GCC # 1202

Tumor Bed Dose Delivery using a Breast Specific Radiosurgery Device, The GammaPod™: A Clinical Feasibility Study

A Study of the Breast Oncology Program of the

University of Maryland, Marlene and Stewart Greenebaum Cancer Center

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1. Introduction

Breast conserving therapy (BCT), consisting of surgical lumpectomy followed by whole breast radiation therapy has become the standard of care for treating early-stage breast cancers. In comparison with mastectomy, BCT demonstrated similar outcomes with superior cosmesis and reduced psychological and emotional trauma based on multiple randomized trials(1-4). At the time of the lumpectomy, the surgeon removes the tumor and a surrounding rim of normal tissue (margin), typically leaving surgical clips to help designate the resection cavity or tumor bed (TB) for the radiation oncologist(5, 6). The current standard of radiation therapy for breast cancer is to deliver treatment to the whole breast to 45-50.4Gy in 25 to 28 treatments Monday through Friday. Following whole breast radiation, a 'boost' is delivered to the TB in order to deliver 60 – 66Gy to the tumor bed. Two prospective trials have demonstrated a statistically significant reduction in local failures with the addition of a boost of 10Gy(in 4 fractions @ 2.5 Gy per fraction) or 16 Gy in 8 fractions @ 2 Gy per fraction), respectively(7, 8).

Boost treatments can be delivered through a variety of techniques(9, 10) including a single electron field (used for superficial tumor beds) or multiple photon fields (2 or 3 fields typically) for tumors that are deep to the skin (usually > 3 cm). With the use of CT simulation to guide the delivery of the boost, the need for deep TB coverage has become more apparent and now most patients receive photons for the boost portion of their therapy because the use of electrons often misses part of the tumor bed (figure 1a). However, when photon beams are used, in comparison to electrons, more generous margins posterior to the surgical cavity are required to account for daily set up error and respiratory motion which is not necessary for a single en face electron field. Furthermore, there are only limited directions along which the radiation can be directed to the TB, and as a result, large volumes of normal breast tissue receive a substantial fraction of the prescription dose (figure 1b) which can lead to internal scarring (fibrosis) and poor cosmesis(8, 11, 12). The largest clinical series evaluating this issue demonstrated increased fibrosis and worse cosmetic outcome using photons(13). The clinical target volume for the boost is the TB, while an additional 1-1.5 cm margin of normal breast tissue is added isocentrically to account for daily set-up error and respiratory motion to define a planning target volume. Typically the boost is delivered after the whole breast portion of treatment, however, in various cases this sequence can be changed. For example, if significant skin breakdown occurs during the whole breast radiation phase, investigators can stop the whole breast radiation therapy and change to deliver dose only to the TB while allowing time for the rest of the breast to heal. This allows a continuous course of therapy to the highest risk of subclinical disease (i.e. the tumor bed).

Hypofractionation, or delivery of greater than standard 1.8 - 2 Gy fraction sizes per day, is a method of shortening overall treatment time in breast cancer. Historically, standard fraction sizes of 1.8-2.0 Gy for whole breast irradiation (WBI) were based primarily on studies examining squamous cell cancers from cervix and head and neck regions. The smaller fraction sizes exploited a biological differential in squamous cell cancer fractionation sensitivity versus normal

tissue fractionation sensitivity. This allowed relative sparing of surrounding normal tissue from low dose per fraction. However, investigators from the United Kingdom hypothesized that the fractionation sensitivity for adenocarcinoma of the breast is close to that of the normal breast tissue. Therefore, with increasing fraction size a sufficiently large reduction of total dose could be implemented to keep late toxicity constant without reducing the probability of tumor control[14,15].

In 2010, the Ontario Clinical Oncology Group published updated findings from a randomized trial with 12-year median follow-up showing that a 3-week hypofractionated WBI schedule yielded similar cancer control and breast cosmetic outcomes to a 5-week conventional WBI schedule[16,17]. These findings reinforced the body of evidence supporting shorter radiation treatment schedules from three prior randomized trials (the United Kingdom's Standardization of Breast Radiotherapy (START-A and START-B) and the Royal Marsden Hospital/Gloucester Oncology Center trials)[18-21].

In 2011, the American Society for Radiation Oncology practice guidelines endorsed hypofractionated WBI as "equally effective for in-breast tumor control and comparable in long-term side effects" with conventional whole breast radiation for patients with early-stage breast cancer who were (1) over age 50, (2) pathologic stage T1 or T2N0, (3) chemotherapy naive, and (4) radiation dose heterogeneity higher or lower than 7% of prescription dose[22]. The guidelines also permitted hypofractionated radiation for other patients with early-stage breast cancer, stating that "this guideline should not be interpreted to prohibit or oppose the use of hypofractionated whole breast radiation for patients not meeting all the criteria". In 2013, the Choosing Wisely initiative, aimed at reducing health care costs, encouraged physicians and patients undergoing breast conservation therapy to discuss the duration of whole breast radiotherapy[23].

In our clinic, the utilization of hypofractionated radiotherapy has increased substantially especially since the NCI sponsored co-operative group trial RTOG 10-05 has closed (February 2014), which was a prospective phase III trial testing hypofractionation using a more sophisticated radiation therapy approach. Conventional fractionation is generally offered to patients with high grade tumors (ER/PR/Her2-neu negative AND any ER/PR status with Her 2 neu positive) and patients whose anatomy dictates a radiation dose heterogeneity.

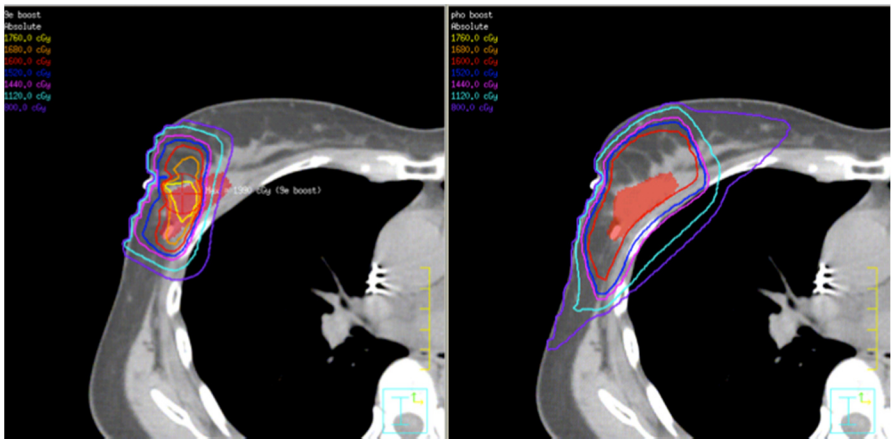


Figure 1. (A) A typical treatment plan using superficial electrons that would under dose the deep portion of the TB (outline in red) which was estimated clinically prior to the common use of CT scans. (B) Photon plans are more commonly used as the target is shown to be deep, but requires a more generous margin posteriorly due to respiratory motion which is not an issue with en face electron fields. This unfortunately delivers more moderate and high dose radiation to the surrounding normal breast and potentially to the normal lung as well.

