CASE WESTERN RESERVE UNIVERSITY/UNIVERSITYHOSPITALS
IRELAND CANCER CENTER

STUDY NO**:** CASE 11107

TITLE: Partial Breast Re-Irradiation for Patients with Ipsilateral Breast Tumor Recurrence, After First Being Treated with Breast Conservation for Early Stage Breast Cancer: An Efficacy Trial Comparing MammoSite® and Intraoperative Radiation

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SCHEMA

Excisional Biopsy Followed by Partial Breast Irradiation for patients with ipsilateral breast tumor recurrence who were first treated with breast conserving surgery and whole breast radiation therapy.

1. Intraoperative Radiation to a Dose of 21 Gy in a Single Fraction.

OR

2. MammoSite® Brachytherapy consisting of a dose of 34 Gy delivered over 10 fractions of 3.4 Gy twice daily over 5 days, with at least 6 hours between fractions.

Eligible patients include:

Patients with a prior ipsilateral breast cancer (invasive, or *in situ*) initially treated with tylectomy and whole breast radiation (with or without tumor bed boost).

Patients who have had at least five years of time elapsed since the end of the prior course of radiation.

Patients with histologically confirmed recurrences comprised of ductal carcinoma in-situ, invasive ductal, medullary, papillary, colloid (mucinous), or tubular histologies.

Patients with histologically confirmed unifocal recurrences measuring $\leq$3 cm.

Patients with negative resection margins with at least a 2 mm margin from the invasive and in-situ cancer or a negative re-excision.

Patients with invasive recurrences that have a negative re-staging work-up consisting of at least a CT chest/abdomen and bone scan.

Hormonal therapy is allowed. If chemotherapy is planned, it must begin no earlier than two weeks following completion of radiation.

Patients must be $\geq$ 18 years of age.

Patients with a negative pregnancy test.

1.0 INTRODUCTION

Despite widespread mammographic screening and increasingly aggressive treatment approaches, breast cancer continues to be a leading cause of both morbidity and mortality in the aging female population. Every year, approximately 180,000 women are diagnosed with breast cancer and about 40,000 women will die of this disease (1). Local treatment options have changed dramatically over the past several decades and increasing numbers of women are now effectively treated with breast conservation. Although treatment patterns vary on a geographical basis, studies show that in some settings, greater than 70% of women with breast cancer are now preserving their breasts (2).

This shift away from mastectomy came after the publication of results from several prospective, randomized studies comparing mastectomy and conservative surgery followed by radiation (3-10). These studies demonstrated similar survival and disease–free survival rates regardless of which treatment approach women chose. In 1992, the NIH Consensus Development Panel was convened to review these studies. This resulted in the 1992 Consensus Statement indicating that breast conservation and mastectomy were equivalent treatment options with respect to survival (11). The primary study done in the United States was the NSABP B-06 published with 12 year results in 1995 (5). This study randomized patients between three arms: mastectomy, conservative surgery alone and conservative surgery followed by radiation treatments. Although the overall survival was similar in all three arms, there were dramatic differences in the local recurrence rates. The conservative surgery alone arm had a local recurrence rate of 39% compared to 10% local recurrence rate in the mastectomy and conservative surgery plus radiation arms. Now with 20 years of follow-up from B-06, the rate of an ipsilateral breast tumor recurrence (IBTR) is approximately 14% (12). This information led to a standard recommendation in the United States that all patients undergoing breast conservation receive post-operative radiation as part of their care (11).

The term breast conserving therapy (BCT) indicates breast cancer treatment that involves resection of the cancer with a rim of normal tissue, axillary lymph node dissection for those with invasive cancer, and breast radiotherapy. The major advantage of BCT is related to the superior cosmetic result and reduced psychological and emotional trauma resulting from this procedure compared to mastectomy.

Standard therapy after tumor excision generally includes five weeks of external beam XRT to the whole breast (45-50 Gy) followed by a boost to the tumor bed with either an additional 8 to 10 fractions (days) of external beam XRT or a two to three day interstitial implant. The rationale for this approach is based upon two principles. First, higher doses of XRT are given to the 'tumor bed' in an attempt to control residual small foci of cancer that may be left behind after excision alone. Second, whole breast XRT is used to eliminate possible areas of occult multicentric in situ or infiltrating cancer in remote areas of the breast. That such remote, multicentric areas of cancer exist has long been established. However, the biological significance of these areas of occult cancer is unknown and the necessity to prophylactically treat the entire breast has recently been questioned. For instance, there are now at least five prospective randomized trials that have been

conducted comparing the outcome of patients treated with excisional biopsy alone or followed by whole breast XRT (5,13-17). In all of these trials, the majority of recurrences in the breast of patients who did not receive XRT occurred at or in the area of the tumor bed. Thus, it would appear that XRT after tumor excision exerts its maximal effect upon reducing breast cancer recurrence at or near the tumor site (17).

