A Phase II Study of Preoperative Stereotactic Ablative Body Radiotherapy (SABR) for Early-Stage Breast Cancer: Introduction of a Novel Form of Accelerated Partial Breast Radiotherapy

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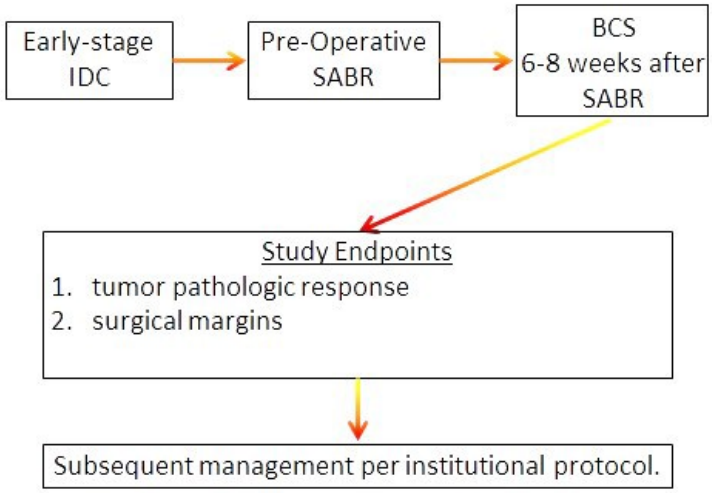

*IDC - Invasive ductal carcinoma

**BCS - Breast-conserving surgery

***SABR - Stereotactic Ablative Body Radiotherapy

ELIGIBILITY CRITERIA

Inclusion Criteria:

A. Understand and voluntarily sign an informed consent document prior to conducting any study related assessments or procedures.

B. Histologically proven invasive adenocarcinoma of breast.

C. Must have marker clip indicating location of target tumor in breast.

D. Unifocal tumor ≤2 cm based on contrast-enhanced prone-breast MRI.

E. The patient must be clinically and radiographically node negative (N0) to participate on this protocol. Clinically suspicious regional nodes by imaging or physical exam require biopsy evaluation to exclude disease involvement.

F. Appropriate candidate for breast-conserving surgery based on multi-disciplinary assessment.

G. Females age ≥ 50 years.

H. Able to tolerate prone body positioning during radiation therapy.

I. No prior ipsilateral-breast or thoracic radiotherapy.

K. As defined on MRI, target lesion must be at least 10 mm distance from skin (defined as volume encompassing first 3 mm from breast surface).

L. Subjects must be estrogen receptor (ER) positive .

M. Must be negative for Her-2 amplification. (Either 1+ on semi-quantitative evaluation of immunostain or negative by fluorescent in-situ hybridization).

N. No implanted hardware or other material that would prohibit appropriate treatment planning or treatment delivery in the investigator's opinion.

O. No history of an invasive malignancy (other than this breast cancer, or non-metastatic basal or squamous skin cancers) in the last 5 years.

P. Must not have received nor be planned for neoadjuvant chemotherapy prior to SABR or surgery.

Q. ECOG performance status <2 (see Appendix Ill).

R. Females of childbearing potential must have a negative urine pregnancy test prior to simulation and within seven days of SABR start as per section 7.2 of the protocol. A female of childbearing potential is a sexually mature woman who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months).

Exclusion Criteria:

A. Subjects must not have invasive lobular carcinoma.

B. Subjects must not have a Tumor > 2 cm as measured on prone contrast-enhanced breast MRI.

C. Subjects must not have presence of histologically proven lymph node disease.

D. Subjects are not a candidate for breast conserving surgery.

E. Subjects must not have prior ipsilateral-breast or thoracic radiotherapy.

F. Subjects must not have history of scleroderma or lupus erythematosus with either cutaneous manifestation or requiring active treatment.

G. Subjects must not have an MRI defined target tumor that is within 10 mm of skin (defined as volume encompassing first 3 mm from skin surface).

H. Subjects must not have amplification of Her-2 (Either 3+ by semi-quantitative immunostain or positive by Flourescent in-situ hybridization (FISH)).

I. Subjects must not have implanted hardware or other material that would prohibit appropriate treatment planning or treatment delivery in the investigator's opinion.

J. Subjects must not have history of an invasive malignancy (other than this breast cancer, or non-metastatic basal or squamous skin cancers) in the last 5 years.

K. Subjects must not have received or plan to receive neoadjuvant chemotherapy either before radiotherapy or before surgery.

L. Subjects must not be a known carrier of BRCA1 or BRCA2 gene mutation.

M. Subjects must not be pregnant or unwilling to undergo pregnancy screening.

HYPOTHESES
Pre-operative breast SBRT will yield at least 10% probability of pathologic complete response.

1.0 BACKGROUND

1.1 Study Disease and Rationale

More than 130,000 women undergo breast-conserving surgery (BCS) annually in the United States. [1] The current paradigm is to deliver post-operative radiotherapy to the retained whole or partial breast to maximize in-breast local control.