1.1. Innovative methods to deliver radiation to the tumor bed

Over the last decade, several more sophisticated approaches(24-28) have been developed to deliver radiation to just a part of the breast including brachytherapy (i.e. MammositeTM) and various intraoperative approaches using either electron beam or low energy x-rays to deliver a single dose in the operating room. These techniques were developed to treat select patients with partial breast irradiation, but initially were tested in combination with whole breast radiation to deliver the additional radiotherapy to the TB through the novel approach. One of the recent methods is named targeted intraoperative radiotherapy (TARGIT)(29). TARGIT utilizes low energy photons intra-operatively to deliver radiotherapy to the tumor bed immediately after the surgical excision of the tumor (prior to being awakened from anesthesia). Radiation therapy is delivered with a single delivery of 20Gy prescribed to the surface of the excision cavity with a rapid dose falloff where tissue1 cm deep from the surface of the excision cavity receives between 5 to 7Gy. After the dose is delivered, the device is removed and surgical closure is completed. One of the major downsides to this intraoperative approach is that the surgical margins cannot be assessed at the time of surgery; subsequently 15-20% were found to have adverse histologic features requiring the addition of whole breast radiation(29). Patients who received whole breast radiation received 45-50Gy in 25 fractions. When this approach was initially tested, whole breast radiation was always delivered *following* the boost. Based on the largest series with long term follow up (median follow-

up of 60.5 months), the 5-year local recurrence rate was less than 2%(30). Similarly, investigators have used intraoperative electrons prior to whole breast radiation. Long-term local control rates and cosmesis appear similar to or better than more conventional techniques. Doses of 9 to 10 Gy in a single treatment in the operating room were delivered typically using 9 MeV electrons prescribed to the 90% isodose line. Lemanski(31) et. al. described no grade 3 side effects in 50 patients treated with this approach, but did have a 12% risk of grade 2 subcutaneous fibrosis which is similar to large series using conventional boost techniques26. In Europe, based on short follow up, there has not been a difference in local control or cosmesis between intraoperative radiotherapy and conventional electrons from EORTC 22881/10882(8).

All of the these treatment techniques described above have the down side of being invasive (i.e. brachytherapy) requiring a second procedure to place the device prior to treatment or lengthening the time under anesthesia (i.e. intraoperative radiation) by at least 30 – 60 minutes. Additionally due to these factors, sophisticated dosimetric evaluation ensuring appropriate dose coverage cannot be performed due to a variety of technique and logistical factors.

Faculty members at the University of Maryland, Baltimore invented a method and device for delivering stereotactic radiotherapy specifically for breast cancer(32). By licensing the technology from University of Maryland and collaborating with the PI and his research team, Xcision Medical Systems, LLC has developed a new breast specific stereotactic radiotherapy machine, the GammaPodTM, with the support of an NIH SBIR grant. Based on stereotactic radiosurgery principles, this new device is capable of delivering focused radiation to the target while sparing the surrounding normal tissues and structures(32, 33). The advantages include: (1) it is completely non-invasive in comparison to other technologies (i.e. Mammosite™ or equivalent devices) currently used for high dose radiation delivery to the breast as described above, (2) the vacuum assisted breast immobilization device has been designed to have improved accuracy and reproducibility, allowing a reduction in the set-up error to less than 3 mm(34). The initial breast immobilization device was tested on an in-house protocol (GCC0727) at the Marlene and Stewart Greenebaum Cancer Center, where the accuracy and comfort was demonstrated although a substantial percentage of the breast immobilization devices became dislodged requiring improvements. A new version of the breast immobilization device was designed and is now being tested on GCC1047 confirming its accuracy and reproducibility. This study is ongoing and data have been used to validate the planned treatment margins for the proposed study GCC1202. Based on the 12 patients for whom data has been analyzed, the reproducibility of target position within the cup remains <3 mm The patient is treated in the prone position, similar to positioning for stereotactic breast biopsy or MR imaging of the breast, thus minimizing the effect of breathing motion. In deciding on a treatment margin to account for overall positional uncertainty, mechanical accuracy of the patient couch (relative to the beam isocenter) must be taken into account in addition to the accuracy of target positioning within the cup. We have conservatively added another 2 mm to the margin to account for couch uncertainties. This is based on a measured couch position

uncertainty within 1 mm. Subsequently, we propose to use a setup margin of 5 mm. (4) This device uses 36 non-coplanar 60Co sources that rotate during treatment to form 36 non-coplanar arcs, producing a dose distribution similar to that of the Gamma KnifeTM for intracranial targets which is substantially more conformal than the 3 field approach which is a standard practice for TB boost (see figure 1B).

This study proposes to proceed to a 1st in human clinical feasibility study by delivering a single moderate dose to the TB using the GammaPodTM on a day shortly before whole breast radiotherapy. The FDA has requested this clinical demonstration of the device with an IDE prior to obtaining FDA marketing clearance via the 510k mechanism. The goal of the study, as proposed by the FDA, was to demonstrate that a treatment could be delivered. The clinical trial protocol for phantom studies to validate the device's accuracy has been discussed with the FDA. Therefore, the primary end point of this study is simply feasibility and patient safety. We will also evaluate overall patient comfort and dosimetric accuracy through patient-specific phantom measurements conducted before the treatment delivery.

1.2. Study rationale

In this study, we plan to deliver a 8 Gy TB boost using the GammaPod^{TM} system followed by a conventional (50Gy in 25 fractions) or hypofractionated (40Gy in 15 fractions) course of whole breast radiation. The clinical target volume receiving 8 Gy will be the surgical cavity as defined by the surgical clips and post-surgical changes + 5 mm. The planning target volume will add 5 mm to the clinical target volume to account for geometric uncertainties. The current standard of care in our clinic when delivering a conventional course of whole breast radiation is to deliver between 60 and 66 Gy to the tumor bed when negative margins are achieved, with the initial ~45-50Gy delivered to the whole breast and the 10-16Gy TB boost delivered in 5-8 fractions. The current standard of care in our clinic when delivering a hypofractionated course of whole breast radiation is to deliver between 50 and 52 Gy to the tumor bed when negative margins are achieved, with the initial ~40-42.5Gy delivered to the whole breast in 15 or 16 fractions respectively followed 10Gy TB boost delivered in 4 or 5 fractions (total 20). The clinical target volume for the TB boost in this study is quite similar to conventional TB boost. The only difference is that the PTV margin is smaller in this study (5mm instead of 10mm) due to the reduced set up uncertainties with the breast cup immobilization and localization devices. The current institutional standard is covering the TB + 15 mm dosimetric margin. Since our reproducibility is improved by 5 mm with the aid of the breast immobilization cup, the TB + 10 mm dosimetric margin will be used on this study. Using the radiobiological equivalent dose (BED) formula, $\{BED = nD(1 + D/(\alpha/\beta))\}$, the 8 Gy single fraction dose is equivalent to 16 Gy delivered in 8 fractions. Wherein the BED formula, n is the number of fractions, D is the dose per fraction and α/β is estimated to be between 3 and 4(35). On this study, we will deliver either 40 Gy in fifteen (15) fractions (hypofractionated) or 50Gy in twenty-five (25) fractions (conventional) to the whole breast following a single 8 Gy boost using

the GammaPod. The summed dose to the boost region will be radiobiologically equivalent to a total dose of 52 (hypofractionated) or 66Gy (conventional).

