients response to open-ended responses to the same questions.[36] McLahlan showed that the QLQ-C30 questionnaire showed expected divergent validity for breast cancer patients who were expected to have different QoL based on such differences as performance status or treatment with chemotherapy.[37] The same study also demonstrated convergent validity between the QLQ-C30 and several widely used QoL scales such as the Psychosocial Adjustment to Illness Scale (PAIS) and the Profile of Mood Status (POMS). Spangers has described the development and validity analysis of a breast cancer specific module, the QLQ-BR23, that measures QoL issues more specific to breast cancer than the general QoL issues assessed by the QLQ-C30.[38] The QLQ-BR23 (See Appendix IV) is a twenty-three-item questionnaire that takes an average of 9.2 minutes (SD, 4.7 min) to complete. It has been found to be reliable and clinically valid in American women with breast cancer.[38] This study will use the QLQ-C30 and the QLQ-BR23 to assess QoL before, during, and after brachytherapy. Permission to use these copyrighted instruments for this study has been obtained. A standard Visual Analog Scale for Pain will be used for general pain assessment.

2.0 OBJECTIVES

2.1 Primary Objectives

1. To quantify the tolerance of HG-PBI by estimating the rate of acute and late treatment-related grade 3 or higher toxicity (per CTCAE, v.4.0) or any other grade 4 or 5 toxicity attributed to the therapy. Toxicities of concern include breast pain, delayed wound healing, persistent seroma fluid accumulation, breast fibrosis and fat necrosis in the treated breast. Rare toxicities include radiation pneumonitis and pericarditis.
2. To estimate the ipsilateral breast tumor recurrence rate at 5 years after HG-PBI as the sole radiation therapy technique following partial mastectomy.

2.2 Secondary Objectives

1. To quantify the proportion of patients who are free of breast cancer recurrence in the regional lymph nodes (defined as the ipsilateral axilla, infraclavicular, supraclavicular, and internal mammary groups) at five years after HG-PBI.
2. To quantify the proportion of patients who are free of breast cancer distance metastases at five years after HG-PBI.

3. To describe quality of life over time as measured by the EORTC QLQ-30 AND QLQ-BR23 questionnaires.
4. To measure cosmesis over time quantitatively by the BRA and pBRA and qualitatively by the Aronson modified Harris scale.
5. To describe the presence of any other complications using CTCAE v4.0 criteria.
6. To quantify the proportion of patients undergoing mastectomy on the treated side at 5 years after HG-PBI.
7. To describe the frequency of any CTCAE v4.0 grade 3-4 toxicities.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. AJCC 7th Edition stage 0 or I *(TisN0 ≤ 2 cm or T1N0)* histologically confirmed carcinoma *of* the breast, treated with partial mastectomy. Axillary sampling is required only for cases of invasive cancers. Tumor size is determined by the pathologist *(Section 6.2).* Clinical size may be used if the pathologic size is indeterminate. Patients with invasive cancer must have no positive axillary lymph nodes with at least 6 axillary lymph nodes sampled or a negative sentinel node.

2. Negative histologic margins of partial mastectomy or re-excision specimen. Margins generally are positive if there is invasive or noninvasive tumor at the inked resection margin, close but negative if the tumor is within 2 mm of the inked margin and negative if the tumor is at least 2 mm away from the inked edge.[41]

3. Invasive ductal, lobular, medullary, papillary, colloid (mucinous), tubular histologies, or mixed histologies *(lesions ≤ 2 cm)* that are estrogen or progesterone receptor positive and do not exhibit HER2/neu gene amplification **OR** ductal carcinoma in situ *(lesions ≤ 2 cm).*

4. Systemic therapy, if planned, must be adjuvant in nature and not be scheduled to begin for at least 4 weeks after completion of HG-PBI.

5. Good candidate for treatment per protocol in the judgment of the PI and/or treating physician following simulation.

6. Postmenopausal status.

7. Age ≥ 50 years at diagnosis.

8. Able to understand and willing to sign IRB-approved written informed consent document.

9. English speaker.

3.2 Exclusion Criteria

1. Presence of distant metastases.

2. *In situ* lobular carcinoma or nonepithelial breast malignancies such as sarcoma or lymphoma.