Conventional post-operative whole breast radiotherapy is well studied and effective. It is, however, inconvenient consisting of 3-7 weeks of daily treatment. Also, due to its comprehensive coverage of all breast tissue, the radiation fields must extend posteriorly and typically include a portion of normal lung and in some cases heart. The unintended irradiation of these organs has been shown to cause late-term increase in cardiovascular mortality. [2, 3]

Following the realization that most in-breast local recurrences occur near or at the previous tumor site, it becomes logical to irradiate only the post-operative lumpectomy cavity and spare the remaining breast. In properly selected patients, this approach has been shown to be effective in preventing tumor recurrence without excessive failures in remaining untreated breast. [4-17]

The widespread adoption and interest for such partial breast irradiation (APBI) has been driven, in part, by its more patient-convenient shortened treatment schedules lasting one week to one day. Also, owing to reduced tissue volume that is irradiated, APBI generally results in reduced radiation exposure to heart and lung.

Several methods of APBI have been developed. Frequently employed invasive techniques include intra- operative radiotherapy (IORT) and interstitial or intra-cavitary brachytherapy. The non-invasive category, which is our interest in this protocol, includes variations on 3D-conformal external beam radiotherapy.

The invasive approaches typically treat a smaller volume of tissue more conformally although there remains operator dependence. [18] Aside from IORT, however, they have generally relied on twice-daily fractionation schedules which diminish convenience and cost benefits while also introducing complication risk from in-dwelling brachytherapy catheters which remain in place for the duration of treatment. [19] Published experiences have also indicated increased risk of conversion to mastectomy from brachytherapy-related soft tissue toxicity. [20, 21]

In highly selected cases, IORT offers the convenience of single-treatment radiotherapy which is completed at the time of surgery. Availability of IORT-equipped facilities is, however, limited and generally IORT increases operating room and anesthesia time by 40-60 minutes--diminishing cost savings and increasing anesthesia time for the typically elderly patients that are candidates for this treatment.

Conversely, external beam-based techniques are widely available, non-invasive, and less operator-dependent. Published experiences describe varied cosmetic outcomes with this approach as well, with some reports of soft tissue toxicity.[22-23] One potential explanation arises from the necessarily large breast volume that is treated when employing conventional external beam APBI because one must account for respiratory motion as well as uncertainty in delineation of the lumpectomy cavity which is often poorly defined on post-operative imaging.[24-26]

In a dosimetric simulation of pre-operative stereotactic radiosurgery for prone-breast targets, Palta et al. have shown significant reductions in volume of ipsilateral breast receiving 100% and 50% of prescription radiation dose from 18% to 3% and 53% to 13.3%, respectively, when compared to patients treated post- operatively.[27]

In a phase 1 investigation of pre-operative stereotactic radiosurgery for breast carcinoma, Blitzbau et al similarly confirm the emergence of markedly smaller target volumes and ease of meeting normal tissue dose constraints. Moreover, no dose-limiting toxicities were encountered at the highest evaluated dose level of 21 Gray in a single fraction (personal communication with Dr. Blitzbau).[28]

We therefore propose to build on this experience and evaluate pre-operative highly conformal stereotactic ablative body radiotherapy (SABR) in a phase 2 context. Our protocol will differ from the experience reported by Blitzbau et al. in an important way in that we will delay surgery for 6-8 weeks following radiotherapy as opposed to 10 days. We feel this is an important distinction because it is likely that 10 days is insufficient time for a pathologic complete response to become fully manifest. It is possible that if more time were allowed to elapse between radiation and tumor resection that more pathologic complete responses will perhaps be observed as has been shown to be the case in other disease sites where radiation is followed by surgical resection.[29]

Another important difference will be the fractionation of treatment over three days as opposed to delivering a single fraction in one treatment session. While perhaps slightly less convenient than single-fraction treatment, it is possible that moderate fractionation will further reduce the risk of soft tissue toxicity in the treated breast. Of note, Blitzbau et al. reported fair/poor cosmetic outcome in all three patients who underwent pre-operative single-fraction breast radiosurgery who then also required post-operative whole breast radiotherapy for adverse findings noted on final surgical pathology. Conversely, Bondiau et al. reported only one grade 3 toxicity in a dose- finding study where patients received pre-operative SABR (maximum 31.5 Gy in 3 fractions of 10.5 Gy each) concurrent with chemotherapy than followed by conventional whole breast radiotherapy after surgery. Similarly, Formenti et al. have reported 2 cases of grade 3 toxicity and 1 local recurrence in one hundred patients treated with post-operative breast SABR at a median 64 month follow-up (30 Gy in 5 fractions of 6 Gy each). These results suggest a toxicity sparing effect with only moderate fractionation of the radiation dose.[30, 31]

Furthermore, historic dogma of radiobiology informs that fractionation of radiation promotes re-oxygenation of hypoxic tumor as well as redistribution of malignant cells into radiosensitive phases of cell cycle; both of which promote radiation mediated cell killing. It is therefore possible that the moderate fractionation proposed in this protocol will augment the probability of obtaining pathologic complete response.

