USC Norris Comprehensive Cancer Center
Part of the Keck School of Medicine of USC

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Protocol Title: Targeted Intra-Operative Radiotherapy for the Management of Ductal Carcinoma In-Situ of the Breast (TARGIT-DCIS Trial): Use of Mammography and Breast MRI to Identify Candidates for IORT

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SCHEMA, SYNOPSIS, OR STUDY SUMMARY

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Abstract

The current standard of care for the management of ductal carcinoma in situ is total mastectomy or wide local excision followed by whole breast external beam radiotherapy when wide local excision can be achieved with acceptable cosmesis. Whole breast external beam radiotherapy requires 6-week course of daily visits to a radiation oncology. This protracted course of radiotherapy sometimes poses a barrier to the selection of breast conserving surgery for many women. In addition, whole breast external beam radiotherapy may also be associated with local and systemic morbidity that increases its burden on patients. Intraoperative radiotherapy (IORT) is a form of accelerated partial breast radiotherapy that focuses the radiotherapy dose on the tumor bed, allowing reduction in the total radiation dose as well as reduction of local and systemic side effects. IORT is not currently the standard of care for the management of breast cancer. However, as an approved treatment for the treatment of malignancy, IORT is currently being evaluated as an alternative to whole breast external beam radiotherapy for the treatment of breast cancer. The principal advantage of IORT is that the breast operation and the entire radiotherapy treatment can be completed while the patient is still under anesthesia. Thus, the entire local therapy of the breast can be completed in one trip to the hospital. The use of IORT as for the management of DCIS is limited by the fact that the IORT dose is delivered before the surgical margin status is known. Consequently, IORT might be given prematurely or inappropriately, particularly when inadequate surgical margins necessitate re-excision or conversion to mastectomy. Generally, surgeons and radiologists must rely on the presence and extent of microcalcifications on pre-operative mammograms to define the extent of DCIS and the portion of the breast requiring excision. Unfortunately, not all DCIS lesions form microcalcifications and among those that do, the total span of microcalcifications may be smaller than the actual span of DCIS. This size discrepancy can lead to underestimation of DCIS lesion size and increased risk of incomplete initial excision. Contrast-enhance breast magnetic resonance imaging (CE-MRI) has become an increasingly important adjunct to mammography for evaluating breast malignancy and has higher sensitivity in the detection of multifocal and multicentric disease. For this reason, CE-MRI has a growing role in defining the extent of disease in patients with known breast malignancy. We hypothesize that the combination of mammography and CE-MRI will improve the surgeon and radiologist's ability to define extent of disease prior to surgical resection, improve the odds of obtaining clear surgical margins, and increase the efficacy of IORT delivered immediately after initial surgical resection. In this investigation, we will determine whether or not patients deemed eligible for 'immediate" IORT based on mammography and CE-MRI can be successfully treated without the need for re-excision or additional radiotherapy due to inadequate surgical margins.

1.0 BACKGROUND AND HYPOTHESES

1.1 Ductal carcinoma in situ of the breast is a heterogeneous group of lesions characterized by proliferation of malignant cells within an intact basement membrane. Ductal carcinoma in situ (DCIS) is a typically a clinically occult breast neoplasm that is usually diagnosed mammographically. With advances in mammographic screening, the prevalence of DCIS has rapidly increased. Approximately 52,000 cases of DCIS were diagnosed in 2006[1], constituting 22% of all breast malignancies diagnosed that year. DCIS is a non-obligate precursor of invasive breast malignancy. If left untreated, most DCIS lesions are expected to progress to invasive breast cancer and create the potential for development of regional and systemic metastases.

Similar to invasive breast cancer, the current standard of care for the management of DCIS is total mastectomy or wide local excision (WLE) followed by whole breast external beam radiotherapy when WLE can be achieved with acceptable cosmesis. Mastectomy is indicated for patients with extensive disease not amendable to WLE or in situations where breast radiotherapy is contraindicated. In addition, approximately 1/3 of patients with low or intermediate grade DCIS may be treated without the use of radiotherapy.

Until the early 1990's, total mastectomy was the standard operation for patients with DCIS. Surgical management began to change following the analysis of the landmark study, National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-06, comparing breast conserving therapy to mastectomy for management of early stage invasive cancer[2]. A small group of women with pure DCIS had been inadvertently enrolled in the sample groups. Subgroup analysis of these patients indicated that lumpectomy and radiation could be an acceptable alternative to mastectomy in terms of reducing local recurrence. To validate the findings of the NSABP B-06, the NSABP undertook the B-17 trial, randomizing over 800 patients with DCIS to treatment with lumpectomy alone or lumpectomy plus whole breast external beam radiotherapy (WB-EBRT). In 2001, the 12-year follow-up results demonstrated excellent local control rates for patients treated with lumpectomy plus WB-EBRT (local recurrence rate of 16%) compared to lumpectomy alone (local recurrence rate of 32%)[3]. Similar benefits of radiotherapy were also demonstrated in the European Organization for Research and Treatment of Cancer (Protocol 19853) and the United Kingdom, Australia, New Zealand DCIS Trial[4,5]. Collectively, these trials established radiation as a standard adjunct to wide local excision for women with DCIS.

Currently, the standard of care for DCIS treated with wide local excision is WB-EBRT (5000 rads divided over 25 treatment) with or without a radiation boost dose (1000 rads divided over 5 treatments) to the surgical scar and tumor bed. Due to local radiation induced toxicity (skin injuring, breast fibrosis, breast edema, breast pain), inconvenience of daily therapy, and treatment non-compliance (20% of patients more than 10 miles from a radiotherapy treatment center never complete the prescribed course[6]), recent developments in breast radiotherapy have focused on accelerated partial breast irradiation (APBI) techniques designed to target the radiation dose to the tumor bed, reduce radiation injury to nearby breast and non-

breast tissues, and reduce overall treatment time. APBI is supported by numerous studies indicating that more than 85% of breast cancer recurrences occur at or near the original tumor site[7,8]. Therefore, limiting the radiation dose to the tumor site allows a therapeutic dose to be delivered to the portion of the breast where recurrences are most likely to occur, while minimizing exposure and collateral injury to more distant breast and non-breast tissues.

The safety and efficacy of ABPI have been evaluated in several case control and cohort studies which have shown ABPI to be a safe and effective method of reducing local recurrence of breast cancer as well as the side effects associated with radiotherapy. However, few of these studies have specifically examined the safety and efficacy of APBI for the management of DCIS. One such trial is the Mammosite DCIS Trial, a multicenter study conducted at USC and 11 other centers, which showed minimal toxicity and effective control of local recurrences in patients receiving APBI following initial wide local excision. The use of APBI is also currently being evaluated in the recently opened NSABP-39 study, comparing WBRT against several forms of ABPI (3D-Conformal Radiotherapy, Interstitial Multicatheter Brachytherapy, and Mammosite Balloon Catheter Brachytherapy) following initial WLE among patients with DCIS and invasive breast cancer.

Currently, there are no clinical trials specifically designed to evaluate the use of IORT, or radiotherapy administered at the time of WLE, in the management of patients with DCIS. However, promising preliminary findings have been reported at The European Institute of Oncology which has included DCIS among more than 1,800 patients (primarily invasive breast cancer patients) undergoing immediate IORT. Since 1999, the Institute reported only a 1.6% incidence of local recurrence and an 8.2% incidence of side effects (severe fibrosis 0.2%, mild fibrosis 2.6%, fat necrosis 4.1%, hematoma 1.3%) among all patients receiving immediate IORT following breast conserving surgery[9]. These statistics are comparable to similar patients receiving WE-BRT following WLE.