One possible attraction for many women who select breast conservation as their treatment, is that if it "fails," only then would they have to have a mastectomy—i.e. they have an initial opportunity to save their breast. The psychological impact of losing one's breast is difficult for some women to accept. The term "salvage" mastectomy has been applied to the setting in which a patient who was initially treated with partial mastectomy and radiation therapy, and who develops an ipsilateral breast tumor recurrence (IBTR) then undergoes a mastectomy. The reasons behind the idea of a salvage mastectomy are several—first, since radiation treatments for breast cancer currently target the whole breast for the majority of the treatment period, by re-irradiating the breast, one would risk the possibility of unacceptable tissue damage, including necrosis and increased incidence of secondary malignancies. Just like all normal tissues, normal breast tissue has a limit as to how much radiation it may receive before the damage becomes irreparable. Second, the breasts of many patients who develop an IBTR may not be able to accommodate a second lumpectomy—i.e., cosmetic outcome can be affected, particularly with inferiorly located recurrences. Finally, studies have shown that patients who elect to have their IBTR removed with a lumpectomy (*without* repeat radiation) may have recurrence rates that can be as high as 35%, which is unacceptably high for most women (18). When counseling a woman considering a salvage mastectomy, it must be made clear that re-recurrence rates (i.e. a 2nd recurrence, this one after the mastectomy) have ranged from 2-32% of patients (19, 20).

Overall survival after mastectomy for an IBTR in a patient previously treated with breast conservation ranges from 52-84% at 5 years, (21, 22). As one might expect, invasive recurrences have a poorer prognosis than do noninvasive (23). Deaths after a noninvasive IBTR occur infrequently—deaths after an invasive recurrence occur more frequently and are often associated with metastatic disease. Having an IBTR increases the rate of developing distant metastases, as well as increases the risk of dying, when compared to women without an IBTR (24).

Many studies have observed that if a patient were to experience an IBTR, the majority of time it would be located in the vicinity of the original primary. But, as breast cancer can be multicentric, by repeating breast conservation surgery, one might "miss" residual tumor left in other areas of the breast. The National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-06 (25), among other things, looked at 110 mastectomy specimens in women whose breast cancer had been treated with breast conservation. They found that 14% of IBTR's were multicentric, however the clinical significance of this multicentricity is unclear. Since many of these patients did not receive adjuvant radiation initially (i.e. were randomized to lumpectomy alone), it is likely that this percentage overestimates the risk of multicentricity in IBTR as it is possible that those receiving adjuvant radiation may have a lower incidence of having a multicentric recurrence.

While the majority of IBTR's occur near the location of the original primary, it is clear that a breast cancer can manifest in any location in the breast. The addition of radiation as well as an increase in the amount of time from the original course of radiation in increases the likelihood that an in breast recurrence represents a new primary breast cancer. Interestingly, studies have shown that the clinical behavior of where the breast recurrences occur differ. Huang and colleagues at MD Anderson performed a retrospective chart review of patients treated with breast conservation, who went on to develop an IBTR as their first recurrence (19). A true recurrence was defined as a cancer with identical histology to the patient's primary, or one in which was located within 3 cm of the original tumor—all other IBTR were considered new primaries. They found that new primaries had statistically significant increased overall survival (77% vs 46%, $p = 0.0002$), increased cause specific survival (83% vs 49%, $p = 0.0001$) and increased distant disease free survival at 10 years (77% vs 26%, $p < 0.0001$), when compared to true recurrences. This suggests for advocates of accelerated partial breast irradiation (treating just the site of surgery rather than the whole breast), that if one were to have a recurrence outside of the radiation field, as suggested by Huang et al, their prognosis might be better.

A corollary can be made to an IBTR in a patient previously treated with breast conservation, that it may be possible, with modern diagnostic equipment, including breast MRI, to identify patients with known unifocal IBTR that may be able to be treated with focal radiation, thus avoiding a mastectomy. There is very little data in the literature looking at re-irradiation for patients with ipsilateral breast cancer recurrences. The largest of which is at report is from The University of Pittsburgh. Deutsch et al, treated 39 patients with repeat radiation therapy for breast cancer—31 invasive and 8 *in situ* cancers. Patients were treated with en-face electrons to a total dose of 5000cGy, directed only at the cavity of the IBTR excision (i.e. partial breast with linac). At last follow-up (median 51.5 months, range 1-180 months), 76.9% of patients had an intact breast free of tumor. At 5 years, overall survival was 78% and disease free survival was 69%. Importantly, no late sequelae of repeat radiation therapy developed other than skin pigmentation changes—cosmetic outcome was reported as good to excellent in 69% of patients (26). There were no rib fractures, pulmonary problems or secondary malignances, despite areas of the breast being exposed to more than 10,000 cGy. All patients except one finished the radiation treatments (RT was discontinued for nonmedical reasons). Distant metastases developed in 8 women (2 with concerning bone scans at the time of diagnosis of IBTR), and 7 of these women died 21-71 months after re-irradiation. Two of the women who developed distant metastases first developed a contralateral breast cancer. Eight women developed a 2nd IBTR after re-irradiation (2 of which had positive axillary lymph nodes), and only 3 of which were in the same quadrant as the first.