Considering the low rates of toxicity and good patient tolerance reported by previous experiences delivering breast SABR in both pre- and post-operative settings, it is appropriate to conduct our trial as a phase 2 investigation aimed at establishing efficacy as measured by rates of pathologic complete response. We have selected our dose at 28.5 Gy in 3 fractions of 9.5 Gy per fraction for two reasons.

First, it has been experimentally suggested that moderately fractionated SABR is efficient at inducing immune activation which is a focus of planned correlative biomarker studies. [32, 33]

Secondly, Bondiau et al. showed no further correlation with pathologic complete response in evaluated doses higher than 25.5 Gy in 3 fractions of 8.5 Gy/fraction and they actually proposed that this be the dose evaluated in a phase 2 trial. An important distinction, however, to our proposed trial is that our patients will not receive concurrent chemotherapy as was done by Bondiau et al. We have therefore chosen the next higher dose cohort to off-set loss of anti-tumor effect resulting from not giving concurrent chemotherapy.

1.2 Pre-operative Treatment

Generally all forms of APBI, invasive and non-invasive, have followed the paradigm of treating post-operatively to the lumpectomy cavity to reduce in-breast recurrence risk. External beam APBI is unique, however, in that it can theoretically be applied pre-operatively. Because other forms of APBI require surgical creation of a cavity for placement of a treatment applicator, they are innately incompatible with pre-operative treatment.

Pre-operative treatment may be advantageous to reduce soft tissue toxicity and optimize breast cosmesis because, generally speaking, an intact breast tumor is smaller than its corresponding lumpectomy cavity following surgery and is also easier to distinguish on treatment-planning images. Therefore delivering APBI pre-operatively is likely to result in smaller and more accurately delineated target volumes, which is expected to reduce normal tissue exposure and attendant risk of soft tissue toxicity. [27, 34-36] Also, because treatment is delivered pre-operatively, subsequent surgery will remove the most heavily irradiated tissue and hopefully reduce risk of fibrosis.

Pre-operative treatment may also overcome theoretical losses in radiotherapy efficacy associated with delays in treatment arising from post-operative recovery time and/or delivery of chemotherapy which typically delays radiotherapy by several months. [37]

Lastly, evaluation of excised tumor following delivery of ablative radiotherapy provides a unique opportunity to study the, as yet, incompletely characterized effects on gene expression and immune system activation of high dose radiation.

1.3 Effect on Surgical Margins

In patients undergoing breast-conserving surgery, it is generally preferred to begin radiotherapy only after negative surgical margins have been achieved because positive margins increase the risk of in-breast local recurrence. [38-40] Typically, 25% of women undergoing breast-conserving surgery will require surgical re-excision for close or positive margins. Between 8-12% of patients requiring re-operation will be converted to mastectomy and, critically, 11% of positive margins will never be re-excised. The challenge of obtaining appropriate margins results in additional surgical procedures that lead to increased patient morbidity and healthcare costs while diminishing cosmesis and, in some cases, optimal treatment. [1, 41-43]

It is unclear if pre-operative SABR would reduce the incidence of re-operation for inadequate surgical margins because the significance of close or positive margins after radiotherapy is unknown and we are unlikely to abandon our entrenched belief that negative surgical margins must be achieved.

Considering, however, that breast tumor excisions do not always result with the target lesion precisely in the center of the excised specimen, it may hold that inducing tumor regression with uniform pre-operative irradiation of the tumor and its peripheral margin may facilitate obtaining sufficient clear margins. [44, 45]

Any reduction in need for re-operation to address margins would constitute an immediate benefit to patients and the payor system. [46]

1.4 Study Agent/Technique: Stereotactic Ablative Body Radiotherapy (SABR)

Stereotactic ablative body radiotherapy (SABR) is an established technique utilized successfully in the non-operative management of brain, spinal, liver, adrenal, nodal, and lung metastases as well as in definitive management of prostate carcinoma, pancreatic carcinoma, and early-stage medically inoperable lung carcinoma with local control rates in excess of 90%. [47-51]

SABR distinguishes itself from conventional fractionated radiotherapy in that significantly larger radiation dose is delivered with each treatment fraction with intent to ablate tissue within the target volume. Owing to this potent biologic effect it is necessary that the treatment planning be undertaken with a high degree of targeting accuracy and dose conformity. This treatment frequently utilizes image guidance, target motion management, and tight immobilization to ensure targeting accuracy.

Therefore all treatment on this protocol will be delivered on a Moffitt linear accelerator with appropriate stereotactic and image-guidance capabilities.

1.4.1 Prone positioning during SABR

Prone patient-positioning equipment is established and widely available for breast radiotherapy. Commercially available prone breast boards can be indexed to the treatment table and enable

comfortable and reproducible patient set-ups. Modern breast boards allow un-obstructed access to nearly 360 degrees of beam direction for treatment planning.

