PROTOCOL **03-179**

Closed to New Accrual

Closure Effective Date: October 13, 2010

No new subjects may be enrolled in the study as described above. Any questions regarding this closure should be directed to the study's Principal Investigator

Partial Breast Irradiation (PBI) for Selected Patients With Early Invasive or Non-Invasive Breast Cancer

NCT00694577

April 3rd, 2012

Protocol Number: 03-179

Approval Date: 7/15/03 (IRB meeting date when protocol/consent approved or conditionally approved)

Activation Date: 9/8/03 (Date when protocol open to patient entry)

Approval signatures are on file in the Office for Human Research Studies, tel. 617-632-3029.

Date Posted	Revised Sections	IRB Approval Date	OHRS Version Date
11/11/03	Protocol replaced due to amendment # 1	11/06/03	-
04/01/04	Protocol replaced due to amendment # 3	03/24/04	-
7/6/04	Consent Form Replaced due to Continuing Review #1	6/3/04	-
7/20/04	Front Sheet – due to Amendment #4	7/20/04	-
11/02/04	Front Sheet Replaced Due to Amendment #5	11/01/04	-
12/13/04	Front sheet Correction	12/13/04	-
12/14/04	Front Sheet - name change for previously approved staff, no new amendment submitted		-
12/15/04	Front Sheet, Consent Form, Protocol – Amendment #6	11/22/04	-
12/15/04	Front Sheet replaced due to Amendment # 7	12/13/04	-
02/22/05	Front Sheet Replaced Due to Amendment #8	02/18/05	-
03/18/05	Correction: Consent form replaced due to typo of Expiration date	N/a	-
05/25/05	Consent Form Replaced due to Continuing Review #2	05/19/05	-
09/07/05	Consent Form, Protocol and Front Sheet Replaced Due to Amendment #10	08/30/05	-
09/14/05	Correction: Front Sheet replaced due to study staff listing incomplete	N/A	-
9/27/05	Consent Form Replaced Due to Amendment #11	9/27/05	-
9/30/05	Front Sheet, Protocol Replaced due to Amendment #12	9/29/05	-
11/02/05	Front Sheet Replaced Due to Amendment #13	11/01/02	-
1/12/06	Front Sheet Replaced Due to Amendment #14	1/11/06	-
2/15/06	Front Sheet, Protocol, Consent Form Replaced due to Amendment #15	1/31/06	-
05/04/06	Consent Form replaced due to Continuing Review #3	04/20/06	-
07/10/06	Temporary Closure: Brisk accrual, administrative reasons/review of funding (Effective: 07/07/06)	07/10/06	-
07/27/06	Front Sheet Replaced Due to Amendment #17	07/25/06	-
08/11/06	Study Reopen to New Accrual due to Amendment # 18	08/11/06	-
09/26/06	Consent and Front Sheet replaced due to Amendment #19	09/26/06	-
11/07/06	Front Sheet replaced due to Amendment #20	10/31/06	-
12/04/06	Front Sheet replaced due to Amendment #21	11/27/06	-
12/26/06	Front Sheet and Protocol Replaced due to Amendment #22	12/15/06	-
04/18/07	Consent Form replaced due to Continuing Review #4	04/05/07	-
07/30/07	Front Sheet replaced due to Amendment #23	07/27/07	-
09/14/07	On Hold removed and Consent Form replaced due to Adverse Event #5 and Other Events #15 & #16	09/14/07	-
11/08/07	Front Sheet replaced due to Amendment #24	11/01/07	-
01/10/08	Consent Form replaced due to Continuing Review #5	12/20/07	-
01/23/08	Protocol and Front Sheet replaced due to Amendment #25	01/03/08	-
01/23/08	Front Sheet replaced due to Amendment #26	01/23/08	-
05/14/08	Front Sheet replaced due to Amendment #27	05/13/08	-
10/16/08	Front Sheet replaced due to Amendment #28	10/16/08	-
11/04/08	Front Sheet replaced due to Amendment #29	10/31/08	-

11/26/08	Study renewal due to Continuing Review #6	11/20/08	-
12/02/08	Correction: Continuing review documents (CF and Memo) taken down since conditional approval still pending. Previous versions replaced.	N/A	-
12/15/08	Protocol, Front Sheet and Consent Form replaced due to Continuing Review #6	11/20/08	-
02/26/09	Front Sheet replaced due to Amendment #30	02/26/09	-
3/19/09	Front Sheet Replaced Due to Amendment #32	3/18/09	-
05/14/09	Protocol, Front Sheet and Consent Form replaced due to Amendment #31	04/14/09	-
07/20/09	Amendment # 33 (No changes to online documents)	07/20/09	-
09/11/09	On Hold alert page posted: per IRB for safety analysis of data. No new subjects may be enrolled.	N/A	-
09/15/09	Correction: Consent Form replaced due to Amendment # 31 (remains closed to new accrual)	N/A	-
09/16/09	Permanent closure to new accrual: per IRB decision	09/15/09	-
11/03/09	Protocol, Consent Form and Front Sheet replaced due to Amendments #35 & 36	10/06/09	-
11/20/09	ON HOLD: All research must stop due to lapsed Continuing Review. Study expired 11/20/09	N/A	-
12/17/09	On Hold removed. Study renewal (CF footer replaced) due to Continuing Review # 7 (Note: 6-month IRB approval: expires 06/01/10)	12/01/09	-
04/01/10	Front Sheet replaced due to Amendment #37	04/01/10	-
05/26/10	Study renewal (CF footer replaced) due to Continuing Review # 8 (Note: 6-month IRB approval: expires 11/13/10)	05/13/10	-
08/03/10	Front Sheet replaced due to Amendment #38	08/03/10	-
10/12/10	Consent Form replaced due to Adverse Event # 23	08/26/10	-
10/14/10	Patient Info Letter added due to Amendment #39	10/14/10	-
10/27/10	Permanent Closure to New Accrual: extended period of time lapsed since temporary closure. Analysis will proceed w/ data collected from 330 pts (Effective: 10/13/10; Amendment # 40)	10/19/10	-
10/28/10	BIDMC site ON HOLD due BIDMC Strategic Hold OE #30	N/A	-
11/12/10	Study renewal due to Continuing Review #9	10/14/10	-
11/12/10	Front Sheet replaced due to Amendment #41	10/28/10	-
01/26/11	Request to remove administrative hold at BIDMC due to Amendment #43	01/25/11	-
02/16/11	Amendment # 44 (No changes to online documents)	02/04/11	-
02/28/11	Patient Info Letter replaced due to Amendment #42	02/03/11	-
04/20/11	Patient Info Letter replaced due to Amendment #45	04/18/11	-
09/20/11	Study renewal due to Continuing Review #10	09/15/11	-
04/27/12	Protocol, Front Sheet and Patient Information Letter replaced due to Amendment #46	04/16/12	-
07/30/12	Study renewal/ Consent Form footer replaced due to Continuing Review #11	07/26/12	n/a
08/13/12	Front Sheet replaced due to Amendment #47	08/06/12	N/A
10/26/12	Front Sheet replaced due to Amendment #48	10/25/12	N/A
01/15/13	Patient Survey added due to Amendment #49	01/02/13	N/A
01/15/13	Correction Am#49: Patient survey removed	N/A	N/A
07/26/13	ON HOLD: All research must stop due to lapsed Continuing Review. Study expired 07/26/2013	N/A	N/A
08/08/13	On Hold removed. Study renewal (CF footer replaced) due to Continuing Review #12	08/06/13	N/A
08/06/14	ON HOLD: All research must stop due to lapsed Continuing Review. Study approval expired 08/06/14.	N/A	N/A

08/06/14	Remove Hold. Study renewal/ Consent Form footer replaced due to Continuing Review #13	08/05/14	N/A
09/30/14	Front Sheet replaced due to Amendment #50	09/30/14	n/a
Date Posted	**Revised Sections**	**IRB Approval Date**	**OnCore Version Date**
08/05/15	ON HOLD: All research must stop due to lapsed Continuing Review. Study approval expired 08/05/15.	N/A	N/A
08/06/15	Remove Hold. Study renewal/ Consent Form footer replaced due to Continuing Review #14	08/06/15	08/06/15
07/28/16	Study renewal/ Consent Form footer replaced due to Continuing Review #15	07/14/16	07/28/16
06/27/17	Front Sheet replaced due to Amendment # 51	06/21/17	N/a
07/13/2017	Study renewal/ Consent Form footer replaced due to Continuing Review #16	07/13/2017	07/13/2017
06/29/2018	Study renewal/ Consent Form footer replaced due to Continuing Review #17	06/28/2018	06/29/2018
08/02/2018	Front Sheet replaced per Amendment #52	08/01/2018	n/a
06/14/2019	Study renewal/Consent Form footer replaced per Continuing Review #18	06/13/2019	06/13/2019

PRINCIPLE INVESTIGATOR: **Alphonse Taghian, MD, PhD**

STUDY TITLE: Partial Breast Irradiation (PBI) for Selected Patients with Early Invasive or Non Invasive Breast Cancer: A Phase I Feasibility/Pilot Study

FUNDING SOURCE: Avon Pilot Grant Awardee and Departmental sources

HYPOTHESIS: Partial Breast Irradiation (PBI) is equal to whole breast irradiation.