The safety and feasibility of delivering the boost dose to the tumor bed using a single fraction external beam is supported by past clinical trials. Besides the use of electrons and external beam from a linear accelerator, intracavitary balloons and intraoperative x-rays and electron beams have also been used to deliver a TB boost. In the TARGIT trial, a single dose of 20Gy is delivered to the TB using the Intrabeam™ device while the dose drops to between 5 and 7 Gy 1 cm into the normal breast. With long term follow up (median follow-up of 60.5 months), the 5-year local recurrence rate was less than 2 %(20). In the largest intraoperative electron experience, investigators *delivered 9 to 10 Gy in a single treatment prior* to whole breast radiation using 9 MeV electrons(31). Long-term local control rates and cosmesis appear similar to or better than more conventional techniques (36). In this proposed study, we plan to deliver 8Gy to the TB rather than 20Gy with low energy x-rays or 9-10 Gy with electrons before whole breast irradiation, based on 1) there is no benefit of dose escalation over the biological equivalent dose of 16 Gy at 2 Gy per fraction(26) which is equal to 8 Gy in 1 fraction and 2) known increased side effects with higher doses to the tumor bed(8, 36). We believe that the proposed dose should be similarly tolerated as observed in these trials, since the volume of normal breast irradiated is similar using a lower dose. In addition, this treatment will similarly shorten treatment by 1 to 1 ½ weeks by replacing the 8 treatments to the TB.

Since the breast immobilization device is secured to the patient's breast under a mild negative pressure, we believe that delivering the boost prior to the whole breast irradiation may minimize the risk of discomfort because patients occasionally experience breast tenderness at the end of a conventional course of whole breast radiation therapy. Based on our two IRB-approved setup reproducibility studies (GCC1047 and GCC0727) testing the breast immobilization device, only one patient had more than minimal irritation of the skin caused by wearing of the cup system, with the development of several blisters on the breast which resolved with conservative management over two weeks. The investigators believe this was related to an improper fit of the breast cup related to volume loss from her prior surgery and fibrosis from her prior whole breast radiation. In this study, patients will not have had prior radiotherapy so the breast will be more pliable and less skin reaction is expected.

The primary objectives of the study are to investigate whether:

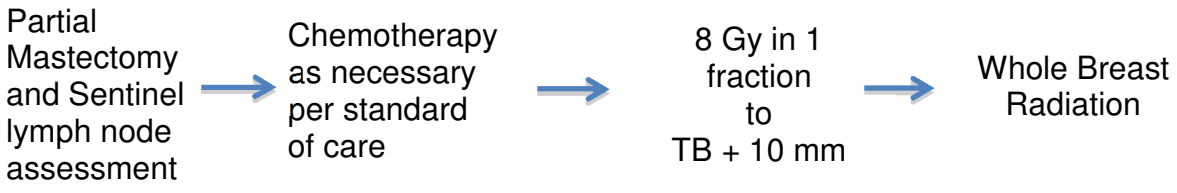
1. Treatment plans satisfy the dosimetric criteria of target coverage as described in section 5.5.4. Treatment plan quality is judged on percentage coverage of the target volume by the prescription dose level, as well as maximum target dose and minimum target dose as percentages of the prescription dose.
2. The treatment procedure can be carried out safely in terms of patient comfort and compliance. However, as part of this study the patient's comfort will be noted along with any observations relative to skin irritation from the cup system or the use of the Hollister Medical

Adhesive spray during the treatment. The adhesive spray has been previously used during the reproducibility studies where CT scans were performed exposing each patient to about 2 cGy over two scans, with no adverse effects noted on follow-up. Nevertheless, though the effect of the radiation on the adhesive spray, as well as the flange and cup materials, is not known or expected to be a concern, each patient's skin, and the materials themselves are to be examined following treatment for any indication of potential risks.

1.3. Schema/procedure

The general treatment sequence is shown in the flow chart below. After lumpectomy and sentinel node biopsy, the patient may or may not be recommended for adjuvant chemotherapy. If chemotherapy is recommended, radiation therapy will start within 6-8 weeks from completion of chemotherapy. If chemotherapy is not recommended or performed prior to surgery, radiation therapy will start within 6-8 weeks following surgery. Rather than delivering the tumor bed boost at the end of the whole breast radiation, we will deliver the tumor bed boost dose of 8 Gy in a single treatment using the GammaPod before whole breast radiation. The clinical target volume for the single treatment is the tumor bed (defined as the surgical cavity including surgical clips and any surgical changes) plus a 5 mm uniform margin. A further 5 mm uniform expansion in all directions will be added to the clinical target volume to make the planning target volume. This 5 mm margin is based on our setup reproducibility study with the current patient loader and breast cup system (GCC1047), as well as conservatively taking into account mechanical uncertainty of couch positioning. Twelve patients have contributed data to the setup reproducibility analysis (see the Pre-Clinical Tests section, Tab 3). The reproducibility of target location within the cup to within two standard deviations of the mean (95% confidence limit) has been found to be 2.9 mm.

After the single fraction GammaPod treatment, standard whole breast radiation therapy delivering 50 Gy in 25 treatments or 40 Gy in 15 treatments will be administered.



Patients will first be simulated in the supine or prone position in preparation for whole breast radiation without the breast immobilization device. If the surgical cavity is clearly visible and the TB volume is less than 25% of the whole breast volume, the patient will be a candidate for single fraction GammaPod boost (this study) and considered for treatment on study. The patients will be approached after the simulation and offered the study if they otherwise meet the eligibility criteria. Otherwise, patients will be off the study and be treated with the standard of care, i.e, start with 25 fractions of whole breast irradiation followed with 5-8 fractions of TB boost. If patients agree for treatment on study and sign informed consent, they will be set up to undergo a second CT simulation in the prone position with the vacuum-assisted breast immobilization device in place followed by the TB boost treatment using the GammaPod system on a day prior to whole breast irradiation (more details below).

For delivering the tumor bed boost dose with the GammaPod, the patient will first be fitted with the breast immobilization cup using silicone inserts and silicone adhesives as necessary to obtain an adequate seal. The negative pressure applied on the cup will be set to -150mmHg based on experience from our setup reproducibility studies using earlier and current versions of the cup system (IRB approved studies GCC0727 and GCC1047 respectively). In GCC0727, pressure settings between -100 mmHg and -175 mmHg were tried, with -150 mmHg being used most commonly. In GCC1047, a pressure of -150 mmHg has been consistently used for all patients, and found to be well tolerated and effective. Consequently, we have decided to use this value for all patients in the proposed clinical use study GCC1202. For context, a typical breast pump for a nursing female generates a peak pressure of about -250 mmHg. Once the negative pressure is established on the breast tissue, the patient will receive a CT scan wearing the vacuum-assisted breast cup that locks onto the GammaPod imaging table. The breast cup and imaging table is show in Figure 2 below. Note the pink silicone flange on the cup to provide a seal onto the patient's chest. The imaging table allows the affected breast with the breast cup on to be locked into the opening of the table surface while the patient is in the upright position. The step of the table is adjustable, so that patients of different heights can have their affected breast placed through the opening on the table. The treatment table has the same surface shape, step adjustment, and rotating mechanism as the imaging table to ensure that imaging and treatment have the same patient setup geometry.