The primary advantage of prone-breast radiotherapy is to displace the breast away from the chest wall, lung, and heart which further enhances sparing of these structures from radiation exposure. [52] Prone positioning attenuates motion of the breast associated with normal respiration thereby simplifying the process for accurate targeting during treatment. [53, 54] Lastly, prone positioning during treatment facilitates image-registration of the diagnostic breast MRI (usually imaged prone) to the treatment planning CT- simulation which will be used to enhance accuracy of target delineation.

1.5 Gender and Age

Breast cancer is a disease diagnosed typically in women over 40 years of age. In keeping with our intent to select patients of lower risk and restrict our patient population to those defined as 'suitable' or 'cautionary' by American Society of Therapeutic Radiation Oncology (ASTRO) consensus for accelerated partial breast radiotherapy, only women ≥50 years of age will be enrolled and men will not be candidates for this protocol.

2.1 OBJECTIVES

2.2 Primary objective

Primary objective: Assess rate of pathologic complete response following pre-operative SABR for early-stage breast carcinoma.

Secondary objective: Assess incidence of re-operation for inadequate surgical margin.

Tertiary objective: Characterize imaging response following SABR (and before surgery) and correlate to observed pathologic responses.

3.1 DIAGNOSIS, IMAGING and PATIENT IDENTIFICATION

3.2 Tissue Diagnosis/Pathology

Whenever possible, patients will undergo diagnostic breast core biopsy at Moffitt facility for tissue diagnosis and storage. Slides/blocks from pre-treatment diagnostic breast core biopsies performed at an outside facility will be obtained to confirm the diagnosis. Outside pathology slides must be reviewed by a Moffitt pathologist. Standard histopathologic features, including the histologic grade and hormone receptor and Her-2 expression will be recorded. Margin status and degree of pathologic response following breast- conserving excision will also be assessed and reported, as per standard of care. All extirpated specimens will be preserved as archived tissue so that additional future analysis can be performed. Currently planned studies include comparative gene expression analysis of matched pre-radiation, post-radiation and germline tissue. Also planned is multiplex immunofluorescence (CD68, CD8, CD4, CD3, FOXP3, PCK, DAPI) in order to highlight specific immune cell types within matched pre-radiation and post-radiation tumor tissue.

3.3 Patient Identification

Patient referrals to the Moffitt Comprehensive Breast Program as well as patients seen in the Moffitt Screening and Prevention program will be screened for participation on this protocol chiefly by

surgical and radiation oncology providers during regular clinical encounters. Potential candidates will also be identified and discussed at our weekly breast treatment planning conference.

Upon identification of a candidate, the patient will be referred to a breast radiation oncologist for patient evaluation and confirmation of participation eligibility, protocol consent and enrollment. (Due to utilization of a novel radiotherapy application in this protocol, all patients' eligibility confirmation, consent, and protocol enrollment will be conducted by a radiation oncologist or radiation oncology research support staff.)

3.4 Magnetic Resonance Imaging (MRI) considerations

Contrast-enhanced MRI of the breast will be performed at baseline and at least 5 weeks but no more than 6 weeks after SABR but prior to breast conserving surgery. When MRI is performed at Moffitt facility, the gadolinium based contrast agent gadobutrol (Gadavist, Bayer HealthCare Pharmaceuticals) will be used at a concentration of 0.1 mmol/kg. The breast MRI technique at our institution is performed at 1.5 T and includes axial dynamic 3D T1-weighted fat-suppressed gradient-recalled echo pulse sequences obtained before and after contrast administration. Dynamic images are obtained every 90-110 seconds adjusted for breast thickness for a total of five acquisition times. Slice thickness is 2 mm. Subtraction images are obtained from the dynamic series. Fluid-sensitive T2-weighted images are also obtained. Diffusion-weighted and ADC map images are also obtained

All data sets are reviewed on a PACS workstation (DynaCAD, Aegis, Hologic) with computer aided diagnosis for review of lesion enhancement kinetics, multiplanar reconstructions, and maximum intensity projections. Examinations are interpreted with available prior breast imaging and clinical history.

For the purposes of this study, imaging parameters to be analyzed will include change in tumor size using the longest diameter measurement, overall evaluation of tumor enhancement kinetics, mass vs non-mass enhancement, and any change in tumor margin description for baseline vs follow-up evaluation as determined by the reading radiologist.

In addition to the qualitative analysis of MRI images described above, quantitative analysis will also be performed. Multiparametric MRI (mpMRI) scans will be pre-processed to match voxel dimensions across patients, scans and scan dates, co-registering pre- and post- SABR images in each patient, computing DCE-MRI parameter maps, computing ADC maps, and calibrating T2W intensities using reference normal tissues. Next, we will develop a response predictor for pathologic complete response and MRI complete response using multispectral (habitats) analysis (primarily through multispectral cluster analysis of habitats) and machine learning (primarily through analysis of tumor voxels using Self-Organizing Maps).

4.1 TREATMENT

4.2 Simulation

A prone-breast immobilization device will be used.

CT simulation will be performed at a minimum of one week after any invasive breast procedure to allow edema to settle. CT slices will be 3 mm. The imaging set will be downloaded to the treatment planning system for contouring and dosimetry.