SPECIFIC AIMS: To evaluate the technical feasibility and potential toxicities associated with PBI directed XRT in selected early stage female breast cancer patients.
To estimate the optimal dose and fractionation used in PBI with acceptable toxicity.

BACKGROUND AND SIGNIFICANCE: The combination of breast-conserving surgery and radiotherapy, known as "breast-conserving therapy" (BCT), is now widely accepted as a treatment option for most women with clinical Stage I or II invasive breast cancer and ductal carcinoma *in situ*. However, there are few data regarding the optimal volume of irradiation.[1-3] One question yet unanswered is whether the entire breast needs to be treated, or only a more limited volume surrounding the tumor.

Traditionally, patients undergoing BCT have been irradiated to the entire breast. However, most of the potential long-term complications of BCT result from either whole-breast or nodal irradiation (e.g., cardiac damage, radiation pneumonitis, brachial plexopathy).[4, 5] Further, giving radiotherapy to the entire breast essentially precludes giving further irradiation to that breast should the patient develop a new primary tumor in the same breast.[1-3]

In addition, the option of partial-breast irradiation (PBI) may lend itself to much shorter treatment schemes than whole-breast irradiation, as the toxicities to the breast should be lessened by treating only a part of the breast. This would make such treatment more convenient for the patient, perhaps allow easier integration of radiotherapy with chemotherapy, and potentially decrease the overall cost of treatment substantially.

In a first phase of the study (protocol 03-179), we have shown that PBI using 3-D conformal external radiation is technically feasible without significant *short-term* toxicity. However, the radiation dose used was 32 Gy in 8 fractions BID over 4 treatment days. Meanwhile, the NSABP-B-39 is starting a prospective randomized trial comparing whole breast RT over 6 weeks period with PBI using 38.5 Gy over 10 fractions BID over 5 treatment days. This study has opened nationally in March 2005. However, the optimal dose for PBI is not known yet. The choice of 38.5 Gy was based on mathematical and biological modeling without clinical data. The aim of this study is to estimate the optimal dose, which could be used in PBI with the least toxicity.

RESEARCH DESIGN AND METHODS: Pilot Feasibility and Dose-Escalation

RECRUITMENT: Patients will be recruited from the clinics of participating surgeons, medical and radiation oncologists. There will be no advertising or remuneration.

RISKS AND DISCOMFORTS: Erythema and dry desquamation in the radiation fields are anticipated to occur commonly. Some patients may develop a moist desquamation, which usually heals within a few weeks. Other toxicity, being evaluated, may include chronic toxicity of the skin or subcutaneous tissues or fat necrosis.

SECTION 2: Protocol Schema

Invasive breast cancer (ductal or special subtypes) pT1pN0M0 or N0(i+)
pT1cNo M0-ER+ (for patients age 70 years or older), or
DCIS, grade (I and II) ≤2 cm

Register for study and undergo treatment planning
Review of treatment plan
Within 4-12 weeks from surgery or
2-6 weeks after chemotherapy

PBI (Partial Breast Irradiation)
First dose-level: 32 Gy in 8 Fractions twice daily over 4-treatment days within an overall treatment time of one week (Patients 1-100)
Second dose-level: 36 Gy in 9 Fractions BID over 4 1/2-treatment days within an overall treatment time of one week (Patients 101-200)
Third dose-level: 40 Gy in 10 fractions BID over 5 treatment days within an overall treatment time of one week (Patients 201-400)

Follow up for first dose level patients will be at 3-5 weeks, at 6-8 weeks, and every 6 months for 5 years, then once every year for 10 years.

Follow-up for second and third dose level patients will be at 3-9 weeks and every 6 months for 5 years, then once every year for 10 years.

TABLE OF CONTENTS

1.0 Introduction

The combination of breast-conserving surgery and radiotherapy, known as "breast-conserving therapy" (BCT), is now widely accepted as a treatment option for most women with clinical Stage I or II invasive breast cancer or ductal carcinoma in situ (DCIS). However, there are few data regarding the optimal volume of irradiation.[2] One question yet unanswered is whether the entire breast needs to be treated, or only a more limited volume surrounding the tumor.

Traditionally, patients undergoing BCT have been irradiated to the entire breast. However, most of the potential long-term complications of BCT result from either whole-breast or nodal irradiation (e.g., cardiac damage, radiation pneumonitis, brachial plexopathy).[5, 6] Further, giving radiotherapy to the entire breast essentially precludes giving further irradiation to that breast should the patient develop a new primary tumor in the same breast.[3]

In addition, the option of partial-breast irradiation (PBI) may lend itself to much shorter treatment schemes than whole-breast irradiation, as the toxicities to the breast should be lessened by treating only a part of the breast. This would make such treatment more convenient for the patient, perhaps allow easier integration of radiotherapy with chemotherapy, and potentially decrease the overall cost of treatment substantially.

1.1 Evidence Supporting the Approach of Partial-Breast Irradiation

There are several lines of evidence suggesting that whole-breast irradiation is unnecessary in a substantial number of patients. It is likely such patients can be defined based on histological and clinical factors:

1) Anatomic data available on the distribution of tumor cells in relation to the index lesion suggests that for most patients the majority of tumor cells in the breast are found quite close to the primary tumor. For patients with invasive ductal cancers, the distribution of cancer cells around the primary tumor mass varies with the histological features of the tumor. Tumors are described as having an "extensive intraductal component" (EIC) when two features were simultaneously present: intraductal carcinoma comprising a prominent portion of the area of the primary mass; and intraductal carcinoma clearly extending beyond the infiltrating margin of the tumor or present in sections of grossly normal adjacent breast tissue.[7] (Predominantly noninvasive tumors, with only focal areas of invasion, are also included in this category.) In a review of 217 mastectomy specimens from patients treated in Nijmegen, the Netherlands, it was found that the presence of an EIC was associated with a substantial likelihood of having residual disease located beyond the boundaries of a cosmetically-acceptable excision in many patients, but in patients without an EIC it was rare for cancer foci to be found more than 2 cm beyond the edge of the tumor mass [8]

2) Similarly, patients who undergo re-excision of the primary site because of initially positive or unknown margin status are more likely to have residual tumor found in the re-excision specimen when the initial excision shows an EIC-positive tumor. [9-13] For example, in a series from the Joint Center for Radiation Therapy (JCRT), the likelihood of finding substantial intraductal cancer in the re-excision specimen was 44% for patients with EIC in the initial excision, compared to only 2% for other patients. In addition, the *quantity* of residual tumor may be substantially greater when the tumor is EIC-positive than when it is EIC-negative. [8, 9]

3) The possibility of patients having multiple synchronous cancers in the breast at the time of initial diagnosis has also been used to justify giving whole-breast irradiation. However, this seems to occur only rarely for patients with *clinically* unicentric cancers. Only 3 patients (1.6%) had multiple lesions without any histopathologic continuity between them in a study of 183 mastectomy specimens of patients with invasive cancers conducted in Tokushima, Japan.[14]

4) Clinical support for these pathologic findings come from the observed patterns of failure within the breast in patients treated with BCT, either with or without irradiation. In the first 5-10 years after BCT with whole-breast irradiation, most recurrences are at or near the original tumor bed, but with increasing follow-up a larger proportion of recurrences are seen in other quadrants of the breast.[3] Similar findings have been noted for patients treated with breast-conserving surgery without irradiation.[15] This suggests that two processes are actually reflected in the observed incidence of breast "recurrence": regrowth of tumor cells left following the initial therapy; and the development of new primary tumors unrelated to the original one.