A group in France utilized post-operative brachytherapy in a small series of patients who opted for repeat breast conservation after IBTR—some refused mastectomy, and some were not candidates—they were treated to a dose of 30 Gy (dose rate not mentioned) (27). Four (26%) of patients developed a 2nd IBTR at a median follow-up of 4 years. There are several criticisms of this study, including the lack of reporting of margin status, or brachytherapy dose rate. Three patients had "major" cosmetic sequelae (one with locally treated skin necrosis), but cosmetic analyses/comment is only available for 8/15 patients involved in the study.

A group from Austria utilized pulse-dose-rate brachytherapy to treat IBTR, obviating the need for mastectomy. At first, patients were treated with whole breast radiotherapy followed by a

brachytherapy boost, but over time treatment was changed to brachytherapy alone. Brachytherapy dose for the group who also received EBRT ranged from 12.5 to 28.0 Gy (mean 22.4 Gy), whereas in the group that received brachytherapy alone, it ranged from 40.2 to 50.0 Gy (mean 46.5) (28). At a median follow-up of 59 months, 12 of the 17 women were alive and had no evidence of local tumor. Twenty-four percent of patients (4) experienced a 2nd IBTR—all within the 1st year and all in the group who received both EBRT and brachytherapy. There have been no 2nd IBTR's in the group receiving brachytherapy alone, suggesting increased local control with increasing brachy dose. Often dose escalation, with the hope of increasing local control, cannot be maximized due to toxicities of normal tissues. In this study, no patients had unacceptable cosmetic results; it was good or excellent in one third of patients.

Recent interest in accelerated partial breast irradiation relies on the principle that since the most frequent location of an ipsilateral breast cancer recurrence is in the tumor bed, by targeting this area one can minimize the cumulative dose to the whole breast (and therefore complications/toxicities that may arise from increased dose to the breast There is also the possibility that if a patient were to develop an ipsilateral breast cancer recurrence following accelerated partial breast irradiation that it may be possible to resect this recurrence and then treat the whole breast with radiation. This study attempts to clarify the feasibility and efficacy of using accelerated partial breast irradiation in patients who have already received whole breast irradiation. It only seems natural, that one might consider utilizing partial breast to treat an in-breast recurrence in someone who, for whatever reason, refuses mastectomy, or is not a candidate for one. By utilizing various techniques of partial breast irradiation, treatment can be targeted to only the surgical lumpectomy cavity. Partial breast irradiation can be accomplished by a multitude of techniques, including 3-D conformal external beam radiation, MammoSite catheter brachytherapy, multi-catheter brachytherapy and intra-operative radiation therapy.

There are currently several groups studying the efficacy of lumpectomy bed irradiation alone in the management of early stage breast cancer patients (29-38). Both interstitial brachytherapy techniques as well as external beam irradiation protocols have been implemented (See Table 1). Preliminary results from these trials are very encouraging and the techniques have been shown to be safe, tolerable, and highly reproducible. In 1993, Vicini et al. initiated a pilot trial of low dose rate (LDR) brachytherapy as the sole radiation modality with BCT (32). As of February 2001, 120 patients have been treated on this protocol. With a median follow-up of 85 months, only 3 patients have developed a local recurrence (five-year actuarial rate of 1%) and cosmetic results were judged as good to excellent in 98% patients (verbal communication). In addition, no adverse sequelae were noted on the protocol. More recently, a second protocol employing high dose rate (HDR) brachytherapy (in the same subset of patients) was also initiated at the same institution (39). Although results were preliminary, no adverse sequelae were noted.