IORT is not currently the standard of care for the management of breast cancer. However, as an approved treatment for the treatment of malignancy, IORT is now being evaluated as an alternative to whole breast external beam radiotherapy for the treatment of DCIS. One of the major barriers to the acceptance of ABPI, and particularly IORT, as an adjuvant therapy option for DCIS is the challenge of delineating the extent of DCIS prior to excision. Discrepancy between the mammographically measured lesion size (e.g., the span of microcalcifications) and the histologically measured lesion size may also lead to underestimation of lesion size and increased risk of incomplete initial excision. To improve estimation of DCIS lesion size and to reduce the risk of incomplete excision, surgeon and radiologists have increasingly used contrast-enhanced magnetic resonance imaging (CE-MRI) to aid delineation of lesion size[10-11]. CE-MRI relies on the presence and distribution of cancer-associated neovascularization to define the extent of disease. Whereas both benign and malignant lesions may experience neovascularization, the specific perfusion kinetics and morphologic patterns of cancer-associated microvasculature aid distinction between benign and malignant lesions. Indeed, in patients with biopsy-proven breast cancer, pre-operative CE-MRI has been shown to a change surgical therapy in up to 30% of breast cancer patients[12-14]. Consequently,

CE-MRI may have important implications in treatment planning in patients considering lumpectomy, particularly in circumstances where a low re-excision rate is mandatory, such as with the use of intraoperative radiotherapy.

1.2 Intraoperative Radiotherapy. Intraoperative radiotherapy is not currently standard treatment for breast cancer. The purpose of this research study is to study the use of intraoperative radiotherapy for the treatment of ductal carcinoma in situ. IORT is emerging as an innovative alternative to WB-EBRT for the management of breast cancer. Several treatment systems are currently in use internationally, including the Liac (Info&Tech, Roma, Italy) and Novac7 (Hitesys Srl, Latina, Italy) mobile linear accelerators in used at the European Institute of Oncology in Milan, Italy, the Mobetron (IntraOP, Stanford, CA) portable linear accelerator currently in use at Stanford University, and the Intrabeam Photon Radiosurgery System (PRS) (Carl Zeiss, Oberkochen, Germany) currently in use at the USC Norris Comprehensive Cancer Center as part of a multicenter, international prospective randomized controlled trial comparing targeted intraoperative radiotherapy to standard WB-EBRT (The TARGIT Trial). The Intrabeam PRS is similar to the other brachytherapy treatments in that it provides APBI to the tumor bed following removal of the tumor. It differs from most others APBI techniques by the use of a low dose (50vK) energy source that, by design, does not require extensive shielding of the treatment area. Therefore, the Intrabeam can be used in the standard operating theater without extensive radiation shielding.

1.2.1 Advantages of the IORT approach include:

a. Convenience and Efficiency. IORT permits breast surgery and radiotherapy to be completed in one sitting while the patient is still under anesthesia. Thus, the entire local therapy of the breast can be completed in one trip to the hospital.

b. Accurate Delivery of Radiation Dose. By permitting delivery of the radiation dose directly to the surgical margins, IORT avoids the problem of geographical miss in which the prescribed radiation dose is inaccurately and incompletely delivered to the tumor bed. Geographic miss is estimated to occur in up to 80% of patients, and may result from patient movement, inconsistent patient set-up, and difficulty identifying the entire tumor site, particularly when radiotherapy is administered several months after surgery. [15].

c. Protection of Adjacent Tissues. Delivery of radiotherapy at the time of surgery allows the surgeon to protect adjacent tissues from exposure to excessive radiation, e.g., by placement of internal radiation barriers on the surface of the pectorals major muscle to protect the underlying heart and lung, and by retraction of the skin away from the radiation source to reduce skin toxicity.

d. Lower Cost. Since IORT allows the entire radiation therapy to be given in one dose rather than multiple doses, the cost of IORT is lower than other forms of radiotherapy. For example, at the USC Kenneth Norris

Comprehensive Cancer Hospital, the cost of IORT using the Intrabeam PRS is approximately $7500 per patient compared to $9000 for WB-EBRT and $28,000 for MammoSite balloon catheter brachytherapy[16].

1.2.2 While IORT for DCIS offers many advantages over alterative forms of breast radiotherapy, it also has several important limitations:

a. Incomplete Pathology Results. The IORT dose is delivered before the surgical pathology results (e.g., margin status) are fully known. As a result, IORT might be given prematurely or inappropriately in patients who are later found to have more extensive disease than initially anticipated. Inadequate surgical margins will necessitate re-excision or conversion to mastectomy, either of which will increase the cost and potential morbidity of breast cancer therapy. These risks can be partially reduced with the use of Intraoperative margin assessment (e.g., frozen sections and specimen radiography) to aid identification of close or inadequate margins.

b. Possible Need for Additional Radiotherapy. Patients found to have inadequate surgical margins after having received IORT may require the addition of WB-EBRT (with or without re-excision). Generally, repeat IORT is not permitted. The addition of WB-EBRT not only increases the cost of radiotherapy, it may also, theoretically, increase the morbidity of radiotherapy. However, based on several studies in invasive breast cancer patients evaluating IORT administered at a boost dose of 1000 rads to the tumor bed, followed by routine WB-EBRT, there is good evidence to suggest that WB-EBRT given after IORT can be administered with good to excellent cosmesis and no grade 3 or 4 adverse effects[17-19]. Currently, there are no published data specifically reporting the efficacy and safety of IORT (with or without combined WB-EBRT) for the treatment of DCIS.

While appropriate candidates for IORT may be easily selected among patients receiving such treatment after analysis of the surgical specimen (hereafter referred to as "delayed IORT"), there are no established criteria for selecting which patients with DCIS are appropriate candidates for immediate IORT. Consequently, the feasibility of administering IORT at the time of WLE (hereafter referred to as "immediate IORT") of DCIS remains to be established.

2.0 OBJECTIVES AND PURPOSE

In this investigation, we will determine whether or not patients with DCIS deemed eligible for 'immediate" IORT based on pre-operative mammography and CE-MRI can be successfully treated with IORT without the need for additional therapy due to inadequate surgical margins or large tumor size. To accomplish these objectives, this study has several specific aims:

2.1 Specific Aim 1: To evaluate the ability of pre-operative mammography and CE-MRI to select suitable candidates for immediate IORT, without the need for re-excision. At USC, the re-excision rate for DCIS is about 20%, compared to published rates as high as 50%[5-7]. In this study, with the use of CE-MRI, a re-excision rate of 15% or less will be acceptable and a rate of 30% or more will be unacceptable.

2.2 Specific Aim 2: To evaluate the ability of pre-operative mammography and CE-MRI to select suitable candidates for immediate IORT, without the need for additional WB-EBRT.

2.3 Specific Aim 3: To evaluate the safety and tolerability of IORT administered at the time of initial WLE (immediate IORT).

2.4 Specific Aim 4: To evaluate the safety and tolerability of IORT administered at the time of re-excision in a patient who has previously undergone a lumpectomy (e.g., a patient who has inadequate margins but is still believed to be an acceptable candidate for lumpectomy and radiotherapy, or a patient who has previously undergone successful lumpectomy but who desires IORT as adjuvant radiotherapy).

2.5 Specific Aim 5: To evaluate the safely and tolerability of post-operative WB-EBRT or mastectomy given after initial unsuccessful IORT (e.g., a patient who initially received immediate IORT but who was subsequently found to an unsuitable candidate for IORT).

3.0 STUDY DESIGN

3.1 Patients with biopsy proven-DCIS selecting WLE will undergo mammography and CE-MRI of the affected breast to evaluate the extent of disease. Patients will be deemed eligible for immediate IORT if the DCIS lesion is estimated to measure ≤4cm and is thought to be resectable with WLE and clear surgical margins. The DCIS lesion size determined by imaging will be compared with lesion size and surgical margin status obtained from the surgical pathology specimen to evaluate the ability of mammography combined with CE-MRI to identify suitable candidates for immediate IORT. For assessment of safety and tolerability of IORT (or other subsequent therapies), the study population will be divided into 3 cohorts:

Cohort 1: Patients who receive IORT at the time of initial WLE (the immediate IORT group).