3. Proven multicentric carcinoma *(tumors in different quadrants of the breast, or tumors separated by at least* 4 *cm)* with other clinically or radiographically suspicious areas in the ipsilateral breast unless confirmed to be negative for malignancy by biopsy.

4. Premenopausal status.

5. Histologically confirmed positive axillary nodes in the ipsilateral axilla. Palpable or radiographically suspicious contralateral axillary, supraclavicular, infraclavicular, or internal mammary nodes, unless there is histologic confirmation that these nodes are negative for tumor.

6. Prior non-hormonal therapy for the present breast cancer, including radiation therapy or chemotherapy.

7. Diagnosis of systemic lupus erythematosis, scleroderma, or dermatomyositis.

8. Diagnosis of a coexisting medical condition which limits life expectancy to < 2 years.

9. Diagnosis of psychiatric or addictive disorders that would preclude obtaining informed consent.

10. History of other malignancy ≤ 5 years previous with the exception of basal cell or squamous cell carcinoma of the skin which were treated with local resection only or carcinoma *in situ* of the cervix.

11. Paget's disease of the nipple.

12. Skin involvement, regardless of tumor size.

13. Unsatisfactory breast for HG-PBI as determined by the treating physician. For example, if there is little breast tissue remaining between the skin and pectoralis muscle after surgery, treatment with HG-PBI is technically problematic.

14. Partial mastectomy so extensive that the cosmetic result is fair or poor prior to HG-PBI as determined by the treating physician.

15. Surgical margins which cannot be microscopically assessed or are positive at pathological evaluation.

16. Time between final definitive breast procedure to HG-PBI simulation is greater than 8 weeks.

3.3 Inclusion of Women and Minorities

Women and members of all races and ethnic groups are eligible for this trial. Because breast cancer occurs rarely in men, men will not be recruited for participation.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. The registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

5.1 Pre-Treatment Evaluations

These evaluations must take place no more than 28 days prior to initiation of treatment.

- History and physical exam by team radiation oncologist.
- Pre-implant cosmesis assessment by qualitative means and BRA (See Appendix III)
- Completion of the EORTC QLQ-30 and BR23 questionnaire

5.2 Radiation Therapy

5.2.1 Timing

HG-PBI must take place no more than 8 weeks from final definitive breast surgery.

5.2.2 Dose Specifications

PTV Cavity: total dose of 15-20 Gy in one fraction.
PTV Cavity + 1 cm Surface: minimum dose of 5-7 Gy in one fraction.

5.2.3 Technical Factors

The guidelines for IMRT in this trial will conform to the policies set by the Advanced Technology Consortium (ATC) and the National Cancer Institute (NCI), which may be found at: http://atc.wustl.edu/home/NCI/NCI_IMRT_Guidelines.html. Each of the target volumes and normal structures listed below must be delineated on each slice from the 3D planning CT in which that structure exists. Megavoltage photon beams with energies ≥ 6 MV and megavoltage electron beams are required. Proton beams are allowed. Co-60 teletherapy is allowed.

5.2.4 Localization, Simulation, and Immobilization

Simulation and treatment may be performed with the patient in the supine or prone position. Patients should be optimally positioned with alpha cradle casts or other methods of immobilization at the discretion of the treating physician.

Methods to minimize the cardiac exposure to RT like heart block, gating or breathhold are allowed at the discretion of the treating physician. For large-breasted patients, including those with a large inframammary skin fold, devices to improve positioning of the breast are permissible.

A treatment planning CT scan in the treatment position will be required to define the clinical target volumes (CTV) and planning target volumes (PTV). The CT required for generation of a virtual plan with 3DCRT or IMRT must be post-lumpectomy. Radio-opaque markers must be placed on external landmarks at the acquisition of the CT scan to facilitate contouring segmentation of the CT data-set. These markers should identify:

1. The lumpectomy incision
2. The outline of the palpable breast tissue circumferentially at least from 2 o'clock to 10 o'clock
3. The superior border of the breast tissue at 12 o'clock based on palpation

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 ≤ 0.5 cm should be employed. External skin localizing marks, which may include permanent tattoos, are allowed.