During simulation external markers may be placed on the target breast skin to facilitate localization during treatment. The simulation CT will encompass the thyroid gland and both lungs in their entirety in addition to both whole breasts. Respiratory gating is not permitted.

Previously obtained prone-breast diagnostic MRI with marker clip in place will be co-registered to the planning CT to aid with accurate delineation of the intact breast tumor. The MRI and CT should be fused based on soft tissue using the visualized breast tumor, breast contour and breast biopsy clip. If there is discrepancy between the MRI and CT, and the fusion is not considered representative then at the discretion of the treating radiation oncologist the patient will either be removed from the protocol or alternatively an image- deformation registration technique may be used to facilitate fusion of diagnostic breast MRI to the planning CT. The final registration must be reviewed by the radiation oncologist for accuracy.

4.3 Dose Specifications

All patients will undergo pre-operative stereotactic ablative body radiotherapy (SABR) to 28.5 Gy in 3 fractions of 9.5 Gy on different days separated by no more than 48 hours.

All specified doses are for the entire treatment course. All volume percentages are rounded to the nearest tenth of a percent for consistency, e.g., a volume of 0.02% shall be recorded as 0.0%.

4.3.1 PTV: D95 = 100%, Dose maximum (Dmax) 130%

Minor variations: D95<100%, ≥97%
Major variations: D95<97%

CTV: D95 = 100%

Major variation: D95<100%

4.3.2 THYROID: Per Protocol: Dose maximum 1.2Gy (4% prescription).

Minor variation: Dose maximum >1.2Gy, <2Gy.
Major variation: Dose maximum >2Gy

4.3.3 CHEST-WALL: Per Protocol: V28.5Gy ≤30cc.

Minor variation: V28.5 Gy >30cc, ≤35cc.
Major variation: V28.5 Gy >35cc

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4.3.4 IPSILATERAL LUNG: Per Protocol: V9Gy < 5%.

Minor variation: V9Gy ≥5%, ≤10%.
Major variation: V9Gy >10%.

4.3.5 CONTRALATERAL LUNG: Per Protocol: V9 <3%

Minor variation: V9Gy ≥3%, ≤5%.
Major variation: V9Gy >5%.

4.3.6 IPSILATERAL BREAST: Per Protocol: V15Gy ≤25%; V25 Gy ≤10%.

Minor variation: V15 Gy >25%,≤30%; V25 Gy >10%, ≤15%
Major variation: V15 Gy >30%, V25 Gy >15%

4.3.7 CONTRALATERAL BREAST Per Protocol: V10 Gy < 7%, V5 Gy <10%

Minor variation: V10 Gy >7%,≤9%; V5 Gy >10%, ≤13%
Major variation: V10 Gy >9%, V5 Gy >13%

4.3.8 HEART Per Protocol: Mean ≤ 2Gy, ≤10cc to get 3Gy.

Minor variation: Mean >2Gy, ≤3 Gy; >10cc getting 3Gy but ≤15cc
Major variation: Mean >3Gy, >15 cc getting 3 Gy

4.3.9 SKIN Per Protocol: D10cc ≤15Gy

Minor variation: D10cc >15Gy, ≤18Gy
Major variation: D10cc >18Gy

If all the above "Per Protocol" dose-volume criteria cannot be met on a given patient, then normal tissue constraints and target prescriptions may be relaxed to the "minor variation" range.

4.4 Structures

4.4.1 Target Volumes

GTV: The gross tumor volume (GTV) will consist of the intact breast tumor as defined on contrast-enhanced MRI and simulation CT. CTV: Clinical target volume

CTV: Clinical target volume (CTV) will constitute the GTV + 15 mm uniform expansion to or subclinical extent of tumor. The CTV will exclude areas not expected to contain tumor including skin, muscle and bone.

PTV: The planning target volume (PTV) will constitute the CTV + 3 mm uniform expansion to account for patient set-up error. The PTV is the volume to which the prescription dose is prescribed.

While the static targeting accuracy of the eligible treatment delivery platform is between 1-2 mm, deformation of the breast, and target movement occurring after imaging but before dose delivery could contribute to targeting uncertainty. Generally, movement of breast tumor in the prone position is minimal. Although the cumulative targeting uncertainty has not been accurately quantified, a 3 mm CTV to PTV expansion will be employed in all cases.

4.4.2 Normal Tissue Structures: CONTOURING REQUIRED

The structures listed below will be contoured and evaluated using dose-volume histogram (DVH) analysis. The normal tissues should be defined based on CT. The MRI is chiefly used in delineating the intact breast tumor.
THYROID: Defined as both lobes of thyroid gland, contoured in their entirety
CHESTWALL: Defined at muscle/bone interface with breast soft-tissue.
SKIN: Defined as volume occupying first 3 mm of tissue from soft-tissue/air interface.
IPSILATERAL LUNG: Defined as entire ipsilateral lung.
CONTRALATERAL LUNG: Defined as entire contralateral lung.
CONTRALATERAL BREAST: Defined as entire contralateral breast (see below).
IPSILATERAL BREAST: Defined as entire ipsilateral breast minus the PTV. The whole breast volume for this protocol approximates the volume that is bounded by conventional tangent fields: anteriorly bounded by skin, posteriorly bounded by chestwall, medially bounded by ipsilateral border of sternum, laterally bounded by anterior edge of latissimus dorsi muscle or mid-axillary line, superiorly bounded by inferior border of clavicular head, inferiorly bounded 1-2 inferior to inframammary fold.
HEART: Defined as heart structure extending from level where pulmonary trunk branches into left and right pulmonary arteries through ventricles and including visualized great vessels and coronary arteries.