Cohort 2: Patients who receive delayed IORT given at the time of a second operation, with or without re-excision of additional breast tissue (the delayed IORT group).

Cohort 3: This is the subset of patients in Cohort 1, who receive WLE and IORT, but who subsequently require WB-EBRT (with or without re-excision) or mastectomy.

3.2 Rationale for Inclusion of 3 Cohorts.

3.2.1 Rationale for Inclusion of Cohort 1. Several randomized and numerous non-randomized trials have been undertaken to evaluate the efficacy of APBI as an alternative to WB-EBRT to reduce recurrences after breast conserving surgery. For the most part, DCIS has been excluded from these trials due to the perceived difficulty in estimating lesion size based on clinical and mammographic findings alone. Since IORT is optimally administered at the time of WLE, prior to complete assessment of the surgical specimen, patients undergoing immediate IORT have a theoretically elevated risk of requiring additional therapy, for example, repeat WLE for inadequate margins. The present study has been developed to evaluate the ability of mammography combined with CE-MRI to identify suitable candidates for IORT, i.e., those who would have a low risk of needing additional surgery or radiotherapy.

3.2.2 Rationale for Inclusion of Cohort 2. Although mammography is the standard imaging tool used for the detection and pre-operative staging of DCIS, the extent of the imaging abnormality may not always correspond exactly to the extent of DCIS within the breast. CE-MRI may enhance the radiologist's ability to evaluate the extent of disease within the breast. However, since CE-MRI is typically performed **after** a core biopsy has already established the diagnosis of DCIS, post-biopsy artifact may lead to over-estimation of lesion size. Given these limitations of imaging, one reason that Cohort 2 has been included is to preserve the option of IORT for patients who may have been excluded from immediate IORT based on imaging or clinical findings but who were ultimately found to be suitable candidates based on surgical pathology. In addition, Cohort 2 also provides an opportunity to examine the safely and tolerability of administering delayed IORT after an initial WLE. Given the limited availability of IORT nationwide, establishing the safety and tolerability of delayed IORT as adjuvant therapy for DCIS is particularly important to referral centers interested in offering IORT to women who have already undergone successful or unsuccessful WLE at another facility, but who now present for definitive care.

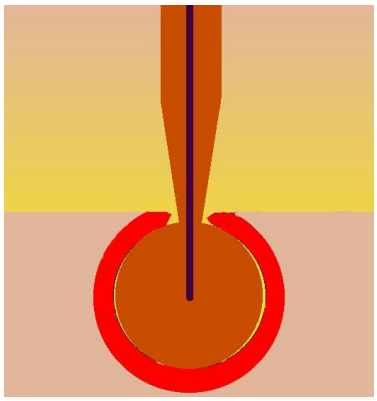
3.2.3 Rationale for Inclusion of Cohort 3. Despite pre-operative mammograms and CE-MRI showing localized DCIS ≤4cm, it is expected that a minority of patients will be found to be unsuitable candidates for IORT on the basis of extensive multifocal or multicentric carcinoma. The rationale for including these patients in the study is to examine the safety and tolerability of breast cancer treatment [e.g., WB-EBRT (with or without re-excision) or mastectomy] in patients who have previously received IORT. Comparison of the preoperative imaging findings and surgical pathology results should ultimately improve our ability to identify pre-operatively these unsuitable candidates for immediate IORT.

4.0 DEVICE INFORMATION

4.1 Intrabeam Photon Radiosurgery System and Applicators. The Intrabeam PRS is a miniature electron beam-driven X-ray source that provides a point source of low

energy X-rays (50kV maximum) at the tip of a 3.2mm diameter tube (Figure 1). The radiation source can be inserted into the breast immediately after excision of the tumor (Figure 2) and switched on for 20-45 minutes to provide targeted IORT accurately to the surgical margins.

Figure 1 

Figure 2. 

The physics, dosimetry and early clinical applications of this low energy x-ray device have been fully evaluated and in 1999 the device received FDA approval for use in any part of the body[20]. Since then, the Intrabeam PRS has already been used for treatment of human malignant brain tumors, hepatic tumors, head and neck tumors, and urological tumors[21-22]. Use of the Intrabeam PRS for treatment of breast cancer was piloted at the University College London Hospital, which treated 185 patients with invasive breast cancer with IORT alone (n=25) or combined IORT and WB-EBRT (n=168) following wide local excision. Excellent cosmesis was observed in both groups with no grade 3 or 4 side effects. No recurrences were reported in the IORT alone group. These studies laid the foundation for the TARGIT Trial, an international randomized trial comparing IORT alone to standard WB-EBRT as adjuvant therapy for invasive breast cancer[23, 24]. To date, over 800 patients have been accrued to the TARGIT Trial among 16 study sites. With short-term median follow-up of approximately 450 days, there appears to be no difference in the local recurrence rates between the two arms of the trials (personal communication).

The Intrabeam PRS x-ray source is a small and lightweight (weight=1.8 Kg; dimensions: X-ray generator body 7 X 11 X 14 cm) device that is mounted on the surgical stand and balanced for ease of delivery and support during treatment. For delivery of breast radiotherapy, the radiation source is covered by one of several spherical applicators ranging in size from 2 to 6 cm in diameter (Figure 3), depending on the dimensions of the cavity to be irradiated. The pliable breast tissue can then be wrapped around the applicator using “purse-string” sutures, which allow the breast tissue to be conformed around the radiation source to facilitate delivery of a uniform field of radiation. If necessary, the chest wall and skin can be protected by tungsten-impregnated silicone shields (providing >93% shielding), which can be cut to a desired size and shape.

Figure 3.

Since the radiation consists of low energy x-rays, the radiation dose is rapidly attenuated as it passes through distant tissues. The total radiation dose delivered is a function of time, which is set to administer a prescribed dose of 20 Gy in a single-fraction to the surface of the tumor bed and 5 Gy at depth of 1cm from the surface of the tumor bed. Following dose delivery, the Intrabeam PRS device is switched off and transmission of radiation ends. Finally, the apparatus is removed and the wound is closed in the usual fashion.

4.2 Mammography. Mammography will be completed prior to determining eligibility for IORT. Mammograms of insufficient quality or those that were performed more than 60 days prior to determination of eligibility and will be repeated. Standard 2-view (MLO and CC views) mammograms will be obtained, in addition to any others projections requested by the radiologist, surgeon, or radiation oncologist. Mammographic lesion size will be measured in 3 perpendicular dimensions using a centimeter ruler, encompassing the entire span of suspicious or indeterminate microcalcifications, densities, or architectural distortions. Lesion size, multicentricity, multifocality, and/or evidence of invasive disease will be documented by a staff radiologist.

The cost of any additional imaging and cost of resulting procedures, if any, will be performed as part of the patient's routine preoperative evaluation and billed to her insurer. Alternatively, prospective participants may complete their imaging work-up by participating in an ongoing study at USC comparing bilateral breast CE-MRI, bilateral whole-breast ultrasound, and bilateral mammography (USC IRB Approved Protocol: Komen-06-01) which provides funding for these studies for uninsured or under-insured patients.

The major limitations of mammographic imaging of DCIS is that not all DCIS lesion form microcalcifications and among those that do, the span of calcification may not exactly correlate to the span of DCIS. High grade DCIS appear to show the best correlation between imaging findings and histological lesion size; low grade DCIS shows the worst correlation. In addition, a variety of microcalcifications (malignant, indeterminate, and benign type microcalcifications) may co-exist within

the breast, which can lead to over-aggressive or inadequate excision of breast tissues if the span of DCIS is judged incorrectly.

4.3 Contrast-Enhanced Breast MRI. CE-MRI of the breast will be required for all patients prior to determination of eligibility for IORT. CE-MRI of insufficient quality or those that were performed more than 60 days prior to determination of eligibility will be repeated.