5.2.5 Treatment Planning/Target Volumes

The definitions for the CTV, PTV and normal structures used in this protocol generally conform to the 1993 ICRU report #50 titled Prescribing, Recording and Reporting Photon Beam Therapy and the RTOG-endorsed consensus guidelines for delineation of target and normal structures for breast cancer found at:
http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx.

5.2.5.1 Target Volumes and Normal Structures

Partial Mastectomy Volumes

PTV Cavity: Contour using all available clinical and radiographic information including the excision cavity volume, architectural distortion, lumpectomy scar, seroma and/or extent of surgical clips. Limit the PTV Cavity posteriorly at anterior surface of the pectoralis major and anterolaterally 5 mm from skin

and should not cross midline. In general, the pectoralis and/or serratus anterior muscles are excluded from the PTV Cavity.

PTV Cavity + 1 cm: PTV Cavity + 1 cm 3D expansion limited to exclude the part outside the ipsilateral breast and the first 5 mm of tissue under the skin (in order to remove most of the build up region for the DVH analysis) and excluding beyond the posterior extent of breast tissue (chest wall, pectoralis muscles and lung) when pertinent. The PTV Cavity + 1 cm should not cross midline. This PTV Cavity + 1 cm is the structure used for DVH constraints and analysis.

Breast Volumes

Breast CTV: Includes the palpable breast tissue demarcated with radio-opaque markers at CT simulation (see Section 5.2.3), the apparent CT glandular breast tissue visualized by CT, consensus definitions of anatomical borders, and the Lumpectomy CTV from the breast cancer atlas (see Partial Mastectomy Volumes above). The breast CTV is limited anteriorly within 5 mm from the skin and posteriorly to the anterior surface of the pectoralis, serratous anterior muscle excluding chest wall, boney thorax and lung. In general, the pectoralis and/or serratous anterior muscles are excluded from the breast CTV unless clinically warranted by the patient's pathology. The breast CTV should generally follow consensus guidelines found at:
http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx

Contralateral Breast

Includes the apparent CT glandular breast tissue visualized by CT and consensus definitions of anatomical borders from the RTOG Breast Atlas. In general the borders are:
Posterior border: At the anterior surface of the pectoralis, serratous anterior muscles excluding chest wall, ribs, boney thorax and lung/heart;
Medial border: The sternal-costal junction,
Lateral border: Varies based on the size of the breast but typically is at the mid-axillary line and excludes the ipsilateral lattismus dorsi muscle.
Cephald border: Should be similar to that of the ipsilateral breast CTV
Caudal:border: Inframammry fold and should be similar to that of the ipsilateral breast CTV.
Anterior border: Skin minus 5 mm to minimize inaccuracy of dose calculation at the skin surface.

Refer to breast contouring atlas found at:
http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx

Ipsilateral Lung

This may be contoured with auto-segmentation with manual verification.

Contralateral Lung

This may be contoured with auto-segmentation with manual verification

Heart

This is to be contoured on all cases, not just the left sided cases. The heart

should be contoured beginning just inferior to the level in which the pulmonary trunk branches into the left and right pulmonary arteries (PA). Above the PA, none of the heart's 4 chambers are present. The heart should be contoured on every contiguous slice thereafter to its inferior most extent near the diaphragm. The following structures, if identifiable, should be excluded from the heart contour: esophagus, great vessels (ascending and descending aorta, inferior vena cava). One need not include pericardial fat, if present. Contouring along the pericardium itself, when visible, is appropriate.

Thyroid
The thyroid is easily visible on a non-contrast CT due to its preferential absorption of iodine, rendering it "brighter" or denser than the surrounding neck soft tissues. The left and right lobes of the thyroid are somewhat triangular in shape and often do not converge anteriorly at mid-line. All "bright" thyroid tissue should be contoured.

5.2.5.2 Treatment Planning

CT-based planning with tissue inhomogeneity correction is required.

IMRT or 3D-CRT are permitted; arc based delivery is allowed; Co-60 teletherapy is allowed.