Table 1: Breast conserving therapy with lumpectomy plus partial breast irradiation

Institution	# Pt	Med F/U (mos)	Scheme (cGy)	Total Dose (cGy)	% LR	% Good /Excellent Cosmetic results
HDR Series*						
Ochsner Clinic[29]	26	20	400 x 8	3200	0	67

Royal Devon/Exeter Hospital, Exeter, England[30]	45	18	1000 x 2	2000	8.8	95
			700 x 4	2800		
			600 x 6	3600		
Orszagos Onkologiai Intezet, Budapest, Hungary[37]	41	17	520 x 7	3640	2.4	Not stated
			433 x 7	3030		
London Regional Cancer Center, London, Ontario[33,36]	39	20	372 x 10	3720	2.6[a]	Not stated
William Beaumont Hospital[39]	79	48	400 x 8	3200	1	98
			340 x 10	3400		
LDR Series**						
Ochsner Clinic[29]	26	20		4500	0	78
Guy's Hospital[31,40]	27	72	40 cGy/hr	5500	37[a]	83
Cionini et al[35]	90	27		5000-6000	4.4[a]	Not stated
William Beaumont Hospital[34]	120	85	52 cGy/hr	4992	1	98
External Beam Series						
Christie Hospital[38,41]	353	65	500	4000	19.6[a]	---
William Beaumont Hospital	31	12	385 x 10	3850	0	100
European Institute of Oncology[42]	86	8	2100 x 1	2100	---	---

[a]Seven year rate
*HDR = High dose rate brachytherapy
**LDR = Low dose rate brachytherapy

Intra-operative Partial Breast Irradiation Experience

Over the last several years, increasing interest in the use of intraoperative radiation (IORT) in the setting of breast conservation has developed. The rationale of IORT is relatively simple. Rather than using external beam radiation to treat the entire breast post-operatively, radiation is applied directly to the surgical tumor bed through the open surgical incision. There are several advantages to this approach. First, the radiation dose is applied directly to the tumor bed with little chance for geographical miss. There is also less irradiation of normal tissues. The radiation is done at the time of surgery, therefore, there is no delay between surgery and the initiation of radiation. This results in a shorter overall treatment course and potentially less cost involved. This approach has been utilized with intraoperative brachytherapy as well. An advantage of utilizing intraoperative electron beam therapy over brachytherapy may be increased dose homogeneity seen with intraoperative treatment compared to brachytherapy. There is also decreased risk to hospital personnel compared to brachytherapy due to decreased radiation exposure and decreased requirements for shielding.

The Mobetron is a lightweight, mobile, self-shielded linear accelerator. It provides electrons with energies of 4, 6, 9, or 12 MeV capable of penetrating to a depth of approximately 1, 2, 3, and 4 cm to the 80% isodose line, respectively. Treatment is delivered through applicators with dimensions from 3-10 cm. The applicators may be either flat or beveled at 30 degrees. The unit weighs 1/6 of what a conventional accelerator does allowing it to be moved from room to room. There is minimal x-ray contamination eliminating the need for a shielded operating room and a beam stopper attached to the unit provides the necessary shielding from X-rays generated by the patient during treatment. The control panel for the Mobetron is located outside of the operating room during treatment and the patient may be directly observed through the windows during the treatment (36). The Mobetron is present at only a handful of institutions both inside and outside of the USA. It is currently being utilized in a variety of tumor sites to provide intraoperative radiation.

Intra-operative external beam irradiation has also recently been explored as an additional method of delivering post-lumpectomy partial breast irradiation in an accelerated fashion. Veronesi et al from the European Institute of Oncology in Milan, Italy recently published their preliminary results from a phase I/II dose escalation study of single-fraction irradiation given immediately after quadrantectomy (42). With minimal toxicity in the first 86 patients treated with dose levels of 17-19-21 Gy per fraction using 3 - 9 MeV electrons, the authors have now proceeded with a phase III trial comparing standard whole breast irradiation (50 Gy plus a 10 Gy boost) to a 21 Gy intraoperative
single fraction. As of February 2002, > 250 patients have been enrolled in this equivalency trial with an accrual goal of over 800 patients (verbal communication).
Vaidya et al recently published their experience with intra-operative partial breast radiation therapy as boost treatment (43). In a pilot study of 35 patients, the post-operative tumor bed boost was replaced with an intra-operative 5 Gy fraction of radiation therapy delivered with the Photon Radiosurgery System. This device emits soft X-rays from a ball-shaped applicator

applied directly against the lumpectomy cavity. With a median follow-up of 24 months, there have been no major complications. A phase III trial has recently been initiated.

MammoSite® Brachytherapy Experience

One of the primary disadvantages of conventional breast brachytherapy is the complexity and reproducibility of the procedure. Breast brachytherapy is used either to deliver a localized boost dose of radiation to the lumpectomy cavity or to deliver the primary radiation to the lumpectomy cavity. In clinical practice, a typical boost prescription is 10 – 25 Gy, a short, intense treatment to the tissue around the lumpectomy cavity. The boost dose is generally followed by external beam radiation to the whole breast. A typical primary breast brachytherapy treatment dose is between 32 and 34 Gy. Conventional breast brachytherapy is an invasive procedure and consists of the placement of up to 20 needles or catheters around the site of the tumor removal. These needles or catheters are loaded with a radiation source for a period of 4-5 days. After completion of radiation the needles or catheters are removed (43). Even using the best imaging available, the technique is difficult and requires a great deal of experience and skill to position the needles or catheters to cover the required treatment area adequately.