Participants will undergo breast CE-MRI on a 1.5 or 3.0 Tesla MRI unit using a dedicated double breast coil. CE-MRI performed at other institutions will be permitted if they are performed on similar equipment and judged to be of appropriate quality. At USC, the following sequences will be obtained with the patient lying prone: (1) Scout-T1 FLASH—coronal/sagittal/axial (12 sec); (2) T2 TSE axial images of the breasts (3 min, 7 sec); and (3) T1 3d FLASH dynamic sequences (5 min, 30 sec including a pre-contrast sequence), contrast injection (15cc Gadolinium/20cc saline IV at 3cc/sec), a 20 second delay, and (4) pre-contrast images subtracted from last post-contrast images (the subtraction images), and (5) maximum intensity projections (MIP) of the subtraction images. Using the T2-weighted images and subtraction images, the area of maximal enhancement will be outlined and measured.

CE-MRI will be interpreted by radiologists with expertise in breast CE-MRI. Morphologic and kinetic analysis for suspicious enhancing lesions will be performed using the American College of Radiology Breast Imaging Radiology and Diagnostic Imaging System lexicon. Morphologic analysis of lesions (masses, foci, and regions) will be made by assessing the size, borders, and homogeneity of enhancement. Lesions that are not round or oval, have irregular borders, and are heterogeneous will be considered suspicious. Kinetic analysis will be performed for the lesion of interest in early enhancement (1-2 minutes after injection) and late enhancement (5-6 minutes after contrast injection). Masses (>5mm) that show at least 50% increase in signal intensity early will be considered suspicious unless there is a benign correlate at mammography or un-enhanced MRI. Foci (<5mm) showing at least 50% increase in signal intensity early with late washout kinetics, and regional enhancement with at least 50% increase in signal intensity early, will also be considered suspicious. Segmental, linear, stippled or clumped enhancement will be considered suspicious for DCIS, regardless of kinetics. Lesions not meeting any of these requirements will be considered benign or probably benign. Lesion size will be measured in 3 perpendicular dimensions by a staff radiologist using a centimeter ruler. Measurement of lesion size, multicentricity, multifocality, or evidence of associated invasive disease will be documented.

All discrete suspicious and indeterminate lesions seen on the CE-MRI will undergo a "second-look" or correlative ultrasound to determine if the lesion is also sonographically visible and amenable to ultrasound guided core needle biopsy if the results of the biopsy would significantly alter surgical management (e.g., conversion from breast conserving surgery to mastectomy or performance of a significantly wider local excision) or effect eligibility for this study. If the lesion is not seen by ultrasound, MRI-guided core needle biopsy will be performed to establish a tissue diagnosis if the results of the biopsy would significantly alter surgical management or eligibility for this study.

The major limitations of CE-MRI are the lack of standardized definitions of neoplasm on CE-MRI, which limits the inter-study specificity of CE-breast MRI (specificity=65-70%)[25,26]. In addition, when overall breast parenchymal density is high, there may be generalized mild parenchymal enhancement or multiple tiny foci of enhancement (e.g., hormonally influenced areas) that can be confused with the enhancement of a true lesion making it difficult to appreciate a smaller or lower grade lesion. To minimize this normal physiologic enhancement of the breast, scheduling of the CE-MRI will be coordinated with the menstrual cycle of pre-menopausal patients, i.e., performed 7-10 after the start of menstrual flow. Equally important, most patients will undergo MRI here at USC where their studies will be performed on the same MRI unit and interpreted by one of 2 experienced radiologists. This should facilitate consistent performance and interpretation of breast MRIs.

4.4 Core needle biopsies. Core needle biopsies will be performed of all additional suspicious lesions (excluding the index cancer) seen on mammography, ultrasound, or CE-MRI to obtain definitive information about the presence or absence of malignancy. Biopsies will be performed using either 14-gauge core biopsy or 11-gauge vacuum-assisted needle biopsy guided by the imaging study that best depicts the lesion.

Radiologists performing core biopsies will meet the Continuing Medical Education and experience requirements analogous to the American College of Radiology accreditation for breast biopsy. For findings observed only on CE-MRI, MRI-guided core needle biopsy will be performed using an 11-gauge vacuum-assisted breast biopsy instrument obtaining a minimum of 6 samples. For calcifications seen only mammographically, 11-gauge vacuum-assisted biopsy will be performed under stereotactic guidance, obtaining a minimum of 6 core samples. Lesions considered amenable to ultrasound-guided core biopsy will be biopsied with either a 14 or 18-gauge core needle or an 11-gauge vacuum-assisted biopsy, obtaining a minimum of 6 core samples. Specimen radiography will be obtained on all biopsied lesions that contain microcalcifications. A microclip or biopsy site marker will be placed to identify the biopsy site.

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Patients with biopsy-proven DCIS, mammographic and CE-MRI evidence of DCIS measuring ≤4cm, and a desire to receive breast conserving therapy, will be considered for participation in this study.

5.2 Patient history, physical examination findings, and demographics (sex, age, height, weight, bra size, etc.) will be performed and documented.

5.3 Inclusion Criteria for Initial Registration (all patients cohorts):

5.3.1 All cohorts

a. Signed informed consent and HIPAA documents
b. Female sex
c. Age ≥ 40 years

d. Localized ductal carcinoma in situ
e. Clinically and/or histologically negative axillary lymph nodes
f. No imaging or clinical findings suggestive of invasive carcinoma.

5.3.2 Cohort 1 (Immediate IORT group)

a. Localized DCIS measuring ≤4 cm on preoperative imaging.

5.3.3 Cohort 2 (Delayed IORT group)

a. Localized DCIS measuring ≤4 cm or less on surgical pathology

i. Delayed IORT could be performed for the explicit purpose of administering IORT or performed following re-excision of a previously operated breast to achieve clear surgical margins.
ii. This cohort includes patients who were excluded from immediate IORT based on pre-operative imaging suggesting ineligibility for immediate IORT, but who are subsequently found to meet histological criteria (localized DCIS ≤4 cm and no invasive cancer) for IORT based on surgical pathology.
iii. Unifocal microinvasive (T1mic or invasive focus ≤1mm in maximal diameter) is allowed following initial WLE if surgical pathology margins were ≥2 mm for both the invasive and non-invasive components.
iv. Delayed IORT must be performed within 3 months of initial WLE.

5.3.4 Cohort 3

a. Subjects who received IORT at the time of initial WLE but whose surgical pathology indicates the need for further therapy:

i. DCIS measuring greater than 5 cm on surgical pathology.

b. Surgical margins width <2 mm.

5.4 Exclusion Criteria for Initial Registration (all patient cohorts)

5.4.1 Male sex
5.4.2 Age <40
5.4.3 DCIS associated with any evidence of microinvasion or invasive carcinoma on pre-operative imaging or core biopsy of the breast or axillary nodes.
5.4.4 DCIS that is multicentric in the ipsilateral breast. Multicentricity will be defined at 2 or more lesions separated by more than 3 cm in the same breast.
5.4.5 Non-epithelial breast malignancies such as sarcoma or lymphoma
5.4.6 DCIS associated with diffuse suspicious or indeterminate microcalcifications
5.4.7 Pregnancy or lactation
5.4.8 Collagen vascular diseases, including Systemic lupus erythematosus, Systemic sclerosis (scleroderma), CREST Syndrome (calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia, and the presence of anticentromere antibodies), polymyositis, dermatomyositis with a CPK level

above normal or with an active skin rash, inclusion-body myositis, or amyloidosis

5.4.9 Serious psychiatric or addictive disorders

5.5 Withdrawal from Study

During the course of the study, it is possible that patients and/or device systems may be withdrawn from the study. Factors that may lead to a withdrawal from the study may include, but, are not limited to the following:

5.5.1 Patient Withdrawal – At any time a patient may voluntarily withdraw from the study. This withdrawal will not affect her future medical treatment.

5.5.2 Patient Lost to Follow-Up – Should a patient be classified as lost to follow-up, efforts to contact the patient will be made.