PTV Cavity should have a minimum dose of 15 Gy and maximum of 22 Gy. PTV Cavity + 1 cm should have a minimum dose of 5 Gy. With these goals a high dose gradient is achieved.

Normal tissue constraints: Skin structure is from skin to skin-3 in the region of the target Dmax ≤ 22 Gy, V20 ≤ 10mL, V10 ≤ 15mL, V3 ≤ 20 mL. Contralateral Lung Dmax ≤ 3 Gy, V5 ≤ 5%; Ipsilateral Lung Dmax ≤ 7 Gy, V5 ≤ 5%; Heart V5 ≤ 2%; Thyroid V5 ≤ 10%.

5.3 General Concomitant Medication and Supportive Care Guidelines

Hormone therapy, chemotherapy, or biologic therapy is not allowed prior to HG-PBI, but may be started at least 4 weeks after the completion of HG-PBI.

5.4 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

Treatment will consist of a partial mastectomy and single fraction of HG-PBI which will take place no more than 8 weeks after final definitive surgical procedure. Treatment will be discontinued if one of the following criteria applies:

- Documented and confirmed disease progression
- Death

- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

5.5 Duration of Follow-up

Patients will be followed according to the scheduled described in the study calendar for 5 years or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.0 DISEASE RESPONSE CRITERIA

6.1 Mastectomy Free Survival

Any form of mastectomy to the treated breast for any reason is a failure for mastectomy-free survival.

6.2 Recurrence of Breast Cancer

Recurrence of breast cancer in the treated breast is an ipsilateral breast tumor recurrence (IBTR). Recurrence in a regional lymph node is a regional failure. The regional lymph nodes are defined as the axillary, supraclavicular, infraclavicular and internal mammary lymph nodes. The definition of recurrence of breast cancer is: histologic evidence of recurrent carcinoma, either invasive or non-invasive *(except LCIS)* in the ipsilateral breast.

Clinical evidence of recurrent carcinoma by physical examination and/or mammogram will not be construed as evidence of treatment failure without biopsy proof, but will be considered as suspicious for recurrence. Ipsilateral breast recurrences will be categorized as local *(infield)* if they occur within the prescription isodose volume, peripheral if between the prescription isodose volume and a volume 2 cm outside of the prescription isodose volume, and non-contiguous or extrafield if they are beyond the peripheral volume described above.

6.3 Cosmesis

At a minimum, cosmesis will be graded by the patient and the radiation oncologist before treatment, 6-10 weeks after HG-PBI, at 4-8 month follow-up, at 10-14 month follow-up, and at yearly intervals thereafter for a total of 5 years following HG-PBI. Cosmesis will be graded on qualitative and quantitative scales.

6.3.1 Qualitative Evaluation

The Aaronson modification of the Harris scale will be used to qualitatively evaluate cosmesis. The patient and physician forms are included in Appendix I and II. The following general descriptors will be used:

- *Excellent* - when compared to the untreated breast, there is minimal or no difference in the size, shape or texture of the treated breast. There may be mild thickening or scar tissue within the breast or skin, but not enough to change the appearance.
- *Good* - there is mild asymmetry in the size or shape of the treated breast as compared to the normal breast. The thickening or scar tissue within the breast causes only a mild change in the shape.
- *Fair* - there is obvious difference in the size and shape of the treated breast. This change involves 1/4 or less of the breast.
- *Poor* - marked change in the appearance of the treated breast involving more than 1/4 of the breast tissue.

6.3.2 Quantitative Evaluation

BRA will be calculated by the radiation oncologist or NP at each follow up assessment. See Appendix III for BRA calculation.

7.0 STUDY CALENDAR

Baseline assessments should be performed no more than 28 days before initiation of treatment.