Figure 2. a) The revised breast cup assembly and b) the patient imaging couch that rotates from near vertical to horizontal for imaging and treatment c)

Regarding ensuring that adequate pressure in maintained throughout the procedure, there are multiple safeguards as outlined here:

(i) During the period that the patient is not being scanned or treated, a therapist will be accompanying the patient and monitoring the pump's pressure gauge. In addition to the gauge there is an LED light that indicates a current drop in pressure to below -100 mmHg and also a "latch" LED that comes on when a drop in pressure occurs and stays lit even if pressure is restored. The conservative value of -100 mmHg was chosen as an alert and interlock (see iii below) threshold with the rationale that a value within the range observed to fully immobilize the skin of the breast provided optimum patient safety. **At any time after CT scanning and prior to treatment, if on examination of the latch LED a pressure drop to below -100 mmHg has occurred, the procedure will be halted and the physician will order a repeated imaging study and if already planned the patient will be re-planned.**

(ii) During CT scanning, the pressure gauge and indicator lights will be visible via the CT room's video camera. Scanning can be halted in the event of a pressure loss.

(iii) During GammaPod treatment, in addition to video monitoring, a pressure monitoring cable from the pump provides an interlock that shuts off the radiation in the event of a pressure drop below -100 mmHg.

It should be noted that the pump is continually on throughout the procedure and can maintain pressure even in the event of small air leaks in the seal between the flange and skin. While the patient is lying prone for scanning or treatment, their weight further reinforces the seal between the cup flange and chest. The routine use of a biocompatible medical adhesive (Hollister 7730

Medical Adhesive Spray, as used for an ostomy – see Figure 3 of Pre-Clinical Tests Section, Tab 3) further helps to establish and maintain a good seal. During the reproducibility studies, significant pressure loss has never been observed during CT scanning while the patient was lying prone in the treatment position. A photograph of the pump, with pressure gauge indicating -150 mmHg is shown in Figure 4 of the Pre-Clinical Tests Section. During treatment, a cable from the pump enables interlocking of the radiation delivery in the event of a preset pressure drop (to -100 mmHg).

Both the CT simulator and the GammaPod unit are within the Department of Radiation Oncology. A typical breast CT simulation takes 10-15 minutes. After the CT scan, the images will be transferred to the treatment planning system, which is specifically designed by Xcision for the GammaPod system. It uses inverse planning principles to optimize a dynamic path of the focal spot to paint the prescribed dose distribution. On the treatment planning system, the target volume will be delineated by the prescribing physician. They can also delineate critical organs and structures and set a dose limit to them. The typical time required for target delineation is 10-15 minutes. After target delineation, a GammaPod treatment plan will be optimized based on the dose prescriptions and dose limitations. Plan optimization takes less than 2 minutes including the final dose calculation.

The treatment plan will be reviewed and approved by the prescribing physician and physicist before being sent to the GammaPod system for delivery. For a plan to be acceptable, the 8Gy isodose line must cover 95% of the PTV (tumor bed plus 10 mm margin), and must be at least 5mm from the breast skin surface. The minimum PTV dose must be greater than 7.2Gy, i.e., a maximum of 10% cold spot is allowed if 95% of PTV is getting 8Gy or more. The maximum PTV dose must be less than 9.6Gy, i.e., a maximum of 20% hot spot is allowed. For the boost PTV, these dose uniformity measures are significantly less as compared to other boost techniques such as MammoSite or Intrabeam, where the hot spot can be over 100% greater than the prescribed dose and encompasses the entire surgical cavity, and has not been associated with poor cosmetic results(29, 37-39).

As the treatment plan is being developed, the patient will be escorted or transported to the GammaPod treatment room with the breast cup in place and the vacuum seal maintained. After the treatment plan is transferred to the GammaPod control console, the patient will then be set up on the treatment table in the same geometry and manner as for CT imaging. The optimized treatment plan will then be delivered by the GammaPod system. For a spherical target size of 5 cm in diameter, the treatment would take about 12 minutes. For a 3 cm target, the treatment time is less than 3 minutes. We expect that the total time from wearing the breast cup for CT simulation to the completion of treatment is less than 75 minutes.

At the conclusion of the treatment, the patients will be asked about the comfort of the cup system and procedure, and their skin will be checked for any signs of irritation from the breast immobilization system or the use of the medical adhesive spray during radiation treatment. The cup and flange will also be visually checked for any apparent effects.

At the time of conventional radiotherapy simulation, it will be determined whether or not the patient is an eligible candidate for GammaPod boost treatment. Whether or not the patient receives GammaPod treatment, her whole breast irradiation will start up to 7-8 days after the day of conventional radiotherapy simulation. This time is needed for physician contours, treatment planning by our dosimetry team, physician plan approval and physics plan approval (typically 4 working days) and also allowing for standard practice of beginning a course of whole breast irradiation on a Monday. This timeline is purely a function of workflow rather than clinical/radiobiological considerations. The CT images acquired with the patient in the supine position during simulation will be used for treatment planning. Whole breast treatments are devised according to our departmental guidelines. GammaPod patients will return on a single day prior to their conventional treatment to be CT scanned in the prone orientation and treated with GammaPod. It is possible that GammaPod simulation and treatment will be on the same day as conventional radiotherapy simulation, depending on schedules and patient availability. The timing of GammaPod boost treatment relative to conventional radiotherapy whole breast treatment does not affect the whole breast radiotherapy dose prescription. This is consistent with current clinical practice concerning boost dose delivery, whether pre (i.e. intraoperative radiotherapy) or post (i.e. external beam radiotherapy or brachytherapy) whole breast radiotherapy. Beginning on the day of GammaPod treatment, patients will be evaluated weekly for acute toxicities, as is our clinic's standard practice.

2. Objectives

The primary study objective is to demonstrate the feasibility and safety of delivering a tumor bed boost dose using the GammaPod^{TM} stereotactic system for patients undergoing breast conserving therapy. Efficacy is not among the objectives of this study.

2.1. End points

2.1.1. Primary Endpoint

Demonstration of the feasibility and safety of delivering a radiation treatment using the GammaPodTM for patients undergoing breast conserving therapy ensuring coverage of the target volume with appropriate dose homogeneity and conformity as defined in the study.