5.5.3 Physician Decision – Should a physician decide that the constraints of the protocol are detrimental to the health and welfare of the patient, the patient may be withdrawn from the study.

5.5.4 Medical Reason – Should the patient's condition deteriorate, the patient may be withdrawn from the study to allow for proper medical care.

6.0 STRATIFICATION/DESCRIPTIVE FACTORS/RANDOMIZATION SCHEME

Patient Selection. This is not a randomized study. The trial will be open to 3 cohorts of patients with a diagnosis of DCIS breast, as outlined in the inclusion criteria (Section 3.0).

7.0 STUDY AGENT ADMINISTRATIONS OR INTERVENTION AND TOXICITY MANAGEMENT PLAN

7.1 Patient Surgery and IORT

7.1.1 Each patient will undergo WLE to remove DCIS and to create a cavity. Each of the following procedures qualifies as WLE: breast conserving surgery, lumpectomy, segmental mastectomy, segmental resection, and partial mastectomy.

7.1.2 Recognizing the potential for DCIS to be larger than demonstrated on imaging, the surgeon will aim to excise the lesion with surgical margins of 10 mm. Multiple localizing wires will be placed pre-operatively to facilitate resection.

7.1.3 Due to the potential for finding occult microinvasive carcinoma in the final surgical pathology, sentinel node biopsy will be allowed at the discretion of

the surgeon.

7.1.4 At the conclusion of IORT, surgical clips will be placed in the resection cavity to mark the surgical margins to facilitate re-excision, if indicated.

7.2 Criteria for Receiving Additional therapy after IORT (Cohort 3)

7.2.1 Patients with DCIS >5 cm will be advised to undergo WB-EBRT (or mastectomy) despite having received IORT, even if surgical margins are clear (≥ 2mm).

7.2.2 Patients with surgical margins width of <2 mm following local excision and immediate IORT will be advised to undergo re-excision. If residual disease is found and new final margins are <2 mm, the patient will be advised to undergo WB-EBRT. However, no addition therapy will be needed if no residual disease is found, or if final margins is ≥2mm.

7.3 Ancillary treatments.

Neoadjuvant hormonal therapy (e.g., Tamoxifen or Fulvestrant) and chemopreventive therapy (e.g., green tea extract) will be allowed provided that the total duration of neoadjuvant hormonal or chemopreventive therapy does not exceed 30 days prior to WLE and immediate IORT.

8.0 ASSESSMENT OF EFFICACY AND SAFETY

8.1 Side effects/Toxicities to be monitored. These risks fall into four (4) general categories:

8.1.1 Surgery. Complications associated with the surgical implantation of the Intrabeam PRS are similar to any tumor removal surgery. These include, but are not limited to infection, loss or impairment of nerve function, breast edema, ecchymosis, hematoma formation, wound seroma, wound dehiscence, keloid formation, skin flap necrosis, and the need for re-excision if margins are inadequate.

8.1.2 Intraoperative Radiotherapy Delivery. Complications arising from the delivery of IORT include, but are not limited to infection, loss or impairment of nerve function, breast edema, fibrosis, and skin effects including dry/moist desquamation, hyperpigmentation, telangiectasia and radiation-induced skin necrosis.

8.1.3 Whole-Breast External Beam Radiotherapy. Complications of WB-EBRT include, but are not limited to loss or impairment of nerve function, breast edema, fibrosis, superficial vein thrombosis, and skin effects including dry/moist desquamation, erythema, hyperpigmentation, telangiectasia and radiation-induced skin necrosis.

8.1.4 Diagnostic Procedures. As part of this clinical study, patients will undergo mammography, CE-MRI, and ultrasound (at the discretion of the radiologist) and will be subject to the associated risks: exposure to additional radiation, allergic reaction to MRI contrast (gadolinium), and the potential risks of additional minimally invasive breast biopsies (bleeding, hematoma, infection, and non-diagnostic or falsely negative results) that may result from the extensive imaging evaluation. The risks associated with these procedures are minimal.

8.1.5 Unanticipated Adverse Device Effects (UADEs) will be documented. UADEs are defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.1.6 Serious Adverse Event (SAE). Serious adverse events are defined as follows: Death or threat to life; Permanent impairment of a body function or permanent damage to a body structure; or events that require medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Events that are considered serious include skin necrosis, non-wound healing, moist desquamation (not resolving within 4 weeks), unresolved bleeding, infection requiring medical or surgical intervention, pneumothorax, seroma/hematoma (symptomatic and/or cosmetically deforming), rib fracture, severe pain (not resolving within the first month and requiring narcotics) and wound dehiscence.

8.2 Dosage change based on toxicity. The prescribed dose is constant among all patients and will not be adjusted. The only variable is the time period for which the dose will be delivered. The treatment time will vary based on the lumpectomy cavity site, with total treatment time adjusted to deliver a prescribed dose of 20 Gy to the tumor surface or 5G at 1 cm depth from the tumor surface.

8.3 Adverse Event Reporting:

8.3.1 All adverse events that occur during the study will be reported, except for observational events: cold, flu, headache, etc. The CTC guideline will be used to grade the severity of all adverse events. Adverse events not included in the CTC, version 3, will be reported with common medical terminology and grading according to definitions in the CTC:

8.3.2 A description of the nature, onset, duration, severity, attribution and outcome of the occurrence will be recorded. Any treatment employed to alleviate the adverse event(s) will also be recorded.

CTC Grading of Adverse Events:

Grade 1 = Mild adverse event
Grade 2 = Moderate adverse event
Grade 3 = Severe and undesirable adverse event
Grade 4 = Life-threatening or disabling adverse event
Grade 5 = Death related to adverse event

8.3.3 All serious adverse events will be recorded on the study data forms throughout the duration of the study.

8.3.4 The physician will document his/her opinion of the relationship of the event to the device as follows:

Unrelated = the event is clearly not related to the device
Unlikely = the event is doubtfully related to the device
Possible = the event may be related to the device
Probable = the event is likely to be related to the device
Definite = the event is clearly related to the device

8.3.5 Any serious adverse device effect, including death due to any cause, which occurs during this treatment, will be reported within 5 working days of learning of the event to Carl Zeiss, Inc. and to the IRB per the IRB requirements.

8.3.6 Serious unanticipated adverse device effects will be reported within 24 hours of learning of the event to Carl Zeiss, Inc. and to the IRB per the IRB requirements.

8.3.7 Patients who are removed from the protocol due to adverse events will be followed until the adverse event has resolved or stabilized and will continue to be followed in the intent-to-treat population. Copies of relevant documentation will be kept with the patient's protocol records.

8.4 Minimization of Risks

8.4.1 Although the risks outlined in Section 8.1 may occur, the likelihood of serious events occurring is considered minimal. Carl Zeiss, Inc. has reduced the potential of the above risks by:

a. Performing complete validation testing of the Intrabeam PRS
b. Implementing quality assurance measures each day prior to using the Intrabeam PRS
c. Providing adequate directions for use in device labeling.

Clinical investigators who are involved in the study are knowledgeable and experienced in the field of surgical oncology and radiation oncology, which will help to minimize risks to the patients involved. Inclusion/Exclusion criteria are intended to reduce the potential of including patients who might be prone to injury or who might be inappropriate candidates of IORT for other reasons.

8.4.2 Potential Patient Benefits

a. The potential benefits of IORT are:
b. Decreased likelihood of tumor recurrence
c. More accurate delivery of radiation dose to targeted tissue
d. Reduced radiation delivered to normal breast and surrounding tissues
e. Reduced delays in systemic/local therapy
f. Reduced risk of infection and skin toxicity compared to standard external beam or other partial breast irradiation techniques
g. Reduced treatment time Improved patient compliance
h. Possibly increased feasibility of breast conserving therapy

9.0 CLINICAL AND LABORATORY EVALUATIONS AND STUDY CALENDAR

9.1 Histological Evaluation of Specimen. The surgical specimen will undergo histological evaluation to determine the following features: DCIS histology, lesion size, surgical margin width, and the presence or absence of invasive carcinoma. The surgical margin width will be measured as distance from the nearest tumor cell to the cut or inked edge of the WLE surgical specimen.