1.2 Clinical Studies of Partial-Breast Irradiation

1.2.1 Randomized Studies Comparing Partial-Breast Irradiation to Whole-Breast Irradiation

There has been only two randomized trials comparing partial-breast irradiation (PBI) to whole-breast irradiation. The first, conducted from 1982-87 in Manchester, England, randomized 708 evaluable patients to receive irradiation to the entire breast and regional lymph nodes (except the internal mammary chain) without a boost (40 Gy in 15 fractions over 21 days, delivered on a 4-MV linear accelerator without the use of wedges) or treatment to the affected quadrant (40-42.5 Gy in 8 fractions delivered over 10 days, typically using 10 MeV electrons to an average field size of 8x6 cm, prescribed to the 100% isodose) without whole-breast or nodal irradiation.[16, 17] Axillary dissection was not performed, and systemic therapy was not used. Most patients did not have pre- or postoperative mammographic evaluation, and specimen margins were not evaluated microscopically. With a median follow-up of 65 months, the incidences of breast recurrence (with or without simultaneous nodal or distant failure) as a site of first failure by 7 years in the two arms were 7% (26/355) and 14% (51/353), respectively. The 5-year actuarial local recurrence rates were 8% and 17%, respectively; the 7-year rates were 11% and 20%, respectively[17].

The most striking difference between the two arms was seen when comparing the results according to the histology of the tumor. The actuarial 7-year breast recurrence rates for patients with infiltrating ductal carcinomas in the whole-breast arm and in the PBI group were 11% (of 272 patients treated) and approximately 15% (exact number not given; derived from their Fig. 2) (of 262 patients treated). For patients with infiltrating lobular tumors the respective recurrence rates were 8% (of 42 treated patients) and 34% (of 53 patients)[17]. Of note, 64% of the failures in the patients with infiltrating ductal carcinomas in the PBI arm were found in the same quadrant as the primary tumor, compared to only 38% of failures among patients with infiltrating lobular carcinomas on the PBI arm that failed. Patients with a microinvasive ductal carcinoma (i.e., their definition of an EIC-containing tumor) had only a slightly lower risk of failure when treated with the whole-breast technique (3/21 patients, or 14%), compared to the local field technique (5/24, or 21%). A recent abstract has confirmed these results.[18] Of note, the failure rate outside the quadrant of the original tumor for patients with infiltrating ductal carcinomas was only 5.5%.

The second such randomized trial is much smaller and still incompletely reported. Seventy-one patients with

pT1N0-1a breast cancers treated at the National Institute of Oncology in Budapest, Hungary were randomized between whole-breast irradiation (50 Gy) or PBI (using high-dose rate interstitial brachytherapy in 28 patients, giving 7 fractions of 5.2 Gy each, and 7 patients with electrons).[19] At a median follow-up of 16 months, there have been no local or regional failures.

1.2.2 Nonrandomized Studies of Partial-Breast Irradiation

Nearly all nonrandomized studies of PBI have been performed using interstitial implantation of the breast with radioactive sources. Results in these series have varied substantially, probably due to patient selection factors. For example, a pilot study of 27 patients treated at Guy's Hospital, London, using implantation alone with low-dose rate iridium-192 to a total dose of 55 Gy, was reported as resulting in cosmetic results comparable to that of patients treated by an implant (20 Gy) at the time of axillary dissection followed by whole-breast irradiation (46 Gy)[20] The local failure rate was high, being 15% (4/27) at a median follow-up of only 27 months. However, a study performed from 1989-93 in Florence using a similar approach (giving doses of 55-60 Gy delivered in 5-6 days) resulted in a local failure rate of 6% (7/115 patients), with median length of follow-up of 48 months [21] One reason for these differences might be that the microscopic margins of resection were negative in 85% of patients treated in Florence but were not generally examined in the Guy's Hospital study.

The two largest experiences with this approach in North America have been at the Ochsner Clinic in New Orleans and at William Beaumont Hospital near Detroit.

A study of PBI at the Ochsner Clinic in New Orleans assigned patients (initially in a randomized fashion, for the first 50 patients) to treatment either with low-dose rate (LDR) brachytherapy (45 Gy given over 3.5-6 days) or high-dose rate (HDR) brachytherapy (32 Gy in 8 fractions given over 4 days in twice-daily treatments, or more recently 34 Gy in 10 fractions over 5 days). All patients had tumors smaller than 4 cm with negative resection margins. Both node-positive (1-3 positive nodes) and node-negative patients were eligible, as well as patients with ductal carcinoma in situ (DCIS).[22, 23] The brachytherapy target volume included 2 cm of breast tissue surrounding the excision cavity. About half of the implants were placed at the time of excision of breast tissue. A total of 150 patients had been treated since 1991 in their most recent report of this study.[23] With a mean follow-up time of 46 months, there were 2 breast failures (1%) and 4 regional nodal failures (3%). Cosmetic outcome was good or excellent in 75% of patients. Grade 3 toxicities (i.e., requiring surgical correction) of abscess and hematoma (1 patient) and fat necrosis (2 patients) occurred in 3% of the study group; the incidence of asymptomatic or mild-moderate fat necrosis was not stated. In another report of this study, 51 patients treated from 1992-1993, with a median follow-up time of 75 months, were compared to a matched group of patients treated with conventional whole-breast irradiation (plus a boost).[24] The local failure rates in the PBI and conventional groups were 2% and 5%, respectively. The rates of acute reactions were lower in the PBI group, with similar rates of Grade 3 chronic complications (8% in the PBI group and 5% in the conventional group). Cosmetic results were similar in the two groups (good or excellent in 75% and 84% of patients, respectively).

The largest published American series is currently that from William Beaumont Hospital.[24-27] From 1993-2000, 174 patients were treated with PBI (120 with LDR and 54 with HDR brachytherapy) without whole-breast irradiation.[27] All had tumors smaller than 3 cm in size, 0-2 positive axillary nodes, and nearly all had margins of excision greater than 2 mm. Most of the HDR patients received 32 Gy in 8 fractions given twice daily, except for 8 patients treated with 34 Gy in 10 fractions; the LDR patients received 50 Gy. A margin of 1-2 cm of normal tissue around the excision cavity was given at the discretion of the treating physician; the implant

needles came no closer than 5 mm to the skin surface to reduce the risk of skin complications. With a median follow-up of 3 years (and 32 patients followed at least 5 years), there were no local failures. One regional failure occurred (a supra-clavicular failure in a patient with positive axillary nodes; Frank Vicini, personal communication, April 2001.) Among those 89 patients observed at least 36 months, the cosmetic result was excellent or good in 90% of patients, 3 patients (3%) developed breast pain, and 4 patients (4%) had asymptomatic fat necrosis. Of note, the authors performed a matched-pair analysis to patients treated with conventional whole-breast irradiation (including a boost). There were no differences in any outcome measure between these groups.

The Radiation Therapy Oncology Group began a protocol (9517) in 1996 that employs PBI using either HDR or LDR brachytherapy, using the Ochsner Clinic selection guidelines, but in the HDR patients a total dose of 34 Gy in 10 fractions given twice daily was given. This study has closed recently, having met its accrual goal. Results are not yet available.