4.4 Treatment Planning Procedure

Inverse or forward planning may be employed. Volumetric modulated arc therapy (VMAT, ie RapidArc or SmartArc) or any form of static-field intensity modulated radiotherapy (IMRT) is permissible. The treatment plan used for each treatment will be based on the volumetric dose requirement of the protocol as described in section 4.2. Any beams entering through contra-lateral breast, heart or lungs on their way to the planning target volume should be avoided as much as possible. Tissue density heterogeneity correction is required for all beams.

4.5 Treatment Delivery

4.5.1 Delivery System

Conventional linear accelerators (linacs) with photon energies from 6 MV to 15 MV are allowed. Linacs should be equipped with stereotactic image-guidance system capable of delivering image-guided IMRT/3D-conformal RT and SABR/SRS.

A kV-orthogonal or cone-beam CT based stereotactic image-guidance system is mandatory for linac-based treatment delivery. An on-board imager (OBI) or equivalent, or the BrainLab ExacTrack system, is required. At treatment, the implanted marker clip and any breast-surface markers (which will be marked for image guidance) will be imaged and used to determine final shifts to the location of the breast target.

The image-guidance procedure may be repeated during treatment at the discretion of the radiation oncologist.

5.0 Management of Toxicity due to SABR

Management of toxicity due to SABR will be provided during the study period at the discretion of the treating physician(s) within the parameters of the protocol and documented. Most patients have grade 2 or lower skin, soft-tissue, or chestwall adverse effects during and after treatment. Symptoms and their management will be documented per routine clinic visit. In very rare cases, patients may experience extreme symptoms including high-grade soft-tissue fibrosis, dermatitis, fatigue, or breast pain. Supportive measures, skin care and medication will be instituted as needed. Common supportive medications include:

- Topical antimicrobials: Antimicrobials such as silver sulfadiazine may be used in areas of skin desquamation. The amounts of the drug(s) used should be documented.
- Topical skin moisturizers: Moisturizing lotions are used routinely in patients undergoing breast radiotherapy and is permitted on this protocol. The use of these products should be documented.
- Hydrocolloid/Hydrogel dressings: Topical hydrocolloid/hydrogel dressings may be used in cases of confluent moist desquamation when deemed appropriate by the supervising radiation oncologist. The use of this product will be documented.
- Analgesics: Analgesics is a broad category, including non-narcotic and narcotic agents. The use of non-narcotic agents, such as acetaminophen, non-steroidal anti-inflammatory agents for radiotherapy treatment-related pain should be documented. Narcotic use as a consequence of treatment should also be recorded.
- Topical steroid: Topical 1% cortisone lotion is often used for radiotherapy related dermatitis and pruritus and is permitted on this protocol. The use of this drug should be documented.

6.0 Duration of SABR

SABR will be completed in 3 treatment sessions (separated by no more than 48 hours) and will be scheduled to begin within 2 weeks of simulation and at least 6 weeks prior to breast- conserving tumor excision.

7.1 CLINICAL AND LABORATORY EVALUATIONS (APPENDIX I)

7.2 Baseline/pretreatment evaluations

- History and physical/ECOG performance status.
- Diagnostic core biopsy with placement of marker clip.
- Post-biopsy contrast-enhanced prone-breast MRI (with marker clip in place).

7.3 Evaluations Before SABR

• Females of childbearing potential, must have a urine pregnancy test (in menstruating women) prior to CT simulation. (A female of childbearing potential is a sexually mature woman who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months). CT simulation for treatment planning

7.4 Evaluations During SABR

- History and physical.
- ECOG performance status.
- NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 toxicity scoring system.
- Urine pregnancy test will be repeated on first day of SABR before beginning treatment if last result is greater than 7 days old.

7.5 Evaluations After SABR

- History and Physical (4-5 weeks after SABR)
- ECOG performance status (4-5 weeks after SABR)
- NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 toxicity scoring system. (4-5 weeks after SABR)
- Pre-operative diagnostic breast MRI (5-6 weeks following SABR)

8.0 Early Discontinuation of Therapy

Patients who experience excessive adverse events as evaluated by their treating physician will be recorded. All attempts should be made to manage adverse events adequately. Because radiation related toxicity typically manifests weeks or months after treatment delivery, it is expected to be low probability that any high grade toxicity will surface before treatment is completed (3-fraction SABR delivered over 3-5 days) and so there will be minimal opportunity for early discontinuation of therapy due to toxicity.