9.2 DCIS histology [histologic type, grade (nuclear, histologic, mitotic), and the presence or absence of comedonecrosis] will be determined using the Philadelphia consensus guidelines (Appendix 1) and assessed in the core biopsy and/or WLE specimen prior to administration of IORT. In addition, The Van Nuys Prognostic Index (VNPI) score will be calculated and reported in the final WLE specimen (Appendix 2).

9.3 Surgical margin width will be measured in all directions (i.e., superior, inferior, medial, lateral, anterior and posterior) in the WLE specimen. The anterior and posterior margins will be considered widely clear if the involved margin(s) approximate the skin (anterior) or pectoralis fascia (posterior) AND these margins have been removed with the surgical specimen.

9.4 DCIS lesion diameter will be measured in the three widest dimensions (e.g., anterior-posterior diameter, medial-lateral diameter, superior-inferior diameter) in the WLE specimen. Specimen weight will also be recorded.

9.5 Study Calendar.

Data Required	Pre-Entry	Surgery/ Applicator Placement	Post Surgery	Follow up
Demographics/Medical History	X			
Inclusion/Exclusion (Eligibility) (TT01*)	X		X	
Mammography (TT02)	X[b]			X[b],
CE-MRI (TT02)	X[d]			X[d]
Pathology (TT06)	X		X	
Intrabeam PRS Placement, Brachytherapy & Removal (TT04, TT10, TT07)		X		
Follow-Up Visit (TT11, TT12, TT05, TT13)				Xa,
Quality of Life Questionnaires (EORTC QLQ-BR23 & QLQ-C30 version 3.)				X[f]
Photographs				X [c]
Cosmesis				X[e]
Adverse Event Reporting at each visit (TT09)		X	X	X

*TT refers to the respective data collection form (see Section 12.0).

a. The patient will be evaluated at 3 months, 6 months, 1 year, and 2 years post-IORT.
b. Mammograms of the treated breast will be performed at baseline within 60 days of accrual and repeated semiannually post_IORT X 2 years
Suspected recurrences and new cancers detected using imaging and/or physical examination will be confirmed histologically.
c. Photos of both breasts will be obtained at 3 months, 6 months, 1 year, and 2 years post-IORT. The first photo will be taken of both breasts with the patient standing with both arms at her side. The second photo will be taken of both

breasts with the patient standing with her hands on her hips. Care will be taken to exclude the patient's face from the photo.

d. MRI will be performed at baseline within 60 days of accrual. MRI may also be performed at any time to evaluate a clinical or mammographic finding or to follow-up on an earlier MRI finding.
e. Cosmesis will be reported at 3 months, 6 months, 1 year, and 2 years post-IORT.
f. Quality of life will be evaluated at baseline (preoperatively), 3 months, 6 months, 1 year, and 2 years post-IORT.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Feasibility Endpoint. The primary efficacy endpoint of the treatment will be re-operation (re-excision or mastectomy) rates following WLE and IORT.

Re-excision (or mastectomy) will be indicated for patients with microscopic surgical margins measuring <1 mm following WLE and immediate IORT.

Additionally, the following data will also be reported and analyzed:

10.1.1 Indications for WB-EBRT. Patients with margins that are margins < 2 mm after reexcision for <2 mm margins, or, DCIS > 5 cm.

10.1.2 Extent of disease. Extent of disease will be determined by measuring the dimensions of the DCIS lesion as demonstrated by pre-operative mammography and CE-MRI and the dimensions of the DCIS lesion contained within the surgical resection specimen

10.1.3 Surgical Margins. Surgical margins will be defined as the distance from the closest tumor cells to the cut or inked edge of the surgical specimen.

10.1.4 DCIS histopathology. DCIS histopathology will be determined by evaluating the histopathological type, grade (histological, nuclear, and mitotic), the presence or absence of comedonecrosis or invasive carcinoma in the pre-operative biopsy and the surgical specimen.

10.2 Safety Endpoint

10.2.1 The overall serious adverse event rate will be assessed for all patients at the stated follow-up periods. Complications associated with each of the following setting will be documented and reported separately:

10.2.2 Complications resulting from immediate IORT

10.2.3 Complications resulting from delayed IORT with or without reexcision

10.2.4 Complications resulting from WB-ERBT following WLE and immediate IORT (e.g., if lesion is > 5 cm)

10.2.5 Complications of mastectomy after initial WLE and IORT

10.3 Cosmesis Endpoint

The surgeons or radiation oncologists will evaluate cosmetic results at stated follow-up periods. Cosmetic results will be assessed using the Harvard Scale:

Excellent - The treated breast looks essentially the same as or better than the opposite breast.

Good – There are minimal but identifiable effects of radiation on the treated breast

Fair – There are significant effects of radiation on the treated breast

Poor – There are severe tissue sequelae secondary to irradiation

The appearance of the breast will be described in detail, including the presence of skin telangiectasia, skin atrophy, scarring, pigment change, erythema, fat necrosis, fibrosis, retraction or contour defect, volume loss, and other significant treatment effects. Each of these features will be documented as "none", "present but does not affect cosmesis", or "present and affects cosmesis".

Digital photos of both breasts will be taken pre-treatment and at each stated follow-up period.

10.4 Quality of Life Endpoint

Patients will be asked to complete Quality of Life (QOL) questionnaires at baseline, and at the 3 month, 6 month, 1 year and 2 year follow-up point using validate QOL instruments published by the EORTC (EORTC QLQ-BR23 & QLQ-C30 version 3.). Quality of life will evaluate physical appearance and symptoms. Patients will be asked to assess differences between the treated and untreated breast and to provide an overall assessment of the appearance of the treated breast. They will also be asked to rate their breast and non-breast symptoms during the 4-week period prior to completion of each QOL questionnaire.

11.0 SPECIAL INSTRUCTIONS:

11.1 None

12.0 DATA COLLECTION AND MONITORING

FORMS TO BE USED IN THE STUDY (TO BE CREATED):

Enrollment Form (TT00)
Eligibility Worksheet Form (TT01)
Entry Form 1 (TT02)
Entry Form 2 (TT03)

Surgery Form (TT04)
Pathology On-Study Form (TT05)
Pathology Form (TT06)
Intraoperative Radiotherapy Form (TT07)
Complication Form (TT09)
Additional Procedure Form (TT10)
Photography Form (TT16)
Lost To Follow Up Form (TT17)
Cosmesis Evaluation (TT18)
Quality of Life Questionnaires EORTC QLQ-BR23 & QLQ-C30 version 3.

13.0 STATISTICAL CONSIDERATIONS

This is a pilot study to evaluate the feasibility of IORT for the treatment of patients with DCIS who undergo WLE of the breast lesion. Currently at USC, about 20% of patients who elect WLE for the treatment of DCIS are found to have surgical margins that measure less than 1mm. For these patients, reexcision (or mastectomy) is recommended unless the small distance occurs at the anterior and posterior margins if the skin has been removed anteriorly or the pectoralis muscle fascia has been removed posteriorly. Among patients requiring re-operation, it can be argued that the decision to undergo IORT was not optimal. Careful use of mammography and CE-MRI should reduce the likelihood that, based on inadequate margins, a re-operation would be necessary. In addition, for tumors that are found to be 5 cm or greater, or that have multicentric or extensive multifocal disease, in the surgical specimens, WB-EBRT is recommended. While there are studies indicating that WB-EBRT can be given safely following IORT, in this setting, the decision to treat these patients with immediate IORT was not optimal.