So far there have been few apparent factors that predict either the risk of recurrence or complications in these studies. As noted above, local and regional nodal failures have been rare, making analysis of such correlations difficult. For example, regional nodal failures occurred in 1/9 node-positive and 2/36 node-negative patients in the Ochsner Clinic series [22]. A recent study from New England Medical Center found an incidence of clinically apparent fat necrosis of 27% (8/30 patients) after a dose of 34 Gy in 10 fractions was given with HDR. They found that the risk of fat necrosis increased with the volume of the breast receiving doses of 3.4, 5.1, and 6.8 Gy/fraction, but they did not report the actual incidences for specific volume ranges.[28] A phase I/II study of 48 patients treated at Massachusetts General Hospital using LDR implants assessed the dose volume relationships of LDR implants. There was a dose escalation from 50 to 55 and 60 Gy, and volumes were in the range of 150-260 ml. The median follow up period for this series was 23 months [29]. Six peri-operative complications occurred (2 had bleeding, 2 had abscesses, one had a hematoma and one had a non-healing sinus tract requiring surgery). There were eight patients who had re-biopsies for abnormal post-treatment mammograms, 3 of them reported fat necrosis. [29].

1.3 Reasons To Perform Partial-Breast Irradiation with External-Beam Techniques Rather than Implantation

Thus, treating only the area adjacent to the primary tumor may be a feasible approach to certain patients with early-stage breast cancer. However, there are substantial reasons why using brachytherapy for such a purpose may be undesirable. Like all surgical procedures, such treatment requires a substantial degree of expertise in order to have good results. The majority of radiation oncologists who treat breast cancer routinely do not perform interstitial implants. There are also stringent quality-control steps that need to be followed for such procedures, which substantially increase the cost of such treatment. Implantation can be performed under local anesthesia with sedation, as well as under general anesthesia, but the need for using an operating room to perform such a procedure brings with it added costs, as well as the possible side effects from the necessary anesthetics. Although uncommon, wound infections, bleeding and similar problems are possible[29]. Finally, such procedures require either a hospital stay (when LDR equipment is used) or multiple hospital visits during which time a patient must continue to have the implanted hollow catheters into which sources are introduced in place (when HDR is used).

In addition, external-beam treatment might have lower toxicity than an implant because of the greater homogeneity of the radiation dose. Implants typically have “hot spots” of 1.5-2 times the minimum target dose, often constituting a fairly large volume of the implant. (For example, in the New England Medical Center

series, patients with fat necrosis had mean volumes of 234 cc receiving 3.4 Gy per fraction, 69 cc receiving 5.1 Gy per fraction, and 21 cc receiving 6.8 Gy per fraction. [28]. In our data with low dose-rate, 3 of 48 patients developed biopsy-proven fat necrosis. [29]. The magnitude of the hot spots with external-beam PBI should be much smaller. Most radiation oncologists believe that the magnitude of the hot spots is what tends to cause the complications.

Therefore, our goal originally was to conduct a study of the feasibility of performing PBI in a selected patient population with external-beam radiotherapy, using 3D-conformal radiotherapy techniques and CT-guided planning that are widely available to and used by radiation oncologists in both academic and community settings. If successful, this approach would provide a readily exportable treatment technique that could be tested against conventional whole-breast irradiation in a randomized trial.

We have accrued 100 patients for the 32 Gy / 8 fractions level in about 2 years and we did not have significant toxicity at 1-year follow-up, which would require the protocol to be closed. We have gained more experience. We believe that the approach we used will provide a readily exportable simple treatment technique that could be tested against conventional whole-breast irradiation in the randomized trial. This study is conducted in the member hospitals of the Dana-Farber/Harvard Cancer Center and Boston Medical Center.

After showing that the technique we used is feasible, our goal is to estimate the optimal radiation dose, which could be used in PBI with the least possible toxicity. Therefore, we started escalating the dose from 32 Gy / 8 fractions, into 36 Gy and 40 Gy in 9 and 10 fractions, respectively (see rationale for dose escalation in section 1.5.2.). At this time, we have accrued 100 patients to the second cohort and 94 patients to the third cohort. We have not seen any significant toxicity from the 40 Gy / 10 fractions requiring the protocol to stop abruptly. We will increase the number of the third cohort from 100 to 200 patients and our primary endpoint of this expanded cohort will be limited to fat necrosis requiring surgery within 3 years of protocol registration. For analyzing this endpoint, all patients who receive 40 Gy (200 patients) will be considered. For details see statistical section (Section 10.0)."

1.4 Video based PBI setup:

This parallel study is not mandated by the protocol and patients will have the choice to participate. This study has been in progress under IRB protocol number 2002p001118 "Quantifying daily patient set-up variations in external beam radiotherapy with Video Images: PI: Dr. George Chen". Briefly, the goal of video based patient setup study is to evaluate ways to improve accuracy of radiation delivery. This is particularly relevant to partial breast irradiation where dose per fraction is larger, radiation portals are smaller, and fewer fractions are given relative to whole breast treatment. This is why we decided to include this study within this protocol.

We have access to a new three-dimensional surface imaging technology that measures the coordinates of the patient surface. By comparing the surface at time of treatment with a reference surface, we can quantify the degree of surface misalignment; the method can also be used to monitor breast surface motion during light breathing, and during treatment. The system does not utilize ionizing radiation. A flash digital image (or video) is taken, and software determines the couch coordinate moves needed to bring the surface on the treatment image into congruence with the reference image of the breast. The system has been extensively tested and is accurate with less than a millimeter and a degree on phantoms.

In the proposed implementation, an image is taken before treatment and at various times during treatment to acquire surface images of the treated breast. These are analyzed to determine variations relative to a reference

surface. If in patients, it is shown that this method is more accurate and reliable than conventional alignment techniques, the method will be adopted as the standard for PBI treatment after approval. The Video based set up study will be not mandated by the protocol.**1.5 Rationale For the Current Study Design**

1.5.1 Patient Selection

To limit the risk of local failure with PBI, it seems desirable to choose patients with tumors that are limited in their spread beyond the index lesion. Infiltrating ductal carcinomas without an extensive intraductal component (EIC) are likely to meet this criterion. The risk of local recurrence should be very low in this population, based on the data presented above. In addition, for such a pilot study we would like to avoid patients with tumors where there may be increased risks of chest-wall, skin, or regional nodal recurrence if these sites are not fully irradiated. Thus, patients with primary tumors with lymphovascular invasion (LVI) or with positive axillary nodes (other than pN0i+ tumors) are excluded. Finally, the cosmetic results of PBI may suffer and complication rates increase if too large a volume is treated. Hence, we have excluded patients with tumors larger than 2 cm.

Some patient groups appear to have low rates of regional nodal failure when specific axillary treatment is not used. In a recent study by Hughes *et al* [30], women 70 years of age or older and who had clinical stage I (T1N0M0) ER+ breast carcinoma treated by lumpectomy were randomized to receive tamoxifen plus radiation therapy or tamoxifen alone. The only significant difference between the two groups was in the rate of local or regional recurrence at five years (1 percent in the group given tamoxifen plus irradiation and 4 percent in the group given tamoxifen alone, $P<0.001$). Therefore, this population should be good candidates for PBI. Another such population is patients who have sentinel node biopsies in which tumor cells can be detected on immunohistochemical staining, but not on conventional H&E staining. For example, in a series from the John Wayne Cancer Institute in Santa Monica, none of 33 patients with micrometastases detected only by immunohistochemistry had further axillary involvement, compared to 14% (5/36) of patients with micrometastases determined by conventional light microscopy [31]. We will therefore include these patients (assuming the tumors cells span <0.2 mm; i.e., pN0i+).

We also believe that patients with ductal carcinoma in situ (DCIS) without invasion may be suitable candidates for this approach. There are both anatomical and clinical lines of evidence suggest that whole-breast irradiation is unnecessary in a substantial number of patients with DCIS: 1) Studies of the distribution of tumor cells in relation to the index lesion suggests that for most patients the majority of tumor cells in the breast are found quite close to the primary tumor. Holland found true multicentric disease (unconnected lesions) in only 1 of 82 cases.[8] Work performed in Osaka has also shown that, even when DCIS appears to be spread widely through the breast, such lesions are monoclonal.[32] In another study, "multicentricity" was much more frequent when the index lesion was more than 2.5 cm in size (13/25 cases, or 52%) than for smaller ones (4/29 cases, or 14%).[33] Since the theoretical likelihood of developing multiple independent tumors in the breast should not depend on the size of the index lesion, these results support Holland's conclusions that nearly all such cases represented clinically unappreciated spread from a single lesion. 2) Clinical support for these pathologic findings come from the observed patterns of failure within the breast in patients treated for DCIS with BCT, either with or without irradiation. The majority of failures are at or near the original tumor bed [34 35 36, 37 38 39](see the Table 1 below). This suggests that two processes are actually reflected in the observed incidence of breast "recurrence": regrowth of tumor cells left following the initial therapy; and the development of new primary tumors unrelated to the original one. The latter appear to be rare.