2.1.2. Secondary Endpoints

- The evaluation of overall patient comfort in the GammaPodTM procedure.
- The evaluation of acute toxicity during and up to 1 month after GammaPodTM TB boost.
- The evaluation of long-term toxicity at one year to assess the presence of subcutaneous fibrosis, and fat necrosis.
- The evaluation of the use of Hollister Medical Adhesive spray for sealing the cup flange during radiation therapy and its effects, if any, on the patient's skin

3. Patient Selection Criteria:

3.1. Eligibility criteria

- The patient must sign consent for study participation.
- The patient must be female and have a diagnosis of an invasive or non-invasive breast cancer that was treated surgically by a partial mastectomy.
- The patient must be deemed an appropriate candidate for breast conserving therapy (i.e. not pregnant, never had radiation to the treated breast, breast size would allow adequate cosmesis after volume loss from partial mastectomy).
- Patients with involved lymph nodes are candidates for the study as long as regional nodal radiation is not required by the treating physician.
- Surgical margins are negative for invasive or non-invasive breast cancer.
- The greatest dimension of the tumor is less than 4cm before surgery.
- The volume of the TB CTV is less than 25% of the whole breast PTV which is a criteria used for partial breast alone trials (NSABP B-39).
- Multifocal disease is allowed if it was removed by a single lumpectomy resection and the patient remained a candidate for breast conservation.
- Age 60 years and older.
- Women of childbearing potential must use an effective contraceptive method such as condom/diaphragm and spermicidal foam, intrauterine device (IUD), or prescription birth control pills. A negative pregnancy test must be obtained prior to study enrollment or waiver signed.
- The surgical cavity is clearly visible on CT images.
- The patient must weigh less than 150Kg (330lb), which is the limit of the imaging couch.

- The patient must be less than 6'6" in height.
- The patient must feel comfortable in the prone position.

3.2. Ineligibility criteria

- Patients with proven multi-centric carcinoma (tumors in different quadrants of the breast or tumor separated by at least 4 cm).
- Prior radiation therapy above the umbilicus
- Unable to fit into the immobilization breast cup with an adequate seal
- Male gender.
- Patient cannot comfortably be set up in the prone position (i.e. physical disability)
- Unable to fit into the breast immobilization device due to breast size or other anatomical reason.
- Mastectomy is the surgery performed.
- Patient has received prior radiotherapy to the involved breast.
- Regional nodal irradiation is part of the treatment plan.
- Tumor bed is less than 5 mm from the skin surface.
- Patients with skin involvement, regardless of tumor size.
- Patients with connective tissue disorders specifically systemic lupus erythematosis, scleroderma, or dermatomyositis.
- Patients with psychiatric or addictive disorders that would preclude obtaining informed consent.
- Patients who are pregnant or lactating due to potential exposure of the fetus to RT and unknown effects of RT to lactating females.

4. Registration

- Consent for enrollment onto protocol will be performed by principal investigator or member of research team.
- Patients can only be registered after eligibility criteria are met following the conventional supine CT simulation which may occur the day of the simulation or within a few days such that GammaPod treatment could be planned prior to whole breast radiotherapy. The conventional supine or prone CT simulation used for whole breast radiotherapy is performed approximately 7-10 days prior to starting whole breast radiotherapy.

- Once a patient is registered, a case number will be assigned to the patient.

5. Radiation Therapy Protocol

5.1. CT simulation for planning whole breast irradiation

The patient will undergo a conventional CT simulation in supine or prone position without the breast immobilization cup. The purpose of the CT simulation is-two-fold: 1) we will see if the TB volume can be accurately delineated and if the TB volume is too large for GammaPod boost; and 2) the CT images are used for planning the patient's whole breast irradiation. If, after viewing the CT images and the patient is deemed a study candidate and consents, they will receive a second CT-sim and the GammaPod TB boost treatment on the same day as described below.

5.2. CT-based treatment planning for the GammaPod treatment

- Patients will be simulated in the prone position using a breast immobilization cup supplied by Xcision. Depending on the fit of the cup, supplemental silicone fillers and supplemental silicone adhesive are used to improve fit and seal of the cup. The cup consists of two layers with an air space in between. A small negative pressure (fixed at -150 mmHg and not adjustable) is applied between the 2 layers to immobilize the breast inside the cups.
- The reproducibility of the breast immobilization cup decreases outside the confines of the cup (Figure 3), such that if any "tumor bed" clip is above the rim of the cup, the patient will not receive treatment with the GammaPod and will be treated off study using departmental standard treatment.
- The CT will start at the thyroid notch and extend below the infra-mammary fold (including the entire lung) with a slice thickness of 1.0 mm through the breast

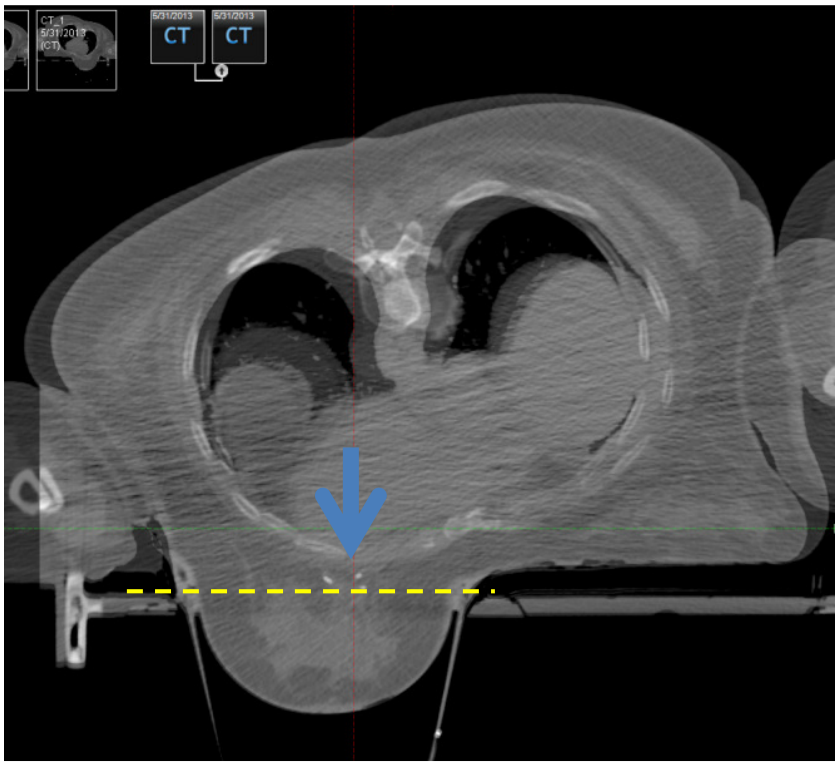


Figure 3. For a patient to be included in the study, all clips need to be below the yellow line demarcated as top of the breast immobilization cup. The image shown here represents a patient ineligible for the study, as would any patient where any clip is above the line.

5.3. Target volumes for TB boost

The following structures will be outlined on all CT slices: the clinical target volume (CTV) and the planning target volumes (PTV).

5.3.1. Clinical Target Volume (CTV)

The CTV will be the tumor bed which is the combination of the surgical changes (surgical cavity) and surgical clips in the surgical bed + 5 mm. This margin incorporates the extent of anatomy that is considered to be required clinically to be covered by the prescribed dose.

5.3.2. Planning Target Volume (PTV)

- The PTV will provide a margin around the CTV to compensate for uncertainty in treatment set up as determined by GCC1047. This study indicates that uncertainty of target position within the stereotactic coordinate system is within 3 mm to two standard deviations. A further 2 mm margin will be used for this study to capture any residual uncertainty due to respiratory motion of the breast and any uncertainty in the positioning of the stereotactic coordinate system relative to the beams.