The primary aim (Section 2.1) of this study is to estimate the likelihood that CE-MRI and mammography were not able to identify patients for whom IORT is not optimal – because a re-operation (re-excision or mastectomy) was required. The secondary aim (Section 2.2) is to estimate the likelihood that CE-MRI and mammography were not able to identify patients for whom WB-EBRT was indicated. In addition, the safety of IORT administered at the time of initial WLE will be evaluated (Section 2.3).

An additional secondary aims, but also very important, will be to document the treatment course and complications of those patients who received delayed IORT (after initial WLE) (Section 2.4) or who received immediate IORT but subsequently required mastectomy or WB-ERT (Section 2.5).

13.1 Study Design and Sample Size Justification

The study design was selected based on the primary aim: to evaluate the ability of CE-MRI and mammography to identify patients for whom IORT is not optimal because of the inability to achieve sufficiently wide surgical margins. If 15% or fewer patients require re-excision, this would be considered acceptable and encouraging for further study; however, a reexcision rate of 30% or higher would not be acceptable.

13.1.1 Accrual to Cohort 1 (Specific Aims 1-3 in Sections 2.1 – 2.3).

Patients will be enrolled in Cohort 1 until 79 patients have received immediate IORT. All patients who are deemed eligible for IORT based on mammography and CE-MRI results will be considered in the decision to stop or continue the trial. There will be one interim analysis when 25 patients have completed WLE and immediate IORT, whether or not additional therapy is needed.

After 25 patients have been evaluated, if 19 or more did NOT require re-excision (based on the surgical specimen), then accrual will continue until 79 patients undergo WLE and immediate IORT. If 7 or more of the initial 25 needed re-excision, then the study will terminate and investigators will conclude that the current method for staging is not sufficiently accurate.

After 79 patients have been evaluated, if 62 or more did NOT need re-excision (based on surgical specimen), investigators will conclude that the chance of correctly identifying a tumor that is suitable for IORT is greater than 70% and that further study of the approach would be justified. If 18 or more of the initial 79 needed re-excision, then investigators will conclude that the chances of correctly identifying a tumor that is suitable for IORT is less than 85%. In this instance, investigators would aim to improve the staging procedures before continuing with this approach.

With this Simon optimal 2-stage design, there will be a 5% chance (alpha) of incorrectly deciding that that approach warrants further study, when the true chance of correctly staging is less than 85%; and there will be a 10% chance (beta) of correctly deciding that this approach warrants further study, when the true chance of correctly staging is greater than 70%.

To evaluate the safety and tolerability of immediate IORT, the following side effects or complications will be taken as evidence that IORT was not well tolerated:

a. any Grade 2 or greater toxicity
b. failure for the surgical incision to heal as evidenced by wound dehiscence, wound infection, or skin ulceration.

If 25% or more of Cohort 1 patients experience the above side effects or complications, this will be considered clear evidence that IORT is not well tolerated and will lead to suspension of accrual to this cohort. The decision to continue unchanged, modify the regimen, or terminate the trial will be based on a careful review of all patients treated to date, and all toxicities and complications experienced. The rules given below will trigger such a review (and are based on the sequential probability ratio test with the theoretical parameters set to α=0.10, β=0.10, p_o=0.05, p_a=0.25). At the completion of the study, all complications and toxicities will be summarized and reported. During the conduct of the trial, when an unacceptable toxicity or complication (as defined above) is observed, the number of patients (X) who

have experienced any unacceptable toxicity or complication will be compared to the number of patients (N) who have begun IORT in this Cohort. If the number of patients, N, is greater than N_X, the number given in the bottom row of the Table 1, then accrual will continue. If N is less than or equal to N_X, then accrual will be suspended for review of the data.

Table 1: Criteria for Suspending Accrual to Evaluate Tolerability											
X: # pts with unacceptable toxicity or a complication	2	3	4	5	6	7	8	9	10	11	12
N_x: Suspend trial if # patients (N) is ≤ N_x	≤6	≤14	≤21	≤29	≤37	≤45	≤53	≤60	≤68	≤76	≤79

These rules were selected to ensure a reasonable chance that the trial would not be suspended if the true chance of unacceptable toxicity were less than 5% and a reasonable chance that it would be suspended if the true chance were 25% to 30% (Table 2). The table below summarizes these probabilities. The values in the table below are based on 10,000 simulations and are accurate to ±0.01 (based on a 95% confidence interval.

Table 2.						
True Chance of Unacceptable Toxicity or Complication	5%	10%	15%	20%	25%	30%
Probability of Suspending Accrual to Review Tolerability	0.07	0.37	0.78	0.96	0.99	0.99

13.1.2 Accrual to Cohort 2 (Specific Aim 4 in Section 2.4)

While Cohort 1 is open to accrual, as part of this trial, IORT will be offered to patients who have previously (within 3 months) undergone WLE and, based on the surgical specimen, are now considered to be eligible for IORT. Our estimate is that approximately 20 such patients will be enrolled. These patients will be enrolled and treated to document the safety and feasibility of IORT when given in the delayed setting,

For this component of the trial, the following side effects or complications will be taken as evidence that IORT was not well tolerated:

a. any Grade 2 or greater toxicity
b. failure for the surgical incision to heal as evidenced by wound dehiscence, wound infection, or skin ulceration.

If 25% or more of Cohort 2 patients experience the above side effects or complications, this will be considered clear evidence that IORT is not well tolerated and will lead to suspension of accrual to this cohort. As above, the decision to continue unchanged, modify the regimen, or terminate the trial will be based on a careful review of all patients treated to date, and all

toxicities and complications experienced. The rules given below will trigger such a review (and are based on the sequential probability ratio test with the theoretical parameters set to α=0.10, β=0.10, p_o=0.05, p_a=0.25). At the completion of the study, all complications and toxicities will be summarized and reported. During the conduct of the trial, when an unacceptable toxicity or complication (as defined above) is observed, the number of patients (X) who have experienced any unacceptable toxicity or complication will be compared to the number of patients (N) who have begun IORT in this Cohort. If the number of patients, N, is greater than N_X, the number given in the bottom row of the Table 3 then accrual will continue. If N is less than or equal to N_X, then accrual will be suspended for review of the data.

Table 3: Criteria for Suspending Accrual to Evaluate Tolerability			
X: # pts with unacceptable toxicity or a complication	2	3	4
N_x: Suspend trial if # patients (N) is ≤ N_x	≤6	≤14	≤20

These rules were selected to ensure a reasonable chance that the trial would not be suspended if the true chance of unacceptable toxicity were less than 5% and a reasonable chance that it would be suspended if the true chance were 25% to 30% (Table 4). The table below summarizes these probabilities. The values in the table below are based on 10,000 simulations and are accurate to ±0.01 (based on a 95% confidence interval.

Table 4.						
True Chance of Unacceptable Toxicity or Complication	5%	10%	15%	20%	25%	30%
Probability of Suspending Accrual to Review Tolerability	0.05	0.23	0.46	0.67	0.83	0.93

13.1.3 Accrual to Cohort 3 (Specific Aim 5 in Section 2.5)

Cohort 3 will be a subset of patients who begin in Cohort 1 (i.e. are deemed candidates for immediate IORT and who receive immediate IORT) but who subsequently are found to require a mastectomy, re-excision alone, re-excision followed by WB-EBRT, or WB-EBRT alone. This cohort will be followed to monitor and document the complications of the mastectomy and WB-EBRT (with or without re-excision) which are performed following IORT. If all 79 patients are enrolled in Cohort 1 (i.e. the study is not stopped early), then we would expect between 8 and 17 patients requiring an additional surgical procedure (mastectomy or re-excision); as soon as 18 patients require an additional surgical procedure, the study will be terminated.

Using the same definition of unacceptable toxicity as above in 13.1.1 for Cohort 1 and in 13.1.2 for Cohort 2 (any Grade 2 or greater toxicity, or failure for the surgical incision to heal as evidenced by wound dehiscence,

wound infection, or skin ulceration), the rules in Table 3 will also be applied to the patients undergoing an additional surgical procedure in Cohort 3. Separately, we will evaluate the tolerability of WB-EBRT following IORT, in the same manner (using Table 3). Unacceptable toxicity of WB-EBRT include any Grade 2 or greater toxicity, skin flap necrosis, skin ulceration, wound dehiscence, or brachial plexopathy.