Table 1: Sites of IBTR after BCT for DCIS

Series	#	FU(mo)	TR/MM	E	Ref
Harvard - No RT[34]	157	40	6%	2%	[34, 40-42]
JCRT - No RT[35]	57	96	14%	3%	[35]
JCRT - RT[35]	76	74	8%	1%	[36]
William Beaumont - RT}[37]	148	86	8%	2%	[39]
Institut Curie - RT[38]	343	92	7%	4%	[38]
Collaborative Study - RT[39]	422	113	7%	3%	[43]

Abbreviations: BCT - breast-conserving therapy; IBTR - ipsilateral breast tumor recurrence; TR/MM - true recurrence or marginal miss; E - elsewhere in the breast; FU - length of follow-up; JCRT - Joint Center for Radiation Therapy; RT - radiotherapy.

Hence, we feel patients with DCIS can also be included in our study. (These patients are also included in the randomized trial organized by the Radiation Therapy Oncology Group and National Surgical Adjuvant Breast and Bowel Project NSABP B-39 comparing PBI and whole-breast irradiation, which has opened in Spring 2005)

1.5.2 Rationale for Dose-Escalation:

The optimal dose used in PBI has yet to be defined. Due to the lack of clinical experience, investigators have used different doses based on mathematical calculations and modeling of biological effective doses [44]. For instance, in patients where HDR interstitial implant was used, Vicini *et al* from William Beaumont Hospital used 4 Gy X 8 BID over 4 days [27], Perera *et al* from London Ontario used 3.72 X 10 BID over 5 days [45], RTOG 95-17 used 3.4 Gy X 10 BID over 5 days [46], Douglas *et al* from Virginia University used 3.4 Gy X 10 BID over 5 days [47] and Polgar *et al* from the National Institute of Oncology in Hungary used 4.33Gy X 7 and 5.2 Gy X 7 in phase I/II and 5.2 Gy X 7 in phase III [19, 48, 49]. Using the Mammosite HDR technique, Keisch et al used 3.4Gy X10 BID [50].

Regarding the use of external radiation in PBI, Veronisi *et al* from the European Institute of Oncology used IORT (Intra-Operative Radiation Therapy) of 21 Gy in single fraction using electron beam therapy [51], Magee *et al* from the Christie Hospital have used a dose of 5 Gy X 8 in 10 days, using a single electron beam [52]. Using the 3-D conformal technique, which is similar to ours, Vicini *et al* from William Beaumont Hospital used 3.85Gy X10, BID over 5 days [53]. Formenti *et al* from NYU used a different fractionation, delivering 6 Gy X 5 fractions QD over 10 days using a prone technique [54]. Each of these different fractionations and radiation doses has a different biological effective dose (BED)[44].

Therefore, the optimal radiation dose, which should be used in PBI, is not yet known. Furthermore, the NSABP B-39 is starting a large randomized trial, which should accrue 3,000 patients. Patients will be randomized between 6 weeks of whole breast radiation versus 4-5 days of partial breast irradiation. The inclusion criteria for this trial are different to ours. It should be noted that the dose used in this trial when 3-D conformal techniques are used is 3.85 Gy X 10 fractions BID over 5 days for a total dose of 38.5 Gy in 5 days, which is around 20% higher compared to our original dose of 32 Gy over 4 days. Therefore, in order to investigate the optimal radiation dose, a dose-escalation study is needed. We are proposing an escalation using

three-dose level: 32 Gy in 8 fractions BID (4 days) for which 85% of the accrual is complete at this point, 36 Gy in 9 fractions BID (4 ½ days) and if toxicity stays acceptable, 40 Gy in 10 fractions BID (5 days). For details see statistical section.

2.0 Objectives

2.1 Primary Objective

To evaluate the feasibility of PBI directed XRT in selected stages 0 and I female breast cancer patients within each dose level. The study will be deemed infeasible if the total percent of patients who have at least one of the following outcomes is large:

a) Within 1 year of protocol registration, the patient develops histological fat necrosis or other grade 4 skin or grade 4 subcutaneous toxicity, or requires surgery for her skin or subcutaneous toxicity

b) Within 1 year of protocol registration, the patient develops any breast cancer recurrence or for any reason has additional ipsilateral breast surgery or other ipsilateral breast treatment

c) Within 1 year of protocol registration, the patient dies from causes judged to be related to her treatment.

d) Within 3 years of protocol registration, the patient treated with 40 Gy develops fat necrosis requiring surgery.

2.2 Secondary Objectives

2.2.1 To evaluate the rate and severity of cutaneous toxicity

2.2.2 To evaluate the risk of breast fibrosis and fat necrosis

2.2.3 To evaluate cosmetic outcome

2.2.4 To evaluate patient satisfaction

2.2.5 To evaluate local control rates, locations, and type of local failures (local control for patients with DCIS will be analyzed separately from those of patients with invasive cancer)

2.2.6 To evaluate distant control rates

3.0 Eligibilty

The following are the eligibility criteria for this study. They may not be waived by the study chair, and are eligible for review in case of an audit.

3.1.1 Histologic Documentation: Patients will have histologically confirmed ***Unicentric*** **Stage I** (T1 N0 M0) Invasive Ductal breast cancer. Histologically negative tumor margin 2 mm or more from any inked edges, or no tumor in a re-excision specimen or final shaved specimen. Tubular, Mucinous and Medullary variant histologies of infiltrating ductal carcinoma are permitted. Lobular histologic features are permitted if the final classification is ductal. DCIS (Grades I and II using the Van Nuys classification.[55]) of $\leq$ 2 cm on pathology and/or mammogram with histologically negative margins of at least 2 mm (or a negative re-excision) is permitted. Gross disease must be unifocal $\leq$ 2.0 cm in one quadrant on pathology and/or mammogram and at the physician's discretion. DCIS on core biopsy with a negative excision is permitted. Women age 70 years or older with T1 invasive ductal carcinoma which are estrogen-receptor positive (ER+) with clinically negative axillary nodes who do not undergo surgical lymph node evaluation are also eligible if patient will take hormonal therapy. Patients with T1N0 (i+) tumors on sentinel lymph node mapping or dissection (i.e. if tumor deposit is 0.2mm or less, regardless of whether the deposit is detected by IHC or H&E staining) will also be eligible.

3.1.2 Prior Treatment: Patient may have been treated with adjuvant chemotherapy; please ensure that enrollment will not make the patient ineligible from previously enrolled adjuvant therapy trials (Such as CALGB or Cooperative Group Trial). Patients may be on adjuvant hormonal therapy or begin hormonal therapy following XRT at the discretion of the Medical Oncologist. Radiation therapy should begin within:

- 4-12 weeks from definitive surgical procedure
- 2-6 weeks after chemotherapy, if chemotherapy given first
- Radiation cannot be delivered concurrently with chemotherapy

3.1.3 Age $\geq$ 18 years of age

3.1.4 ECOG Performance Status 0

3.1.5 Required Initial Laboratory Data prior to the beginning of therapy, for patients treated with adjuvant chemotherapy.

Granulocytes	$\geq$1,500/µl
Platelet count	$\geq$100,000/µl

3.1.6 Signed Informed Consent

3.2 EXCLUSION CRITERIA

The following guidelines are to assist physicians in selecting patients for whom protocol therapy is safe and appropriate. Physicians should recognize that **the following may seriously increase the risk to the patient entering this protocol and should not be considered to participate (ineligible)**:

3.2.1a Multicentric IDC of the breast defined as discontiguous tumors separated by at least 5 cm of uninvolved tissue; alternatively, discontiguous tumors that are clinically or mammographically within separate breast quadrants or subareolar central region.