- The PTV expansion will be defined as a uniform 5 mm expansion of CTV.
- The PTV will be limited to 5 mm from the skin surface and 0 mm from the pectoralis muscle posteriorly.

5.4. Treatment planning for tumor bed boost

The PTV will be used as the target for treatment planning

5.4.1. Dose prescription and delivery

The PTV will receive 8 Gy in 1 fraction.

5.4.2. Dose limitations for normal tissues.

- The dose at the skin surface must be less than 95% of the prescription dose.
- The dose at 1 cm from the PTV should be less than 30% of the prescription dose.
- The chest wall will receive less than the prescription dose.
- No rib should receive more than 75% of the prescription dose.
- The maximum dose to lung should be no more than 2.5Gy. This limit is slightly less than the single fraction dose given in hypofractionated whole breast irradiation (3.3Gy in START trial(18) and 2.66Gy in Ontario trial(16)).
- The maximum dose to the heart should be no more than 2.5Gy. This limit is slightly less than the single fraction dose given in hypofractionated whole breast irradiation (3.3Gy in START trial and 2.66Gy in Ontario trial).

5.4.3. Criteria for judging deviations from plan

- No deviation (acceptable): 100% prescription isodose surface covers at least 95% of the PTV. Maximum dose to the PTV should not exceed prescription dose by >20%. Minimum dose to the PTV should not be lower than 7.6Gy (below the prescription dose by 5%). All specified critical normal tissue DVH limits as described in 5.4.3 have been met. As compared with TB boosts with FDA approved brachytherapy techniques and intraoperative treatments, which are associated with dose "hot spots" of 100% - 400%, a 20% dose inhomogeneity within the TB PTV should be acceptable.
- Minor deviation but acceptable: 95% prescription isodose surface covers between 95% and 100% of the PTV. No portion of the PTV receives <93% of the prescription dose. Maximum dose to PTV exceeds prescription dose by >20% but <30%. All specified critical normal tissue DVH limits fall within 5% of the guidelines.
- Major deviations (unacceptable): 95% isodose surface covers < 95% of the PTV. A portion of PTV receives < 93% of prescription isocenter dose. Maximum dose to PTV exceeds prescription dose by >30%. Any critical normal tissue DVH limit exceeds 5% of the specified value.
- If a major deviation is required for treatment delivery, then the Gamma Pod treatment will not be delivered and the patient will be taken off study.

- Treatment delivery will not be performed if the seal of the breast cup is lost or pressure falls below a pre-determined value following the CT simulation. Such an event will be recorded.
- If the cup pressure drops to below 100 mmHg, which is signified by an alarm on the pump, the physician will do the following:
  - If it occurs before the simulation CT scan, continuation with the study should proceed once pressure is reestablished.
  - If pressure loss occurs following the simulation CT scan and before treatment, the CT simulation will need to be repeated to ensure the reproducibility of target position between CT scanning and treatment. The event will be recorded and the treating physician will decide whether to proceed with GammaPod treatment or treat the patient conventionally off study.
- Treatment delivery will not be performed if the breast cup cannot be locked into the treatment table. Such an event will be recorded.
- Treatment delivery will not be performed if the patient feels uncomfortable following the placement of the breast cup. Such an event will be recorded.

5.5. Institutional guidelines for whole breast irradiation treatment planning

5.5.1. Whole breast RT target volumes

5.5.1.1. Gross Tumor Volume (GTV)

No GTV

5.5.1.2. Clinical Target Volume (CTV)

- Tumor bed is delineated by identifying post-operative seroma and associated surgical clips + 5 mm
- Whole breast PTV will be determined following the tangents placed/finalized by the treating physician, by subtracting 5 mm from the block edge, skin and the lung/rib/intercostal muscle interface. See Figure 4.
- Tumor bed coverage in the whole breast radiation: The tumor bed CTV is expanded by 15 mm in all directions (anatomically constrained by skin and not the chest wall). The block edge of the tangent will be at least 15 mm to ensure dose coverage of the tumor bed CTV

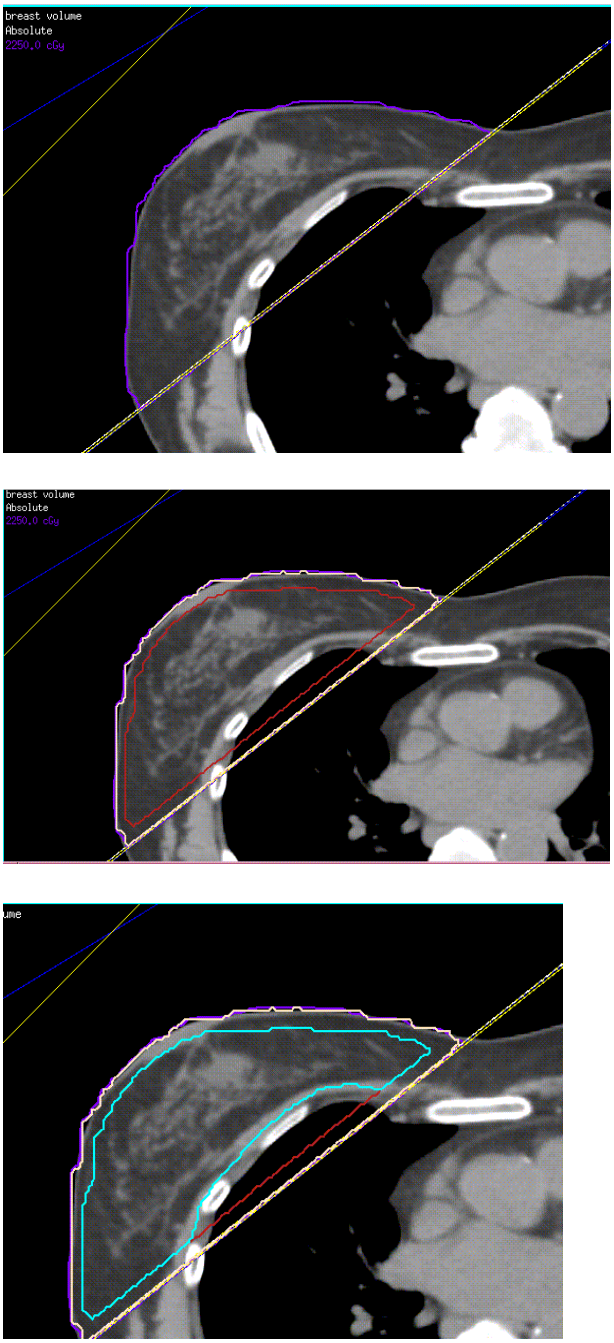


Figure 4. Steps to generate whole breast PTV (A)The purple line represents the 50% isodose line which is used to create volume. (B) The red line represents the 50% volume subtracting 5 mm from the skin and 1 cm superiorly and inferiorly.(C) The blue line subtracts the lung + 5 mm.