The MammoSite® applicator was developed to address these disadvantages. The MammoSite® allows an easier implant and reproducible radiation delivery to the target tissue area. The MammoSite® is a nylon tube (for the radiation source to travel in) with a balloon attached at the end to expand and conform to the cavity. The MammoSite® applicator is inserted into the cavity created by the tumor removal surgery, either at the time of lumpectomy or post lumpectomy. The MammoSite® applicator is then inflated and expands to fill the cavity. The radiation can then be delivered using commercially available radioactive sources using the center nylon tube of the MammoSite® applicator. This central source creates a symmetrical radiation delivery from the inside of the cavity to the adjacent tissues where residual cancer is most likely to exist while reducing damaging radiation delivery to the surrounding vital organ structures.

In a Phase II clinical trial with the MammoSite®, 43 patients received radiation therapy as primary treatment. Short-term cosmesis has been good to excellent on the Harvard Scale in 88% of the women treated. Patients experienced only mild to moderate side effects, including skin erythema (57%), dry desquamation (13%) and moist desquamation (5%) short term that were related to the radiation therapy dose. The study demonstrated that the device was safe and well tolerated which resulted in FDA clearance of the device on May 6, 2002 (44, 45). The safety and effectiveness of the MammoSite® Radiation Therapy System (RTS) as a replacement for whole breast irradiation in the treatment of breast cancer is currently being investigated.

Current Trial Design

Patients enrolled in this protocol will be selected to insure that their cancers have been adequately excised and that tumor bed irradiation alone will be feasible. Depending on individual patient characteristics (for example, proximity of the tumor cavity to the skin,

patient's ability to tolerate another surgical procedure) a decision will be made jointly by the breast surgeon, radiation oncologist and medical oncologist at our multi-disciplinary conference as to which method of partial breast irradiation is best suited for the patient. Practical considerations will also be taken into account, in the decision of which type of radiation to offer—that said, provided a patient is medically eligible for either type of radiation, she will be given the opportunity to decide which treatment she would like. Some patients may not be deemed medically fit to undergo another surgical procedure, and might then be offered MammoSite based APBI, because the catheter does not necessarily have to be placed in the operating room. Another example in which one therapy might be more advisable than another, is woman who has a history of immune deficiency and resultant life threatening infections—rather than leaving a MammoSite catheter with an open wound for more than one week, one might opt for a single treatment in the operating room at the time of lumpectomy. One endpoint of the study will be to evaluate which patients are best suited for treatment by each of the available partial breast irradiation options.

The aim of the study will be to evaluate patient acceptance of the concept of partial breast re-irradiation for an IBTR, in the hope that there will be an alternative treatment to the recognized standard of care (mastectomy). We will also evaluate cosmetic outcome following the procedure. Long term outcome data regarding further in-breast recurrences as well as tumor bed recurrence will also be recorded and analyzed.

2.0 OBJECTIVES

2.1 To determine the in breast recurrence rate following repeat radiation to the breast. These patients will be followed for a period of five years following completion of radiation to determine these rates.

2.2 To determine the cosmetic outcome resulting from partial breast re-irradiation using different techniques, including both physician and patient rated scales.

2.3 To determine patient satisfaction of partial breast re-irradiation as it pertains to their overall treatment experience as measured by a questionnaire.

2.4 To determine if there are patient factors illuminated during a discussion of informed consent, which limit a patient's suitability to receive partial breast re-irradiation delivered by a particular technique.

2.5 To evaluate tylectomy wound healing and overall complication rate after partial breast re-irradiation.

2.6 To determine ipsilateral breast tumor recurrence rates as well as tumor bed recurrence rates. These patients will be followed for a period of five years following completion of the second course of radiation to determine these rates.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients' recurrences must have histologically confirmed ductal carcinoma in-situ, invasive ductal, medullary, papillary, colloid (mucinous), or tubular histologies.

3.1.2 Lesion size $\leq$ 3 cm treated with a tylectomy. Patients with clinically and radiographically negative axillas should not undergo an axillary lymph node dissection unless they did not have prior axillary lymph node sampling (i.e. previous cancer was DCIS).

3.1.3 Unifocal breast cancer recurrence.

3.1.4 Negative resection margins with at least a 2 mm margin from invasive and in-situ cancer or a negative re-excision.

3.1.5 Hormonal therapy is allowed. If chemotherapy is planned, the radiation is delivered first and chemotherapy must begin no earlier than two weeks following completion of radiation.

3.1.6 Patients must be $\geq$ 18 years of age.

3.1.7 Signed study-specific informed consent prior to study entry.

3.2 Ineligibility Criteria

3.2.1 Patients with distant metastatic disease

3.2.2 Patients with invasive lobular carcinoma, extensive lobular carcinoma in-situ, extensive ductal carcinoma in-situ (spanning more than 3 cm), or nonepithelial breast malignancies such as lymphoma or sarcoma.