9.1 DOSING DELAYS/DOSE MODIFICATIONS

9.2 Study Agent

N/A

9.3 Other Agent(s)

N/A

10.0 AGENT FORMULATION AND PROCUREMENT

N/A

11.0 ADVERSE EVENT (TOXICITY) REPORTING

The descriptions and grading scales found in the revised National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4 will be used for adverse event reporting. A copy of the CTCAE v4 can be downloaded from the CTEP web site http://ctep.cancer.gov/reporting/ctc.html.

Adverse events monitoring will begin following initiation of SABR and continue for 28-35 days following completion of SABR. For purposes of this protocol, we will record any grade 2 or greater adverse events. Grade 1 adverse events will be omitted from toxicity reporting.

12.1 Definitions

12.2 ***Adverse events*** (AE's) will use the descriptions and grading scales found in the NCI Common Toxicity Criteria in Appendix II.

Adverse events: Any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Each AE is a unique representation of a specific event used for medical documentation and scientific analysis.

12.3 A ***serious adverse event*** (SAE) is defined in the FDA CFR 312 as any adverse drug 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, or a congenital anomaly/birth defect.

SAEs are defined by FDA and therefore seriousness (not severity) serves as a guide for defining regulatory reporting obligations for patient/subject safety. **Serious** is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

13.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please follow directions for routine reporting provided in the Data Reporting Section). Additionally, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

Events resulting from concurrent illnesses and reactions to concurrent medications must be reported as adverse events. (grade 1 adverse events will not be collected)

Any worsening of the patient's clinical condition while the patient is on study will be considered to be an adverse event unless it is within the normal range of disease fluctuation for that patient.
Determination of Reporting Requirements
Reporting requirements may include the following considerations:

1) whether the patient has received an investigational or commercial agent;
2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event;
3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: *Identify the type of event using the NCI Common Toxicity Criteria (CTC)*.

The CTC provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTC can be downloaded from the CTEP home page (http://ctep.cancer.gov). Additionally, if assistance is needed, the NCl has an Index to the CTC that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTC.

Step 2: *Grade the event using the NCI CTC*.

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).*

Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

13.2 Reporting Methods

All serious, unusual life-threatening or lethal adverse which may be study related will be reported within 24 hours. For all fatal events (Grade 5) while on study or within 30 days of treatment, the IRB must be notified within 24 hours of site notification.

13.3 IRB Reporting

13.2.1 Report of AEs and SAEs must be reported according to IRB policy and procedures.

13.3 Follow-up Reporting

For all SAEs, the investigator is obligated to pursue and provide follow-up reporting information until the event has resolved to < grade 3 or until an acceptable medical endpoint, per treating physician, has been reached or the patient is lost to follow-up.

14.0 CRITERIA FOR DISCONTINUATION OF THERAPY

The patient may elect to withdrawal from this protocol at any time prior to SABR. During SABR the patient will be maintained under audio and video observation and so can indicate discontinuation at any time during treatment.

Patients who are enrolled on the study but not treated will be excluded from the analysis.

15.0 DATA REPORTING

Data will be submitted according to the protocol requirements for ALL patients treated with SABR. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

16.0 STATISTICAL CONSIDERATIONS

Under the assumption that the true pCR rate following pre-operative SABR is 25%, compared with the null hypothesis that pCR is 10%, a two stage design with total 40 subjects will give us 80% power at 5% 1- sided significance level. In particular, the study will enroll 22 patients in the first stage, and if 2 or less subjects achieve pCR, the study will be terminated for futility; and, if 3 or more patients achieve pCR, then additional 18 patients will be enrolled for a total 40 patients. The null hypothesis will be rejected if 8 or more patients achieve pCR out of the 40 total subjects enrolled in the study.

Descriptive statistics will be summarized for patient demographics and patient characteristics, which include patient age, tumor grade, tumor size, tumor histology, timing after surgery, minor variations on target coverage or not, lymphatic-vascular space invasion, presence of ductal carcinoma in situ, and ASTRO consensus risk group. Fisher's exact test will be performed to examine the association between pCR and each of the patient characteristics, as well as the association between surgical margins and the patient characteristics. Multivariate logistic regression and linear regression will be conducted to explore the association between pCR and surgical margins with these patient characteristics.

17.0 Interim monitoring

The Research Team will continuously monitor study accruals, toxicities and clinical outcome. The Moffitt Cancer Center Data and Safety Monitoring Committee (DSMC) will meet on a monthly basis and will continually assess for subject safety and recommend changes to protocol and study as required to preserve subject safety and to prevent any untoward toxicity. DSMC oversight of the

conduct of this trial includes ongoing review of adverse event data and periodic review of trial outcomes.

18.0 Reporting Exclusions

N/A

19.1 Investigator Responsibilities

The investigator will ensure that this study is conducted in accordance with all regulations governing the protection of human subjects and Good Clinical Practices (GCP) guidelines. The investigator will ensure that all work and services described in or associated with this protocol will be conducted in accordance with the investigational plan, applicable regulations, and the highest standards of medical and clinical research practice.