5.5.2. Dose prescription

The dose delivered to the whole breast PTV for patients in the study will be 50 Gy in 25 fractions OR 40 Gy in 15 fractions with the dose prescribed to the ICRU reference point.

5.5.3. Treatment delivery technique

- 3-D conformal RT with control points is the standard (40), with the maximum of 4 control points.
- Hybrid inverse planned IMRT will be attempted(41), if:
  - Whole breast V105 >75 cc in conventional fractionated plan or V105 > 50 cc in hypofractionated 3D plan
  - Whole breast Dmax> 110%
  - 95% of the Tumor bed PTV cannot be covered by 95% of the prescription dose
  - 95% of the Tumor bed CTV cannot be covered by 95% of prescription dose
- Hybrid plan will be used in preference to 3D conformal RT with control points, if hot spots are decreased by 20% as measured by the absolute volume of V105 (i.e. if V105in forward plan is 100 cc, hybrid plan has to reduce to 80 cc or less)as they decrease fibrosis and acute skin toxicity (41-43) or coverage is improved by 20%

5.5.4. Dose-volume analysis for the whole breast

- 95% of the Whole breast PTV receives >95% of prescribed dose
- 95% of the Tumor bed CTV receives > 95% prescribed dose
- 95% of the Tumor bed PTV receives > 95% prescribed dose

5.5.5. Dose-volume analysis for normal structures

- Normal structures(22), unfortunately there is no clear DVH criteria that predicts increased side effects – values chosen were arbitrary based on clinical practice
- Ipsilateral lung: V20 < 20%
- Heart: V30 < 5%, mean heart dose <5Gy

5.5.6. Timing

Treatment to the whole breast will begin within 7-8 days from the tumor bed boost (GammaPodTM) treatment unless an adverse event occurred from the GammaPod treatment.

6. Surgical Resection

- Lumpectomy and lymph node sampling or dissection should be performed according to institutional standard of care.
- Surgical clips to delineate the surgical bed is the standard of care of our referring surgeons.

7. Adjuvant Systemic Therapy

- Chemotherapy and/or hormonal therapy may be given pre-operatively or post-operatively according to standard of care and will be recorded.
- Hormonal therapy, if used, will be delivered concurrently and recorded.

8. Pathology

Pathology assessment of the lumpectomy and lymph node assessment will follow current standard of care.

9. Patient Assessments

9.1. Study parameters

Assessment	Pre-Entry	During Radiation	At 6 weeks[e]	At 6 months[e]	At 1 year[e]
H&P, Breast Exam	X		X	X	X [d]
Weight	X			X	X [d]
Bra cup size	X			X	X
Disease status	X		X	X	X [d]
Mammograms	X			X[f]	X [c]
Toxicity		X [b]	X [b]	X [b]	X [b]
Photographs	X[a]	X[a]		X[a]	X[a]

a. Photographs will be obtained prior to GammaPod treatment, following the removal of the breast immobilization device after the treatment is delivered, on the day whole breast radiation starts and on the last day of treatment as well as at their 6 and 12 month follow up.

b. Patients will be seen on day of GammaPod treatment and following GammaPod treatment on day of 1st whole breast treatment, then weekly during whole breast radiation and all toxicity will be recorded at each of the time points or more often as clinically indicated.

c. Yearly thereafter

d. Clinical examination and disease status assessment at 6-month intervals for the first 3 years, and yearly thereafter

e. Time points are from the start of radiation therapy

f. Mammogram 6 months after radiation therapy, then yearly thereafter.

9.2. Adverse event reporting

9.2.1. Anticipated toxicities

- Fatigue is the anticipated systemic reaction to radiation treatment.
- Skin irritation, erythema and desquamation may also occur.
- Breast edema, tenderness, and myositis are potential acute side effects.
- Long-term complications may include radiation pneumonitis, rib fractures, cardiac complications, and wound healing complications. Although the additional risk from this single treatment should be minimal in comparison to the whole breast radiation.
- Patients will be seen on day of GammaPod treatment and following GammaPod treatment on day of 1st whole breast treatment, then weekly during whole breast radiation and side effects will be recorded at each of the time points.

9.2.2. Toxicity reporting

Acute radiation effects will be evaluated and scored using the NCI CTCAE v. 4.0. A copy of the CTC version can be downloaded from the CTEP homepage (http:ctep.info.nih.gov). Please note that this study will not be using separate toxicity scales for acute and late radiation effects. All acute effects and late effects that occur within one year will be recorded in ONCORE. Data and safety monitoring will be reported to the in-house data safety monitoring board bi-annually.

9.2.3. Photographs to evaluate toxicity

- Digital images of the breast will be taken prior to GammaPod treatment, following the removal of the breast immobilization device after the treatment is delivered, on the day whole breast radiation starts and on the last day of treatment as well as at their 6 and 12 month follow up.
- All images will exclude the patient's face.
- The first image will be a close up of the ipsilateral breast undergoing planned therapy in a straight frontal view with both arms elevated above the patient's head.
- The second image will be a close up of the ipsilateral breast undergoing planned therapy in a straight frontal view with both hands on the patient's hips.
- The third image will be a straight frontal view encompassing both the patient's breasts with the patient's hands on her hips.

9.2.4. Life-threatening and grade 4 events

All life-threatening events (events, which in view of the investigator, place the patient at immediate risk of death from the reaction) or Grade 4 events that are definitely, possibly, or probably related to protocol treatment using radiation therapy will be reported according to IRB reporting policy. Every Severe Adverse Event (SAE) will be reported on FDA 3500 A (MedWatch Form).

9.2.5. Fatal events (Grade 5)

All deaths with the attribution of definitely, possibly, or probably related to protocol radiation therapy must be reported according to IRB reporting policy. Every Severe Adverse Event (SAE) will be reported on FDA 3500 A (MedWatch Form). All deaths during and within 30 days of completion of protocol radiation therapy, regardless of attribution, must be reported according to IRB reporting policy. Every Severe Adverse Event (SAE) will be reported on FDA 3500 A (MedWatch Form)

https://www.accessdata.fda.gov/scripts/medwatch/.

If the event is more than 30 days from completion of radiation treatment, but is felt to be definitely, possibly, or probably resulting from protocol radiation therapy, this event must be reported according to IRB reporting policy. Every Severe Adverse Event (SAE) will be reported on FDA 3500 A (MedWatch Form).

10. Statistical Considerations

10.1. Objectives

The primary objective is to demonstrate the feasibility and safety of delivering a tumor bed boost dose using the GammaPod stereotactic system for patients undergoing breast conserving therapy. Primary feasibility endpoints will include an estimate of reproducibility of the radiation technique. Reproducibility will be assessed on the basis of radiation therapy being scored as acceptable, marginally acceptable, or unacceptable using the criteria described in Section 5.4.3. The proportion of patients eligible for a GammaPod TB boost will be based on clinical and pathological findings. Secondary safety endpoints will include the number and type of serious adverse device-related events, the incidence of acute radiation. Acute toxicity will be assessed using the NCI CTCAE v4.0 criteria. Toxicities will be defined as acute if they occur within one month of protocol therapy. TB boost is not experimental. Delivering a single large dose to the TB is also not new. Based on previous intracavitary, intraoperative TB irradiations with 20 to 21 Gy(30, 44-46), we do not expect elevated significant late side effects. To reiterate, this study will treat only to 8 Gy as opposed to 20 to 21 Gy and is treating a similar volume as other intraoperative experiences where thousands of patients have been treated. Subsequently, the late toxicity profile will not be part of the statistical evaluation in this feasibility study. However, toxicity will be reviewed at 12 months after the completion of the radiation therapy and the data will be captured. Acute effects may be related to placement of the immobilization device but since it is placed prior to the whole breast radiation, the one month post whole breast radiation endpoint is appropriate.