3.2.1b Multifocal IDC of the breast, defined as discontiguous discrete foci of invasive carcinoma, separated by uninvolved intervening tissue, but within an overall span of 5cm, or within the same breast quadrant or subareolar central region.

3.2.2 Tumor > 2.0 cm, nodal involvement (> 0.2 mm), or metastatic involvement

3.2.3 Histological evidence of:

Lymphovascular invasion (LVI): Cases with convincing lymphatic invasion are excluded. *Cases termed focally suspicious for LVI but where no definitive LVI is found are considered eligible.*

Blood Vessel Invasion (BVI)

EIC (Extensive Intraductal Component): *defined as the presence of intraductal carcinoma both within the primary infiltrating ductal tumor (comprising at least 25% of the tumor area) and intraductal carcinoma present clearly beyond the edges of the invasive tumor, or as a predominantly intraductal tumor with one or more areas of focal invasion*[7, 56].

Invasive Lobular Carcinoma and infiltrating carcinoma of mixed ductal and lobular type. Note that cases with ambiguous histologic features which can be classified as entirely ductal through the use of E-cadherin immunohistochemical staining are considered eligible[57,58].

DCIS with microinvasion, and DCIS suspicious for microinvasion are also excluded

Infiltrating micropapillary carcinoma

Margins: *In-situ or invasive* carcinoma present *less than* 2 mm from the inked resection margin.

3.2.4 Known mutation carrier, including BRCA1 and BRCA2

3.2.5 History of cosmetic or reconstructive breast surgery

3.2.6 Psychiatric illness which would prevent the patient from giving informed consent

3.2.7 Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or connective tissue diseases (lupus, systemic sclerosis or other collagen vascular diseases) which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.

3.2.8 Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and considered by their physician to be at less than 5% risk of relapse within three years.

3.2.9 Patients with diffuse (> 1 quadrant or > 5cm) suspicious microcalcifications

3.2.10 Women who are pregnant

4.0 Patient Entry

4.0.1 Recruitment Methods: Patients will be recruited from the clinics of participating surgeons, medical and radiation oncologists. There will be no advertising or remuneration.

4.0.2 Registration, Stratification, Data Submission, And Modality Review

- **Informed Consent:** the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. (Human protection committee approval of this protocol and a consent form is required.)
- **Registration** To register/randomize a patient on a protocol, contact the AQACT, 375 Longwood Ave, Suite L7 Tel.(617) 632-3761, FAX (617)-632-2295 **before treatment begins*** Monday – Friday 9am – 5pm**.** Any patient not registered to the protocol before treatment begins will be considered ineligible; registration will be denied. The QACT will ask for the following information:
  - ✓ Your name, telephone number and pager #
  - ✓ Protocol name and number
  - ✓ Date treatment begins
  - ✓ Patient name, address, date of birth, and diagnosis
  - ✓ Patient ID number
  - ✓ Treating Physician
  - ✓ Primary treatment institution
  - ✓ Confirmation of eligibility (checklist when applicable)
  - ✓ Copies of Consent Form
  - ✓ Verify that the Consent Form is signed

5.0 Treatment Program/ Radiotherapy

5.0.1 Partial Breast Irradiation: 32 Gy in 8 fractions or 36 Gy in 9 fractions or 40 Gy in 10 fractions, given ***twice daily*** over 4-5 treatment days and 1 week period.

- **Equipment**

- ◊ **Modality:** Any combination of photon beams of energy 4 MV or higher, with or without the addition of electrons of any energy, may be used for treatment provided the dosimetric requirements of adequately treating the planning target volume of homogeneity are met. (Examples include mini-tangents plus en-face photons, mini-tangents plus en-face electrons, or wedge-pair photons plus en-face electrons or photons.) Mixed modality using photons / electrons to minimize the dose received to the lungs are strongly encouraged. Intensity-modulated radiotherapy (IMRT) and proton beam may be used. Please refer to Appendix 1 for examples.
- ◊ **Energy:** As above.

- **Planning Target Volume –** Tumor bed plus 1.5 – 2.0 cm lateral margins; from 5 mm below the skin surface of the chest wall
- **Treatment Dose-** 32 Gy in 8 fractions, given twice daily over 4 days and 1 week overall time, 36 Gy in 9 fractions, given twice daily over 4 ½ treatment days and 1 week overall time or, 40 Gy in 10 fractions over 5 treatment days and 1 week overall time. There must be a minimum ***interval between fractions of at least 6 hours*** (For example, patient may receive the first treatment each day at 8AM and the second at 2PM). Treatment may be started on any day of the week.
  - ◊ **Prescription Point:** The minimum isodose line that completely encompasses the planning target volume. Inhomogeneity corrections are to be used.
- **Time-Dose Considerations:**
  - ◊ Dose per Fraction**:** 4 Gy to the prescription point
  - ◊ Deliver Two Fraction per Day
  - ◊ Total Elapsed Time: 4 to 7 days
- **Homogeneity and Reference Points**
  - ◊ The dose within the PTV must be within 100-115% of the prescribed dose
  - ◊ The change in dose from minimum to maximum within the treatment volume will be < 15%
- **Dose Restraints for Ipsilateral and Contralateral Lung Volume**

  ◊ **Ipsilateral Lung:**

  Volume receiving 20 Gy should not exceed 3%.

  Volume receiving 10 Gy should not exceed 10%.

  Volume receiving 5 Gy should not exceed 20%.

  ◊ **Contralateral Lung:**

  Volume receiving 20Gy should not exceed 1%.

  Volume receiving 10Gy should not exceed 2%.

  Volume receiving 5Gy should not exceed 3%.
- **Treatment Technique**
  - ◊ Treatment planning may be performed at any time **after** consent and registration.
  - ◊ Treatment **must** be performed using CT-Guided planning with the capability of performing true 3-dimensional reconstruction.

◊ The radiation oncologist will identify the tumor bed by noting contrasting areas of density as well as the presence of clips in the breast. The use of intravenous contrast for this purpose is optional, at the discretion of the treating physician.

5.1 Dose Adjustments/Delays/Modifications/Removal from study

5.1.1 **Treatment Breaks/Interruptions:** Radiotherapy is given in continuous course. It is not anticipated that treatment breaks should be needed. If a break seems necessary or must be given due to unavoidable medical necessity (i.e., intercurrent illness), the situation should be discussed with Dr. Alphonse Taghian or Dr. Abram Recht.

5.1.2 **Removal From Study**: Dr. Taghian or Research Nurse Manager Karleen Habin, RN (617-726-1922) or CRA Laura Cerroni (617-643-0056) should be notified within 48 hours by telephone or e-mail and within 7 working days by writing of the removal of a patient from protocol.

5.1.3 **Inability to Adequately Perform Treatment Planning**: If the radiation oncologist cannot adequately identify the tumor bed or is otherwise unable to devise a dosimetrically-satisfactory treatment plan, then the patient will be removed from study.

5.1.4 **Recurrence During Treatment**: Any evidence of local, regional or distant recurrence during the period of therapy will result in removal from study. Further, local-regional and systemic therapy will be at the discretion of the attending physicians. Patients who develop recurrence subsequent to the completion of the treatment program will be managed as deemed appropriate by the attending physicians.

5.1.5 **Undue Toxicity**: Refer below. Treatment may terminated prior to its planned completion should the attending physicians feel that the patient is suffering undue toxicity. Such situations should be discussed with Dr. Taghian or Dr. Recht before removing the patient from study.

5.1.6 **Patient Refusal to Continue Treatment**: A patient may withdraw her consent to participate at any time. In this case, alternative therapy, or no further therapy, may be given at the discretion of the attending physician.

5.2 Adverse Events

5.2.1 **Anticipated Toxicity:** Erythema and dry desquamation in the radiation fields are anticipated to occur commonly. Some patients may develop a moist desquamation, which usually heals within a few weeks. Cellulitis is rare, however.