13.2 Analysis of Results

The outcome of all patients who are registered onto this study will be reported. The results of patients in Cohorts 1, 2, and 3, will be summarized separately.

For those patients whose CE-MRI and mammography results suggested that they would be candidates for IORT (i.e. Cohort 1), the surgery results will be summarized in terms of whether or not a re-operation was indicated (because of inadequate margins or for any other reason) or whether or not WB-EBRT was recommended (because of small margin size or large tumor size, or another reason). For those patients who subsequently underwent re-excision +/- WB-EBRT or who subsequently received WB-EBRT alone (or mastectomy), all complications and side effects will be summarized.

For all patients, the size of the lesion as estimated by the imaging modalities will be compared to the size measured in the surgical specimen.

14.0 REGISTRATION GUIDELINE

Registration will be done with the Clinical Investigations Support Office into the Cancer Center database.

15.0 BIOHAZARD CONTAINMENT

No radioactive elements are used in the delivery of IORT. Background radioactively will be actively monitored by the radiation physicist during the delivery of IORT to ensure patient and staff safety. WB-EBRT, if indicated, will be delivered per usual radiation oncology protocols established by the Radiation Safety Committee.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

All institutional and Federal regulations concerning the Informed Consent form will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

17.0 REFERENCES

1. American Cancer Society, Cancer Facts and Figures 2006. Atlanta: American Cancer Society 2006.
2. Fisher B, Anderson S, Bryant J et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347(16):1233-41.
3. Fisher B, Land S, Mamounas E. Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the National Surgical Adjuvant Breast Project experience. Semin Oncol 2001;28(4):400-18.
4. Bijker N, Meijnen P, Peterse JL. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organization for Research and Treatment of Cancer randomized III trial 10853—a study of the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol 2006;24(21):3381-7.
5. UK Coordinating Committee on Cancer Research (UKCCCR) Ductal carcinoma in situ (DCIS) Working Party on behalf of the DCIS Trialists in the UK, Australia, and New Zealand. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomized controlled trial. Lancet 2003;362:95-102.
6. Athas WF, Adams-Cameron M, Hunt WC et al. Travel distance to radiation therapy and receipt of radiotherapy following breast-conserving surgery. J Natl Cancer Inst 2000;92(3):269-71.
7. Fisher ER, Dignam J, Tan-Chiu E et al. Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of protocol B-17. Cancer 1999;86:429-38.
8. Holli K, Saaristo R, Isola J et al. Lumpectomy with or without postoperative radiotherapy for breast cancer with favorable prognostic features: results of a randomized study. Br J Cancer 2001;84:164-9.
9. Personal communication. Umberto Veronesi.
10. Chung A, Saouaf R, Scharrew K, Phillips E. The impact of MRI on the treatment of DCIS. Am Surg 2005;71(9):750-710.
11. Menell JH, Morris EA, Dershaw DD et al. Determination of the presence and extent of pure ductal carcinoma in situ by mammography and magnetic resonance imaging. Breast J 2005;11(6):382-90.
12. Hata T, Takahashi H, Watanabe K et al. Magnetic resonace imaging for preoperative evaluation of breast cancer: a comparative study with mammography and ultrasonography. J. Am Coll Surg 2004;198(2):190-7.
13. Bedrosian I, Mick R, Orel SG. Changes in Surgical Management of patients with breast carcinoma based on preoperative magnetic resonance imaging. Cancer 2003;98(3):468-73.
14. Schelfout K, Van Goethem M, Kersschot E, et al. Contrast-enhanced MR imaging of breast lesions and effect on treatment. Eur J Surg Oncol 2004;30(5):501-7.
15. Benda RK, Yasuda G, Sethi A et al. Breast boost: are we missing the target? Cancer 2003;97(4):905-9.
16. Personal Communication
17. Kraus-Tiefenbacher U, Bauer L, Kehrer T et al. Intraoperative radiotherapy (IORT) as a boost in patients with early-stage breast cancer – acute toxicity. Onkologie 2006;29(3):77-82.
18. Kraus-Tiefenbacher U, Bauer L, Scheda A. Long-term toxicity of an intraoperative radiotherapy boost using low energy x-rays during breast-conserving surgery. Int J Radiat Oncol Biol Phys 2006;66(2):377-81.

19. Reitsamer R, Peintinger F, Kopp M et al. Local recurrence rates in breast cancer patients treated with intraoperative electron-boost radiotherapy versus postoperative external-beam electron-boost irradiation. A sequential intervention study. Strahlenther Onkol 2004;180(1):38-44.
20. Vaidya J. Intraoperative radiotherapy for breast cancer. Lancet Oncology. 2004;5(3):165-73.
21. Kalapurakal JA, Goldman S, Stellpflug W et al. Phase I study of intraoperative radiotherapy with photon radiosurgery system in children with recurrent brain tumors: preliminary report of first dose level (10 Gy). Int J Radiat Oncol Biol Phys 2006;65(3):800-8.
22. Koniaris LG, Chan DY, Magee C et al. Focal hepatic ablation using interstitial photon radiation energy. J Am Coll Surg 2000;191(2):164-74.
23. Vaidya JS, Baum M, Tobias JS et al. The novel technique of delivering targeted intraoperative radiotherapy (TARGIT) for early breast cancer. Eur J Surg Oncol 2002;28(4):447-54.
24. Kraus-Tiefenbacher U, Bauer L, Scheda A. Intraoperative radiotherapy for breast cancer using the Intrabeam System. Tumori 2005;91:334-349.
25. Bazzocchi M, Zuiani C, Panizza P et al. Contrast-enhanced breast MRI in patients with suspicious microcalcifications on mammography: results of a multicenter trial. AJR Am J Roentgenol 2006;186(6):1723-32.
26. Bluemke DA, Gatsonis CA, Chen MH et al. Magnetic resonance imaging of the breast prior to biopsy. JAMA 2004;292(22):2735-42.

APPENDICES

Appendix I Philadelphia Consensus Guidelines for Classification of DCIS

A. Low grade nuclei *(NG 1)*

Appearance: Monotonous *(monomorphic)*
Size: 1.5-2.0 normal RBC or duct epithelial cell nucleus dimensions
Features: Usually exhibit diffuse, finely dispersed chromatin, only occasional nucleoli and mitotic figures. Usually associated with polarization of constituent cells.
Caveat: The presence of nuclei that are of similar size but are pleomorphic precludes a low grade classification.

B. High-grade nuclei *(NG 3)*

Appearance: Markedly pleomorphic
Size: Nuclei usually >2.5 RBC or duct epithelial cell nuclear dimensions
Features: Usually vesicular and exhibit irregular chromatin distribution and prominent, often multiple nucleoli. Mitosis may be conspicuous.

C. Intermediate grade nuclei *(NG 2)*

Nuclei that are neither NG 1 nor NG 3

Necrosis Quantification

Comedonecrosis: Any central zone necrosis within a duct, usually exhibiting a linear pattern within ducts if sectioned longitudinally.

Punctate: Non-zonal type necrosis *(foci of individual cells necrosis visible under 10X, 40X is not needed)*

Appendix 2 The USC/Van Nuys Prognostic Index scoring system for DCIS

Score	**1**	**2**	**3**
Size (mm)	**≤15**	**16-40**	**>40**
Margins width (mm)	**≥10**	**1-9**	**<1**
Pathologic Classification	**Non-high grade Without necrosis (Nuclear grades 1 or 2)**	**Non-high grade with necrosis (Nuclear grades 1 or 2)**	**High grade with or without necrosis (nuclear grade 3)**
Age	**>60**	**40-60**	**<40**