3.2.3 Patients with multicentric carcinoma (tumors in different quadrants of the breast or tumors separated by at least 4 cm). Palpable or radiographically suspicious contralateral

axillary, ipsilateral or contralateral supraclavicular, infraclavicular, or internal mammary lymph nodes unless these are histologically or cytologically confirmed negative.

3.2.4 Extensive intraductal component (EIC) by the Harvard definition, i.e. 1) more than 25% of the invasive tumor is DCIS and DCIS present in adjacent breast tissue. Presence of an EIC increases the chance of local recurrence, and as such, one might not be a candidate for repeat breast conservation.

3.2.5 Patients with Paget's disease of the nipple.

3.2.6 Patients with skin involvement.

3.2.7 Patients with collagen vascular disorders, specifically systemic lupus erythematosis, scleroderma, or dermatomyositis.

3.2.8 Patients with psychiatric, neurologic, or addictive disorders that would preclude obtaining informed consent.

3.2.9 Other malignancy, except non-melanomatous skin cancer, < 5 years prior to participation in this study.

3.2.10 Patients who are pregnant or lactating due to potential fetal exposure to radiation and unknown effects of radiation on lactating females.

3.2.11 Patients with known BRCA 1/BRCA 2 mutations.

4.0 REGISTRATION PROCEDURES

Investigators will register patients by contacting the Cancer Center Clinical Trials Unit study coordinator. Patients will be registered by the study coordinator online via the Clinical Trials Unit Oncore database. A registration card, copy of the informed consent, and copy of the signed eligibility checklist must be completed prior to a patient starting treatment.

5.0 TREATMENT PLAN

Patients enrolled on the study will receive partial breast irradiation delivered as 1) a single intra-operative dose of 21 Gy or 2) MammoSite® brachytherapy consisting of a dose of 34 Gy in 10 fractions delivered over 5 days. Patients will be followed for a period of five years following completion of radiation.

5.1 Surgery

5.1.1 Patients will undergo excisional biopsy or needle localization removal of the tumor.

5.1.2 Patients with margins < 2 mm undergo re-excision of the biopsy cavity.

5.1.3 For patients undergoing IORT, the skin around the excision site will be dissected and small skin flaps will be raised. The breast tissue is then loosely sutured so that the lateral margins are brought into apposition. The applicator will then be positioned to encompass the entire tumor bed with a 1 cm margin. After radiation has been delivered, sutures will be removed and the tumor bed will bed closed in the typical fashion.

5.2 Radiation Therapy – Consultation via presentation at our multi-disciplinary breast conference between the surgeon, radiation oncologist and medical oncologist will take place to determine suitability for undergoing partial breast radiation and a recommendation will be made as to which modality is best suited for the patient. Clinical characteristics, including but not

limited to, distance of tumor from skin, patient's ability to tolerate another surgical procedure, patient's ability to come into the radiation department twice daily for treatment, will be considered in making this decision. All patients will be seen in consultation by the radiation oncologist prior to enrollment.

5.2.1 Intraoperative Radiation:

5.2.1a Applicator selection should allow for treatment of the tumor bed with a 1 cm radial margin.

5.2.1b Dosimetry on all applicators should be available to the radiation oncologist upon request in the operating room.

5.2.1c Energy of electrons should be such that the tumor cavity with a 1 cm margin will be covered by the 90% line. *The energy of the electrons will be at the discretion of the radiation oncologist and determined at the time of treatment to ensure proper coverage of the tumor cavity.*

5.2.1d A dose of 21 Gy will be prescribed to the 90% isodose line.

5.3.1 MammoSite® Brachytherapy:

5.3.1a Applicator Placement:

5.3.1a1 The MammoSite® applicator may be placed either at the time of surgery or in a separate procedure using ultrasound guidance after surgery. The MammoSite® applicator should be selected to best fit the cavity created by the surgical removal of the tumor.

5.3.1a2 The balloon of the MammoSite® applicator should be inflated with a saline/contrast mixture (maximum of 25% contrast) to fill the cavity at the time of placement. The balloon will remain inflated throughout the duration of the radiation and will be removed after the last fraction.

5.3.1a3 Post implant imaging should be performed after insertion of the MammoSite® to evaluate the patient for skin spacing, symmetry and conformance of the applicator.

5.3.1b Treatment Planning

5.3.1b1 CT image is recommended for treatment planning. Standard brachytherapy treatment planning will be conducted using commercially available software and equipment. The treatment should be performed using available high dose rate (HDR) brachytherapy.

5.3.1b2 CT imaging or plain orthogonal x-rays will be performed prior to treatment to ensure adequacy of implant.