10.2. Trial design

Sample size for the trial is based on a primary endpoint of quality of the radiation dose distribution. As described above, the GammaPod dose will be scored as acceptable, acceptable but with a minor deviation, or unacceptable using the criteria described in Section 5.5.4. All eligible patients will be included in the analysis. If a treatment plan is graded as unacceptable, the treatment will be aborted and the GammaPod boost will not be delivered. The patient will in that case be treated with a conventional boost following whole breast radiation (i.e. 16 Gy in 8 fractions using electrons or photons with conventional linear accelerator). The optimal two-stage trial design by Simon will be used(47). This tests the null hypothesis that, for a population of patients, the true proportion of patients for whom the GammaPod treatment planning system is able to generate an acceptable dose distribution is less than or equal to 60% (a chosen value signifying that the device has significant clinical utility if the null hypothesis is false). Given only a limited sample size in the study, the proportion of patients in the study for whom treatment plans must be acceptable for the null hypothesis to be found false (to a low uncertainty) must in fact be considerably higher than 60% (see below). Specifically, the number of acceptable plans and the total number of plans must be such that there is a certain low probability (chosen here as less than 5%) that the device will be found acceptable in the trial when in fact it would be acceptable for less than 60% of patients in a very large population of patients. That is, there is only a 5% chance that the device will be found to have significant utility when in fact it does not. In the design, there is also an alternative hypothesis that the true proportion of patients with an acceptable dose distribution is greater than or equal to 90%. Again, the required total number of patients in the study and the number for whom plans are acceptable must be sufficient for there to be a certain low probability (chosen as less than 10%) that the null hypothesis is found to be true when in fact the alternative hypothesis is true. That is, there is only a 10% chance that the device will be found to not have significant utility when in fact it has high utility. Furthermore, the Simon Two Stage design allows for the trial to be aborted if after plans have been generated for a subset of the total number of patients (stage 1) the number of acceptable plans is below a certain number. Using tables for Simon Two Stage design, an appropriate design has been determined to be the following:

After evaluating the device on 8 patients in the first stage, the trial will be terminated and the device rejected if the dose distribution is acceptable for only 5 or less patients. If the trial goes on to the second stage, a total of 17 patients will be studied. If the total number of patients for whom the dose distribution is acceptable is less than or equal to 13 the device will be rejected. If the null hypothesis is in fact true, there is a 4.4% probability of falsely concluding that it is false (the target for this value was 5% in designing the trial). This is the probability of falsely concluding that the true proportion of patients with an acceptable dose distribution is greater than 60% when in fact it is less than or equal to 60%. On the other

hand, if the alternative hypothesis is true, there is a 9.5% probability of falsely concluding that the null hypothesis is true (the target for this value was 10%). This is the probability of falsely concluding that the proportion of patients with an acceptable dose distribution is less than or equal to 60% when in fact the true proportion is at least 90%. This scheme gives a power of 90.5% (1–9.5%: the probability of concluding correctly that the null hypothesis is false when the alternative hypothesis is true). The probability of early termination after stage 1 if the null hypothesis is true is equal to 68% (early termination occurs if 5 or fewer patients are acceptable after stage 1) and the expected sample size for this trial is 10.8 accounting for the probability of early termination.

11. Potential Risks/Discomfort

GammaPod is a new radiation treatment device that has not been used on patients before. Although there has been extensive pre-clinical testing with phantoms, it is still possible that the GammaPod treatment deviates from the intended in geometry and dosimetry. Patients may not be able to tolerate the breast immobilization cups due to the negative pressure and the duration of treatment in the prone position.

To minimize the dosimetric discrepancy, the physicist co-investigator must perform a hand calculation to verify the treatment time is within 5% to the treatment time calculated by the treatment planning system before the treatment can be started. The total treatment time is a function of the target volume, the prescribed dose and the dose rate.

$$t \approx PTV * D_p / \dot{D} V_f$$

where t is beam on time, PTV is the planning target volume, D_p is the prescription dose to the PTV, $\dot{D}$ is the dose rate on the day of treatment, and V_f if the focal spot volume at the 50% isodose surface.

The maximum dose to lung and heart should be less than 2.5Gy. This limit is slightly less than the single fraction dose given in hypofractionated whole breast irradiation (2.66 Gy in Ontario trial(16), and 3.3Gy in UK START trial(18).

To minimize the geometric error, the tumor location relative to the breast cup will be displayed on the treatment control console after the plan is transferred to the treatment control console. The envelope containing all movements of the radiation focal point of the GammaPod during the entire treatment will also be displayed against the target. The envelope of the focal spots should generally conform to the target volume and a visual verification must be confirmed before the treatment can be started.

The primary goal of the study is to assess the feasibility of using GammaPod to deliver high doses of focal radiation to the target in human breast. Patient tolerance to the breast cup and adhesive during radiation treatment, and to the prone setup, is part of the evaluation. Because we have evaluated the breast cup and prone setup in an earlier study and all subjects tolerated it well, the likelihood of intolerable discomfort or irritation is very small. Nevertheless, if 2 of the first 5 patients or more than 1/3 of the subjects thereafter complain about either the breast cup or the prone treatment setup, the study will be suspended until patient comfort is further improved.

12. Potential Benefits

The characteristics of the GammaPod dose delivery allow the GammaPod to deliver a focal radiation dose with a fast dose fall-off away from the target. It is this ability of lower dose spillage to the normal breast tissue and surrounding organs such as the lung and the heart that makes it possible to deliver an equivalent biological dose to the tumor bed in a single treatment as the conventional boost treatment that takes 8 treatments to complete. Therefore, the direct benefit to the subjects enrolled in the study is the shortening of the treatment duration by one and 1/2 week. If such dose delivery is proven feasible, the implications on the management of early-stage breast cancer are far more important. Currently in the US, more than 90% of the breast cancer patients who choose breast conservation therapy receive 33 radiation treatments that last 7 weeks. Such a protracted regimen significantly worsens the quality of life for these patients and increases health care costs.

13. Cost/Payments

The radiation treatment delivery using the GammaPod is considered experimental. The Department of Radiation Oncology will not charge the patient or her insurance company for the associated costs. The participant and/or their health plan/insurance company will need to pay for some or all of the costs of treating the cancer in this study.
The whole breast radiation therapy subsequent to the GammaPod single fraction tumor bed boost is not experimental but standard of care. The hospital will bill the patient/payer as with conventional radiation therapy.

No payment will be given to the patients for participating in this feasibility study.

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