5.2.2 **Toxicity Management:** Appropriate medical care should be given according to standard practices

5.2.3 **Dose Modification**: Refer above

6.0 Adverse Event Reporting:

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE (Adverse Event) or SAE (Serious Adverse Event) as provided in this protocol. During the study, when

there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

6.1 Definition of Adverse Event: An adverse event is any untoward medical occurrence in a patient or trial subject that is administered a drug or biologic agent (medicinal product) or that is using a medical device; the event does not necessarily have a causal relationship with that treatment or usage. Adverse events include the following:

- Significant or unexpected worsening or exacerbation of the condition/indication under study
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New Conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study
- Signs, symptoms or clinical sequelae of a suspected reaction

6.2 Reporting Adverse Events

6.2.1 Reporting Acute and Sub-acute Noncutaneous Toxicity: Any acute or subacute noncutaneous toxicity of grade 2 or higher according to the NCI Common Toxicity Criteria version 3.0 should be reported within 48 hours by telephone and within 7 working days in writing (by mail, fax or e-mail)

To:

Alphonse Taghian, MD, PhD
Department of Radiation Oncology
Massachusetts General Hospital
Cox 3 Room 302
100 Blossom Street
Boston MA 02114
Phone: 617-726-6050
Fax: 617-726-3603
Email: ataghian@partners.org

Marissa Frongillo
Cancer Center Protocol Office
Massachusetts General Hospital
326 Cambridge Street 2nd Flr
Boston, MA 02114
Phone: 617-724-7578
Fax: 617-726-4319
Email: mfrongillo@partners.org

6.2.2 Chronic Toxicity: Any chronic toxicity of the skin or subcutaneous tissues of grade 4 or higher or the development of fat necrosis (see

APPENDIX 2) or other complication requiring surgery should be reported to Dr. Taghian within 48 hours by telephone and within 7 working days.

6.2.3 Poor Cosmetic Results: Any fair or poor cosmetic results (see APPENDIX 3) should be reported to Dr. Taghian within 48 hours by telephone and within 7 working days in writing the first time that this is observed.

6.2.4 Reporting Events to the Office for the Protection of Research Subjects (OPRS): The following events need to be reported to the Dana Farber Cancer Institute Institutional Review Board (IRB):

- Grade 2 (moderate) and Grade 3 (serious events) – Only events that are Unexpected and Possibly, Probably, or Definitely Related/ Associated with the Intervention (PBI)
- All Grade 4 (life-threatening) events – unless mentioned otherwise in this protocol
- All Grade 5 (fatal) events – When the patient is enrolled and actively participating in the trial or when the event occurs within 30 days of the last study intervention

6.2.4.1 Full written SAE report must be submitted to OPRS as soon as possible, but no later than 10 working days from notification of the event.

6.2.4.2 If the patient is in long-term follow up, death may be reported at the time of continuing review.

7.0 Required Data

	Prior to Registration	Post-registration	Baseline[6] evaluation	Post-Treatment[5]	Follow up[4, 7]
Tests & Observations				Week 4-9	
History and Progress Notes	X			X	Q 6 mos x 5 yrs then q 1 yr for 10 yrs
Physical Examination	X		X	X	Q 6 mos x 5 yrs then q 1 yr for 10 yrs
Performance Status	X				
Radiotherapy Toxicity Assessment (see Appendix)	X		X	X	Q 6 mos x 5 yrs then q 1 yr for 10 yrs
Simulation/Positioning Photo	X				
Cosmetic Outcome Assessment (see Appendix)	X		X[4]	X[4]	Q 6 mos x 5 yrs then q 1 yr for 10 yrs[8]
Staging					

Bilateral Mammogram	X[1]				At 6 months post-XRT and Q 1 yr for 15 years
Breast MRI	X[2]				X[9]
Histologic Review	X[3]				

1. Recommended, but not required, to obtain post surgical mammogram if calcifications involved in primary diagnosis or wire localization required as part of surgical procedure
2. Recommended, but not required, breast MRI before treatment to rule out occult malignancy.
3. For outside pathology
4. By a medical provider
5. An early follow up at 3-4 weeks could be done to evaluate the skin reaction and the cosmetic results. This is not mandated by the protocol.
6. Baseline evaluation: Could be done either before or within the treatment period (till last day of treatment)
7. A 2-month window period is permitted for each 6 month follow up assessment, and a 3-month window period is permitted for each 12 month follow up assessment; however, this time point does not have to be from the completion of PBI. This will ensure that subjects are seen twice annually, but will ease the schedule to accommodate changes in scheduled appointments.
8. If the patient evaluation of cosmetic outcome form is missed or cannot be completed during a follow up visit, the form can be mailed to the patient. Alternatively, the form can be completed by the clinical research coordinator or designated study staff during a phone call to the patient.
9. MRI may be substituted for mammography. This will be left at the discretion of the treating physician.

7.1 Follow-up Mammograms

Patients will have the first follow-up bilateral mammogram at 6 months (+/– 3 months) following the completion of their radiation therapy and then bilateralmammograms yearly. Breast MRI can be substituted for one of the bilateral mammograms. This decision will be made at the discretion of the treating physician.

Data Submission: Forms should be submitted to QACT at the Dana Farber Cancer Institute in compliance with the Data Submission schedule below.

- The original forms must be mailed to the QACT

Form		Submission Schedule
	On-Study Form	Within 14 days of patient entry
	During Treatment	After completion of therapy
	Cosmetic Outcome	• Baseline (pre-treatment or within treatment period) • 3-4 weeks post treatment (not mandated) • First evaluation (within 3-9 wks) after treatment • q 6 months for 5 years and q 1 yr for 10 years after treatment
	Radiation Data	• RT 1 Form at completion of Simulation • RT 2 and RT3 (Radiation, Physics and Dosimetry) Forms at completion of therapy • DVH graph to PI[1]
	F/U Data[2]	• Every 6 mos yr 2-5 • Yearly after year 5

1.DVH (dose-volume histogram) graph should include DVH for lungs, heart, GTV, PTV, and non-target breast tissue (whole breast minus PTV) and whole breast (see forms RT3 or Dosimetry form).
2. The Mammography form should be submitted every 6 months to capture the results from each mammogram for the first 5 years then yearly after that.

8.0 Modality Review/Quality Assurance and Documentation:

- The treatment plan will be approved prior to the start of radiation therapy by the site-specific PI (Dr. Taghian for MGH and BMC, Dr. Recht for BIDMC, or Dr. Harris for BWH/DFCI).

- Submit copies of the following to the site PI (Alphonse Taghian, MD, PhD, at MGH or Abe Recht, MD, at BIDMC) upon completion of treatment to

Alphonse Taghian, MD, PhD, Department of Radiation Oncology, Massachusetts General Hospital Cox 3 Room 302, 100 Blossom Street, Boston MA 02114. Phone: 617-726-6050 Fax: 617-726-3603 email: ataghian@partners.org

Abe Recht, MD, Department of Radiation Oncology, Beth Israel Deaconess Medical Center, Department of Radiation Oncology, East Campus, Finard Building B25, 330 Brookline Avenue, Boston, MA 02215.
Phone: 617-667-2345 Fax: 617-667-4990 email: arecht@bidmc.harvard.edu

- Final approved RT plan (including axial, sagittal and coronal cuts at the isocenter), also dose-volume histograms of the target volume, ipsilateral and contralateral lungs, heart (for both sides), PTV,

GTV (seroma), and non-target breast tissue (breast minus PTV), whole breast. *(*A copy of these records should also be sent to the overall PI Dr. Alphonse Taghian, MD, PhD at MGH).*

- Radiotherapy Initial Report Form (RT-1).
- Radiotherapy Total Dose Record (RT-2).
- Radiotherapy Physics/Dosimetry Record (RT-3).
- Treatment record (show daily doses).

- Note: If Polaroid or other photographic process for the duplication of localization and verification films is employed, ensure that these images are of sufficiently good quality for review. Photograph these films at a sufficiently close distance to ensure that the portal (or verification) film fills the entire Polaroid print.
- Direct questions regarding dose calculations or documentation to: Alphonse Taghian MD, PhD (617)-726-6050 or Abram Recht, MD (617)-667-2345.
- Direct questions regarding the radiotherapy section of this protocol to: Alphonse Taghian MD, PhD (617)-726-6050 or Abram Recht, MD (617)-667-2345.