	Surgery	Baseline	No more than 8 wks post-surgery	2 wks[a]	8 wks[b]	6 mo[c]	12 mo[c]	18 mo[c]	24 mo[c]	36 mo[c]	Yr 4	Yr 5
Informed consent		X										
Physical exam		X		X	X	X	X	X	X	X	X	X
Mammogram		X[f]				Yearly						
Simulation		X										
Partial mastectomy	X											
HG-PBI			X									
EORTC-QLQ30 and BR23, Brief Pain Assessment		X		X	X	X	X	X	X	X	X	X
Aronson modified Harris scale		X			X	X	X		X	X	X	X
BRA calculation		X			X	X	X		X	X	X	X
Adverse events		X		X	X[d]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]

a: after HG-PBI
b: +/- 2 weeks
c: +/- 2 months
d: monitoring for acute toxicities
e: monitoring for late toxicities
f: baseline mammogram is not required within 28 days before initiation of treatment
g: EORTC-QLQ30 and BR23attached as appendix IV, Brief Pain Assessment attached as appendix V

8.0 DATA SUBMISSION SCHEDULE

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Registration Form Eligibility Form Demographics Form On-Study Form	Prior to starting treatment
Surgery Form	Following surgery
HG-PBI Form	Following RT
Follow-Up Form EORTC-QLQ30 EORTC-BR23 Patient Cosmetic Evaluation Form Physician Cosmetic Evaluation Form Pain Assessment Form	Baseline (all but follow-up form) 2 weeks 8 weeks 6 months 12 months 18 months 24 months 36 months 4 years 5 years
Mammography Form	Baseline 6 months 18 months 36 months 4 years 5 years
Acute Toxicity Form	8 weeks
Late Toxicity Form	6 months 12 months 18 months 24 months 36 months 4 years 5 years

9.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 9.2.

9.1 Definitions

9.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:

http://www.hhs.gov/ohrp/policy/advevntguid.html

9.1.2 Serious Adverse Event (SAE)

Definition: any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

9.1.3 Unexpected Adverse Experience

Definition: any adverse experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

9.1.4 Life-Threatening Adverse Experience

Definition: any adverse experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

9.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

9.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

9.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

9.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

9.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within 10 days of receipt of IRB acknowledgment via email to a QASMC auditor.

9.4 Timeframe for Reporting Required Events

Reportable adverse events will be tracked for 30 days following the last day of study treatment. For the purposes of this protocol, grade 4 myelosuppression or aplasia are not considered reportable. All events of interest should be captured on the adverse event data form.

10.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

11.0 STATISTICAL CONSIDERATIONS

11.1 Specific Aims

11.1.1 Specific Aim 1

We will quantify the tolerance of HG-PBI by estimating the rate of acute and late treatment-related grade 3 or higher toxicity (per CTCAE, v.4.0) or any other grade 4 or 5 toxicity attributed to the therapy. Toxicities of concern include breast pain, delayed wound healing, persistent seroma fluid accumulation, breast fibrosis and fat necrosis in the treated breast.

Rare toxicities include radiation pneumonitis and pericarditis. *Hypothesis:* Morbidity occurs in approximately 5-8% of patients with a maximum allowable proportion with grade 3-5 toxicities of 12%. A sequential probability ratio stopping rule will be used to monitor the toxicity rate during the trial.

11.1.2 Specific Aim 2

We will estimate the ipsilateral breast tumor recurrence rate at 5 years after HG-PBI as the sole radiation therapy technique following partial mastectomy. *Hypothesis:* The IBTR will be less than 15.9% with 95% confidence resulting in a treatment strategy worthy of further investigation in a larger clinical trial.

11.1.3 Specific Aim 3

We will estimate the change in breast cosmesis over time using the validated, quantitative parameter pBRA. *Hypothesis:* The pBRA will not significantly change over time. We have previously demonstrated this in the setting of multicatheter APBI.[20]

11.2 Study Endpoints

The principal endpoints are the proportion of patients who are free of serious treatment related toxicity as discussed below and the proportion of patients who are free of breast cancer in the treated breast (IBTR). Secondary endpoints are the proportion of patients who are free of breast cancer in the regional lymph nodes (ipsilateral axilla, infraclavicular, supraclavicular, and internal mammary groups), free from distant disease, and proportion surviving. Additional secondary endpoints are quality of life as measured by the EORTC QLQ-C3 and QLQ-BR23, cosmesis as measured quantitatively by the BRA and pBRA, cosmesis as measured qualitatively by the Aronson modified Harris scale, the presence or absence of complications, the occurrence of mastectomy after completion of initial breast-conserving treatment and the frequency of any CTCAE v4.0 grade 3-4 toxicities.