5.3.1c Brachytherapy Treatment:

5.3.1c1 Brachytherapy should start between 3 - 7 days after implant.

5.3.1c2 The dose is 34 Gy prescribed to a depth of 1 cm from the balloon surface delivered over 10 fractions of 3.4 Gy over 5-10 days. The fractions are delivered twice a day with at least six hours separating each fraction.

5.3.1c3 All treatments should be done using a commercially available HDR and ^{192}Ir radioactive sources.

5.3.1d Applicator Removal:

5.3.1d1 The removal of the applicator should be scheduled after the completion of brachytherapy.

5.3.1d2 The applicator should be removed using standard sterile technique.

5.3.1d3 The applicator exit/entrance site should be dressed according to standard medical practice.

5.4 Data Safety and Monitoring Plan

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan, version 2 guidelines in accordance with NCI regulations. The Data and Safety Toxicity Committee will review all serious adverse events and toxicity reports as well as annual reviews.

6.0 MEASUREMENT OF EFFECT

The endpoints of this study are as follows:

6.1 Determination ipsilateral breast tumor recurrence rates as well as tumor bed recurrence rates. The breast quadrant of recurrence will be recorded. Patients will be followed for a period of five years following completion of radiation.

6.2 Cosmetic outcome as determined by an established scale employed by the radiation oncologist and the surgeon.

6.3 Patient satisfaction with the procedure as determined by a questionnaire to be completed by the patients.

6.4 Wound healing and overall complication rate after partial breast re-irradiation.

6.5 Determination of which patients are best suited for each individual technique of performing partial breast irradiation. Measurement of this will be observational.

7.0 STUDY PARAMETERS

Study Parameters	Pre-Treatment	Follow-up
H&P/clinical evaluation	**X**	**1 month after RT & Q3mos for one year, then annually for 5 years.**
Mammogram	**X**	**Ipsilateral breast 6 mos after dx, bilateral annually**
CXR	**X**	**Annually x 5 years**
CT chest/abdomen/pelvis	**X**	**If clinically indicated**
Bone Scan	**X**	**If clinically indicated**
Cosmetic Evaluation/QOL assessment	**X**	**1 month after RT & Q3mos for one year, and at 5 years.**
Skin Assessment		**Last day of RT**
Breast MRI		**If clinically indicated**

8.0 STATISTICAL CONSIDERATIONS

The primary objective is to determine the feasibility of partial breast irradiation after repeat breast-conserving surgery for an IBTR. Thirty patients will be enrolled for this study and we expect to finish the enrollment within 5 years. For the safety of patients, interim analyses will be performed after 6, 12, 18 and 24 patients have reached 3 months and 1 year post treatment period. The protocol will remain open to enrollment during the interim analyses. The trial will be stopped if:

a) The 3 month adverse event rate is determined to be in excess of 10%.

b) A one-year local recurrence rate is more than 5%.

Assume the probability of 3 month adverse event (or 1 year local recurrence) is p, allowable maximum adverse event rate (or 1 year local recurrence rate) is $p_0$and the type I error is α.. The early stopping rules are based on the following statistical hypothesis test:

H_0: $p \leq p_0$ vs H_A: $p > p_0$

Based on the exact probability of Binomial distribution, we will reject the null hypothesis (i.e. stop the trial) if we observe k or more adverse events (local recurrences), where

$$k = \min\{l : \sum_{i \geq l} \binom{n}{i} p_0^i (1-p_0)^{n-i} \leq \alpha/2\},$$

and n is the number of patients at the time of the interim analysis.

The trial will be stopped if the 3 month adverse event rate is in excess of 10%. The trial will also be stopped if the 1-year local recurrence rate is more than 5%. The following table is based on α = 0.05.

Minimum number of adverse events during first 3 months to stop the trial	Minimum number of local recurrences during the first 1 year to stop the trial	Number of patients treated
3	2	6
4	3	12
5	4	18
6	5	24

Safety analysis will be performed on all patients enrolled in the study. The incidence and its confidence interval of 3 month adverse events and 1year local recurrences will be estimated. The time to local recurrence is calculated from the date of completion of radiation. Data for patients who remain free of local disease are censored as of date when the last follow-up information is obtained. At the end of the study, the cumulative local recurrence rate will be estimated by Kaplan-Meier method (46) for all patients (intend-to-treat) and 5-year recurrence rate will be then obtained and compared with those in the literature. The overall incidence and its confidence interval of acute complications following lumpectomy will be estimated. Also, we will estimate the overall incidence and the degree of fibrosis as defined on four-level scale of cosmetic outcome in appendix I.

9.0 RECORDS TO BE KEPT

At time of registration – Patient consent form, signed eligibility checklist and registration card.