19.2 Confidentiality/Monitoring

The investigator must ensure that each subject's anonymity will be maintained and each subject's identity will be protected from unauthorized parties. A number will be assigned to each subject upon study enrollment and the number and the subject's initials will be used to identify the subject for the duration of the study. The investigator will maintain all documents related to this study in strict confidence. All electronic documents will be kept under password protection known only to the principal investigator.

The PI of this study is ultimately responsible for every aspect of the design, conduct and actions of all members of the research team. This includes the final analysis of the protocol.

The PI will ensure that the monitoring plan is followed, that all data required for oversight of monitoring are accurately reported to the DSMC and/or to the Protocol Monitoring Committee (PMC) and IRB as required, that all adverse events are reported according to protocol guidelines, and that any adverse actions reflecting patient safety concerns are appropriately reported.
Data will be captured in Oncore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Internal monitoring will be performed regularly to verify data is accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/amendments, Good Clinical Practice (GCP), and applicable regulatory requirements.
The PMC monitors provide monthly review for: adverse event reporting, data and safety monitoring, and internal audit findings. The PMC upon review of any agenda item may approve the study for continuation, require revisions, suspend or close a protocol.

Investigators of studies shall provide a statistical report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study or more often if applicable.

The DSMC will meet on a monthly basis and will continually assess for subject safety and recommend changes to protocol and study as required to preserve subject safety and to prevent any untoward toxicity.

19.3 Informed Consent and Permission to Use Protected Health Information

It is the responsibility of the investigator or designee to obtain written informed consent from each subject participating in this study after adequate explanation, in lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The investigator or designee must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason) and receive alternative conventional therapy as indicated. Prior to study participation, each subject will sign an IRB approved informed consent form and receive a copy of same.

The investigator or designee must explain to the subject before enrollment into the study that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB.

19.4 Source Documentation and Investigator Files

The research team will maintain adequate and accurate records to fully document the conduct of the study and to ensure that study data can be subsequently verified. Subject clinical source documents will corroborate data collected on any CRF's. Subject clinical source documents would include hospital/clinic patient records; physician's and nurse's notes; original laboratory, radiology, pathology, and signed informed consent forms.

At a minimum the following source documents will be collected:

- Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify protocol randomization criteria.
- Study number, assigned subject number, and verification that written informed consent were obtained (each recorded in dated and signed notes on the day of randomization into the study).
- Progress notes for each subject visit, including treatment toxicity.
- Documentation of treatment.
- Adverse events (action taken and resolution).
- Condition and response of subject upon completion of or early termination from the study.
- Radiation treatment Dose Volume Histograms.

19.5 Non-Protocol Research

No investigative procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB.

19.6 Ethics

The investigator agrees to conduct the study in compliance with the protocol, current good clinical practices, and all applicable (local, FDA, local ethics committee) regulatory guidelines and standard of ethics.

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APPENDIX I STUDY CALENDAR

	Baseline Evaluation	Prior to SABR	Day of SABR	4-5 weeks post SABR	5-6 weeks post SABR	6-8 weeks post SABR
Medical History [1]	X[1]		X[1]	X[1]		
Physical Exam [1]	X[1]		X[1]	X[1]		
ECOG [1]	X[1]		X[1]	X[1]		
Diagnostic core biopsy [2]	X					
Post biopsy breast MRI [3]	X				X	
Record Adverse Events [4]			X	X		
Urine pregnancy test (menstruating women only)		X [5]	X [5]			
CT Simulation		X [6]				
Tumor Excision and submission for pathological evaluation						X [7]

(1)+/- 28 day window
(2) Moffitt facility preferred. Non-Moffitt pathology must be over-read by Moffitt breast pathologist. During the biopsy procedure, a marker clip will be placed indicating location of biopsied tumor. Placement and location of marker clip will be confirmed on post-biopsy MRI that follows.
(3) Moffitt facility preferred. Non-Moffitt diagnostic MRI must be over-read by breast radiologist. This MRI occurs following biopsy and placement of marker clip.
(4) NCI CTCAE v4
(5) Urine pregnancy test will be performed in all females of childbearing potential prior to any radiation exposure for purpose of this protocol. The results of urine pregnancy test will remain valid for seven days.
(6) CT simulation will be performed no less than 1 week following any invasive procedure to the target breast (ie biopsy) in order to allow procedure related edema to settle.
(7) Patient will undergo breast conserving tumor excision by Moffitt breast surgeon 6-8 weeks following SABR. Specimen will be delivered for pathologic evaluation as per standard practice.

APPENDIX II

NATIONAL CANCER INSTITUTE (NCI) COMMON TOXICITY CRITERIA (CTC)
The NCI CTCAE criteria v4 may be viewed on-line at the following NCI web site:

http://ctep.cancer.gov/reporting/ctc.html

APPENDIX Ill

PERFORMANCE SCALES

ECOG SCALE

0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours
4	Completely disabled. Cannot carry on self-care. Totally confined to bed
5	Death