11.3 Study Design and Analysis Plan

This is a single arm, non-randomized phase I/II study of 50 patients with stage 0 (tumor size $\leq$ 2cm) or I breast cancer. The primary study goal is to quantify the tolerance of HG-PBI by estimating the rate of acute and late treatment-related grade 3 or higher toxicity (per CTCAE, v.4.0) or any other grade 4 or 5 toxicity attributed to the therapy. Toxicities of concern include breast pain, delayed wound healing, persistent seroma fluid accumulation, breast fibrosis and fat necrosis in the treated breast. Rare toxicities include radiation pneumonitis and pericarditis. These are expected to occur in approximately 5-8% of patients with a maximum allowable proportion with grade 3-5 toxicities of 12%. A sequential probability ratio stopping rule will be used to monitor the toxicity rate during the trial. For example, the study will be suspended for review of toxicity if 4 cases of grade 3-5 toxicity are seen among the first 14 patients, or 5 among the first 26 patients. The full criteria for monitoring are given in the table below. All toxicities and other serious adverse events will be reported to the Clinical Trials Office and to QASM as described.

The study will be suspended for review if:	
this number of patients are	before this number of patients

observed with grade 3-5 toxicity:	have completed the trial:
4	14
5	26
6	38
7	50

Patients will be followed for 5 years. The primary goals of the study involve tolerance to treatment; the proportion of patients who are breast cancer free 5 years after treatment will be calculated with a 95% confidence interval. Cosmetic outcome will be assessed qualitatively by patients and physicians over the years after treatment. The two sets of scores will be plotted using histograms showing the proportion rating the outcome excellent, good, fair and poor. Kappa statistics with 95% confidence intervals will be calculated to assess the agreement between patient and physician scores before treatment, at 4-6 months at 1 year, and at subsequent visits. The pBRA will be used to assess cosmesis quantitatively. This instrument includes a formula expressing the extent of displacement of the treated breast relative to the contralateral breast and other anatomical features. pBRA scores will be plotted at the assessment points and presented graphically. Quality of life will be assessed using the 30 items of the EORTC QLQ-C30 and 23 items of the QLQ-B23 and the Visual Analog Scale for Pain. The QLQ-C30 includes 6 general questions and 24 questions in 9 subscales measuring physical, role, emotional, cognitive and social function, as well as global health status, nausea/ vomiting, pain and fatigue. The QLQ-B23 provides 23 questions in 8 breast cancer specific subscales, 4 measuring symptoms and 4 measuring function. Each of the subscales will be tabulated and presented graphically over the assessment times. Mixed repeated measures models will be generated to describe the nature of change in quality of life over time. Complications will be tabulated and frequencies presented graphically. The rate of mastectomy within five years of treatment will be calculated with a 95% confidence interval.

11.4 Sample Size and Study Power

Although the primary goals of this study include tolerance to treatment, the sample size for this study is based on the proportion of patients who remain free from an ipsilateral breast cancer recurrence (IBTR) 5 years after treatment which will be compared with the current expected value in the medical literature. Fyles reported that the five-year IBTR in a large population of women ≥ 50 yr with pT1N0 estrogen receptor positive breast cancers treated with partial mastectomy and tamoxifen but no radiation therapy was 5.9%[39]. HG-PBI will be considered worthy of further investigation if 1) the treatment-related toxicity rate as described above is less than 12% and 2) the five-year IBTR is not significantly greater than 10% higher than that observed in the Fyles study. Binomial proportion power analysis, assuming an alpha-level of 0.05, determined that we will obtain approximately 70% power to detect a proportion significantly larger than 15.9% given the true five-year IBTR is the same as that observed in the Fyles study. If 50 patients complete the trial and more than 3 recurrences are observed in the first five years, then the observed rate will be significantly larger than the acceptable proportion. Consequently, if 3 or fewer recurrences are observed among 50 patients and the tolerance parameters are met, the study will conclude that there is preliminary evidence that HG-PBI as performed in this trial is worthy of further study.