Following breast conservation surgery for the second time, prior to beginning breast re-radiation, the cosmetic results of breast conservation will be assessed. Appendix I should be used. The same will be used to reassess the patient during radiation therapy, at one month post-radiation therapy, and every three months thereafter for one year, followed bi-annually for the remainder of the 5 year follow-up.

Follow-up Form - at time of disease response assessment, every three months during the first year and every 6 months thereafter for 5 years.

10.0 PATIENT CONSENT AND PEER JUDGEMENT

All institutional, NCI, FDA, State and Federal regulations concerning informed consent and peer judgement will be fulfilled. Typically, patients choosing to participate in this trial will be consented either at the time of consultation with, or shortly after their meeting with the radiation oncologist. As the referral to the radiation oncologist can come at varying stages in the diagnostic/treatment process (i.e. right after biopsy, but before lumpectomy, or after lumpectomy and before chemotherapy etc…), his/her participation in out Multidisciplinary Tumor Board is paramount. It is at these weekly meetings that treatment recommendations are formulated—if a patient is scheduled to have a lumpectomy and her case is presented at tumor board, then the radiation oncologist may then see the patient right before surgery and assess interest in the study prior to surgery. That said, even if a patient has already had a lumpectomy with negative

margins, she may always be taken back to the operating room if she decides to be in this trial and if it is deemed that to perform the radiation, she needs to be taken to the OR (i.e. for IORT, or for MammoSite placement).

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APPENDIX I

COSMETIC GUIDELINES

Patient #: _____

Following breast conservation surgery, prior to beginning breast re-radiation, the cosmetic results of breast conservation will be assessed using these guidelines. The same guidelines will be used to reassess the patient during radiation therapy, at one month post-radiation therapy, and every three months thereafter for one year, then biannually for a total of 5 years.

Circle the number next to the word that best describes the cosmetic result.

1. EXCELLENT: When compared to the untreated breast or the original appearance of the treated breast, there is minimal or no difference in the size or shape of the treated breast. The way the breast fells (its texture) is the same or slightly different. There may be thickening, scar tissue, or fluid accumulation within the breast but not enough to change the appearance.

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

3. FAIR: Moderate deformity of the breast, with an obvious difference in the shape and size of the treated breast. This change involves ¼ or less of the breast. There can be moderate thickening or scar tissue of the skin and the breast, and there may be obvious color changes.

4. POOR: Marked change in the appearance of the treated breast involving more than ¼ of the breast tissue. The skin change may be obvious and detract from the appearance. Severe scarring and thickening of the breast, which clearly alters its appearance may be present. In retrospect, the breast may have been better treated by a mastectomy.

Code a response for each of the following items:

1. None
2. Yes, seen on close observation
3. Yes, seen on casual observation

_____ skin telangectasia
_____ skin atrophy
_____ hyperpigmentation
_____ erythema
_____ fibrosis
_____ skin dimpling or indentation
_____ other significant treatment effects
specify:_____

During radiation therapy the patient will be evaluated weekly by the radiation oncologist. The following scale will be used to classify the acute skin reactions during treatment:

1. no change noted
2. faint erythema
3. bright erythema
4. dry desquamation with or without erythema
5. small to moderate area of moist desquamation
6. large area of moist desquamation
7. ulceration, hemorrhage, or necrosis

Signature of person completing the form: _____

Date: _____

APPENDIX II

Patient Cosmesis/QOL form

Date Questionnaire Completed: _____ Patient #: _____

My treatment was: (check one)

- ○ One time radiation treatment during surgery
- ○ MammoSite radiation after surgery

Circle the number next to the word that best describes the cosmetic result.

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

2. GOOD: There is slight difference in the size or shape of the treated breast as compared to the opposite breast or the appearance of the breast before treatment. There may be some mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes a mild change in its shape or size.

3. FAIR: There is an obvious difference in the shape and size of the treated breast. This change involves ¼ or less of the breast. There can be moderate thickening or scar tissue of the skin and the breast, and there may be obvious color changes.

4. POOR: There is marked change in the appearance of the treated breast involving more than ¼ of the breast tissue. The skin change may be obvious and detract from the appearance. Severe scarring and thickening of the breast, which clearly alters its appearance, may be present. In retrospect, the breast may have been better treated by a mastectomy.

My satisfaction about the treatment and results is:

1. I am totally satisfied with the treatment and results.
2. I am <u>not</u> totally satisfied but would choose the same treatment again.
3. I am not totally satisfied and would choose the standard 5-6 week course of radiation if I had it to do all over again.
4. I am dissatisfied with my treatment.

Before any treatment to your breast, the size and shape of my breasts was:

1. The same on both sides.
2. Larger on the right side.
3. Larger on the left side.

The size of my breasts now is:

1. The same on both sides.
2. Larger on the right side.
3. Larger on the left side.

Signature of person completing the form: _____