11.5 Treatment Failure

It should be noted that ipsilateral breast tumor recurrences (IBTR) do not cause a diminished overall survival. Nonetheless, they do represent a failure of breast conservation. We will assess the

possibility of an unexpected rise in IBTR by comparing the observed IBTR rate to that expected from an exponential distribution with an event rate of 5% over 5 years. The assessment is repeated every 6 months during the patient accrual phase of the study and once a year thereafter to the end of the five-year follow-up period. A Hochberg stepdown procedure, implemented by SAS proc multtest, will be used to adjust the p-values for multiple looks.

11.6 Accrual

It is estimated that less than 10% of the patients treated in this study will be lost to follow up. Therefore, because the accrual goal is 50 evaluable patients (at 5 years post-treatment), target accrual is 55 patients to account for the 10% anticipated drop-out. It is estimated that patient accrual will take two to three years.

The investigators are well aware that several prior clinical trials that involved breast cancer at the Washington University Medical Center and the Siteman Cancer Center suffered from poor accrual. We believe that this trial will have excellent patient accrual. The primary source of patients who may be eligible for this study is via the breast surgeons of the Section of Endocrine and Oncologic Surgery here at Washington University. The chief breast surgeon is a collaborator in this study and is very supportive. The fact that a large fraction of patients with a common cancer disease are eligible for this study should lend further reassurance that this study ought to enjoy excellent patient accrual. The following series of conservative estimates provide an approximation of patient accrual: in 2012 more than four hundred patients with breast cancer were seen by physicians in the Department of Radiation Oncology. A conservative estimate is that 20% of these patients had an early stage breast cancer that would be eligible for this study. A further conservative estimate is that a third of these patients will consent to participate in this study. This yields an estimated accrual of just over 25 patients per year.

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APPENDIX I: Patient Evaluation of the Treated Breast

You have been treated with breast-conserving therapy for breast cancer. As you know, a reason for choosing this treatment is the potential for keeping a breast that looks and feels as close to normal as possible. Your opinion concerning the appearance of your breast is valuable to us.

I. Please circle the word below which best describes your judgment of the cosmetic results of therapy at this time:

EXCELLENT when compared to the untreated breast, there is minimal or no difference in the size or shape of the treated breast. The way the breast feels (its texture) is the same or slightly different. There may be mild thickening or scar tissue within the breast or skin, but not enough to change the appearance.

GOOD there is mild asymmetry between the breasts, which means that there is a slight difference in the size or shape of the treated breast as compared to the opposite breast. There may be some mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes only a mild change in the shape.

FAIR moderate deformity of the breast, with an obvious difference in the size and shape of the treated breast. This change involves 1/4 or less of the breast. There is moderate thickening or scar tissue of the skin and the breast, and obvious color changes.

POOR marked change in the appearance of the treated breast involving more than 1/4 of the breast tissue. The skin changes are very obvious. There is severe scarring and thickening of the breast.

II. In summary, regarding your breast conservation therapy, your overall feeling is:
A) completely satisfied with the treatment and results.
B) not totally satisfied, but would choose breast conservation therapy again.
C) dissatisfied with breast conservation therapy.

III. If you had it all over to do again, would you prefer to have your breast cancer treated:
A) just the way you were treated.
B) with a mastectomy, not requiring radiation therapy.

IV. It is sometimes very difficult to tell if the changes in your treated breast are due to the surgery, the radiation therapy, or both. Try to remember what the breast looked like after the surgery, but before the radiation treatments began. Now compare that memory to the appearance of the breast now. The changes within your breast at this time are in your opinion:
A) caused mostly by the radiation.
B) caused by both the radiation and surgery, but mostly by the radiation.
C) caused by both the radiation and surgery, but mostly by the surgery.
D) caused mostly by the surgery.
E) can't judge which treatment caused the change.
F) there are no changes.

PLEASE PRINT YOUR NAME: _____ DATE: _____

APPENDIX II: Physician Evaluation of the Treated Breast

The physician should never share his evaluation with the patient, as it may influence subsequent patient evaluations. Also, do not glance at previous evaluations...it is the evolution of cosmetic changes we are studying.

PATIENT'S NAME:_____ DATE: _____
EVALUATOR: _____

I. Please assess the cosmetic results of breast conservation therapy <u>at this time</u> (Circle one):

EXCELLENT when compared to the untreated breast, there is minimal or no difference in the size or shape of the treated breast. The way the breast feels (its texture) is the same or slightly different. There may be mild thickening or scar tissue within the breast or skin, but not enough to change the appearance.

GOOD there is mild asymmetry between the breasts, which means that there is a slight difference in the size or shape of the treated breast as compared to the opposite breast. There may be some mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes only a mild change in the shape.

FAIR moderate deformity of the breast, with an obvious difference in the size and shape of the treated breast. This change involves 1/4 or less of the breast. There is moderate thickening or scar tissue of the skin and the breast, and obvious color changes.

POOR marked change in the appearance of the treated breast involving more than 1/4 of the breast tissue. The skin changes are very obvious. There is severe scarring and thickening of the breast. In retrospect, the breast may have been better treated by a mastectomy.

II. In the physician's opinion, the changes within the treated breast are:
A) caused mostly by the radiation.
B) caused by both the radiation and surgery, but mostly by the radiation.
C) caused by both the radiation and surgery, but mostly by the surgery.
D) caused mostly by surgery.
E) can't judge which treatment caused the change.
F) there are no changes.

III. *Instructions:* For each of the breast characteristics presented above, please rate the treated breast *as compared to the untreated breast*. Place a check mark in the appropriate cell for each characteristic.

	No Difference	**A Small Difference**	**A Moderate Difference**	**A Large Difference**	**Not Evaluable**
	0	**1**	**2**	**3**	**4**
Breast Size					
Breast Shape					
Skin Color					
Location of the areola and nipple					
Shape of the areola and nipple					

IV. How would you rate the appearance of the surgical scars? Please circle your assessment.

0 = Very unobstrusive
1 = Visible but not affecting cosmetic results
2 = Visible and detracting somewhat from cosmetic results
3 = Visible and detracting a great deal from cosmetic results
4 = Not evaluable

V. Measure and record the Breast Retraction Assessment parameters (see Appendix III):

a_1 = _____

b_1 = _____

a_2 = _____

b_2 = _____

APPENDIX III: Quantitative Cosmetic Analysis

Determining the Breast Retraction Assessment (BRA) and percent BRA (pBRA). From [32]

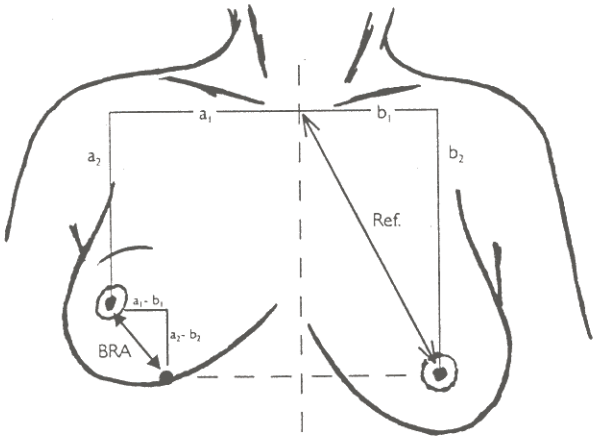

Fig. 1. Illustration of the BRA measurements.
BRA = $\sqrt{(a_1 - b_1)^2 + (a_2 - b_2)^2}$;
reference length (ref.) = $\sqrt{b_1^2 + b_2^2}$;
pBRA = (BRA/reference length) × 100.

APPENDIX IV: EORTC QLQ-C30 and BR23

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|

Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|

Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall <u>health</u> during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall <u>quality of life</u> during the past week?

1 2 3 4 5 6 7

Very poor Excellent

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

APPENDIX V: Brief Pain Assessment

INSTRUCTIONS:

Make a mark on the line below showing how severe your breast pain is at this moment.

No Pain — The Worst Imaginable Pain