9.0 Dose Modifications And Management of Toxicity

9.1 Hypersensitivity Reactions: Radiotherapy is given in continuous course. It is not anticipated that treatment breaks to the breast should be needed. If a break seems necessary the situation should be discussed with Dr. Recht or Dr. Taghian.

9.2 If a break must be given due to unavoidable medical necessity (i.e., concurrent illness), please discuss with Dr. Taghian or Dr. Recht.

9.3 Anticipated Toxicity and Adverse Reactions: Erythema and dry desquamation in the radiation fields are anticipated to occur commonly. Some patients may develop moist desquamation, which usually heals within a few weeks. Cellulitis is rare. Appropriate nursing care for this should be given according to standard practices. Should a prolonged treatment break seem necessary (refer above), the situation should be discussed with Dr. Recht or Dr. Taghian. Some patients may have mild tenderness in the treated area.

10.0 Accrual Goal and Statistical Power:

The primary objective of this study remains to determine if accelerated partial breast irradiation is feasible in this patient group. However, this feasibility will now be determined based on events occurring to the patient within 1 year of registration, rather than within 3 years. (See the Introduction for justification of this decision.) The design is also being changed to include accrual at three dose-levels (32 Gy, 36 Gy, and 40 Gy). In addition, accrual used to be 40 patients per year, but since APBI has been widely-publicized, the accrual rate became around 40-50 patient per year in this last year and is expected to increase possibly more than 50 patients per year when the consensus statement is published.
The original statistical design of this study was based on a single radiation dose, using a two-stage design, with a maximum of 34 patients to be entered on the first stage and a maximum of 66 patients on the second stage. There was no pause after the first stage of accrual, but the study was to be stopped at any time that 5 patients of the first 34 entered were noted to have a bad event (defined below) or at any time that 9 patients (entered in

either stage) had been noted to have a bad event. Using this design, there was a 59% chance of terminating accrual during the first stage if the true rate of a bad event is 15% and a 9% chance if the true rate of a bad event is 7%. There was a 5% chance of deeming the treatment feasible if the true rate of a bad event is 15% and an 80% chance if the true rate of a bad event is 7%. We have not yet had 34 patients followed for at least 1 year on the first dose (this will occur in July 2005), and at this early time there is no reason to think that the 32 Gy dose is associated with unacceptable toxicity.

A dose level will be deemed infeasible if too many patients have at least one of the following outcomes:

a) The patient has a breast cancer recurrence (local, regional, or distant) within 1 year of protocol registration (since this will necessitate her removal from study, see section 5.1.4).
b) The patient dies from causes judged to be related to her treatment within 1 year of protocol registration.
c) The patient develops fat necrosis or other grade 4 skin or grade 4 subcutaneous toxicity or requires surgery for her skin or subcutaneous toxicity within 1 year of protocol registration.

In the rest of this section, a patient who has at least one of these 4 outcomes is said to have "a bad event."

We will continue to use a two-stage design for each of the three dose-levels. With the increased accrual rate, at the time the decision has to be made on whether to increase the dose level, there will be 50 patients who have been followed for at least 1 year. We have therefore changed the size of the first stage of accrual to 50 patients (and made the size of the second stage 50 patients, in order to keep the maximum number of patients at each dose-level at 100).

Since the decision to increase the dose will be based on the results in the first 50 patients, and since higher doses might have higher toxicity rates, we have also changed the probabilities of the null and alternative hypotheses for the first two doses to 13% and 5%, respectively. For the third and final dose-level, the null and alternative hypotheses are unchanged at 15% and 7%, respectively.

Even the one-year period needed to observe the patient for fat necrosis or other grade 4 skin or grade 4 subcutaneous toxicity remains too long to pause accrual after the first stage of a two-stage design. However, we will continue to keep the provision to stop the study as soon as an unacceptable number of patients with a bad event have been observed. In addition, if at any time (during either its first or second stage of accrual) the toxicity rate at a dose is found to be unacceptable (based on follow-up of 1 year or longer), accrual to any higher dose will also terminate.

For each of the first two dose levels (32 Gy and 36 Gy), accrual will be terminated at any time there has been 5 patients with a bad event among the 50 patients entered on the first stage of each dose level. For the second stage of each of these dose levels (that is, after the first 50 patients have been accrued), accrual will be terminated at any time that there have been a total of 8 patients with a bad event on this dose. With this design, there is an 80% chance of terminating accrual to this dose (and the entire protocol) early if the true probability of a bad event with this dose is 13%, and a 10% chance if the true probability of a bad event on this dose is 5%. There is a 4% chance of deeming the dose level feasible if the true probability of a bad event on this dose is 13%, and an 83% chance if the true probability of a bad event on this dose is 5%.

For the third (and final) dose level, accrual will be terminated at any time there has been 6 patients with a bad event among the 50 patients accrued during its first stage. During the second stage, accrual will be terminated at any time there have been a total of 9 patients with a bad event on this dose. With this design, there is a 64% chance of terminating accrual early on this dose if the true probability of a bad event on this dose is 15%, and a 6% chance if the true probability of a bad event on this dose is 7%. There is a 5% chance of deeming this dose level feasible if the true probability of a bad event on this dose is 15%, and an 82% chance if the true probability of a bad event on this dose is 7%.

There could be an interim analysis of the events when the first 50 patients for each dose level (the 36 and 40 Gy) have been followed for at least 1 year.

At this time, the number of patients in the third cohort will be increased from 100 to 200 patients. All patients in this cohort will be treated with the same dose as the third cohort (40 Gy). For analyzing our endpoints, all patients in the third cohort will be combined (for a total of 200 patients). Our primary endpoint for this expanded cohort will be limited to fat necrosis requiring surgery within 3 years of protocol registration.

We expect that 90% of the 200 patients will be available for assessing fat necrosis for 3 years after registration (with the remaining 10% having a recurrence, developing metastases, dying, or being lost to follow-up before the end of 3 years). If more than 5% of the 180 patients (i.e., more than 9 patients) have fat necrosis requiring surgery by 3 years after registration, then the dose of 40 Gy will be considered too toxic. Using this design, if the true probability of this toxicity is 3%, then there will be a 0.05 chance of declaring this dose too toxic; if the true probability of this toxicity is 9% then there will be a 0.97 chance of declaring this dose too toxic.

If none of the 180 patients have this toxicity, the 95% confidence interval (CI) for the probability of fat necrosis requiring surgery will be 0 to 1.7%; if 9 of the 180 patients have this toxicity, a 95% CI will be 2.3 to 9.3%.

The old stopping rule (based on bad events occurring within the first year after registration) will still be in force for the third cohort (these patients have not all yet been followed for a year). That is, all accrual to this protocol will end if 6 or more of the first 50 patients in the third cohort have a "bad event" within a year of protocol registration or if 9 or more of the 100 patients in the third cohort have a "bad event" within a year of protocol registration.

There could be a first interim analysis of the events when the first 50 patients for the 40 Gy dose level have been followed for at least 1 year. Other analysis can follow if the information is deemed by the PI as worthwhile to be published.

11.0 Accrual Rate:

This study has been designated by the Dana Farber/Harvard Cancer Center (DF/HCC) as a rapidly accruing study. We expect an average of 40-50 patients per year to enter this study. If accrual in any 12-month period drops below 20 patients, we will consider terminating the study for lack of accrual.

References

1. Hetelekidis S, Schnitt, S., Silver, B., Manola, J., Bornstein, B., Nixon, A., Recht, A., Gelman, R., Harris, J., Connolly, J. The significance of extracapsular extension of axillary lymph node metastases in early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 2000;46:31-34.

2. Recht A. Breast carcinoma: in situ and early-stage invasive cancers. In: Gunderson LL TJe, editor. Clinical Radiation Oncology. New York: Churchill Livingstone; 2000. pp. pp 968-998.

3. Recht A, Come, SE, Troyan, S, et al:. Local-regional recurrence after mastectomy or breast-conserving therapy,. In: in Harris JR LM, Morrow M, et al (eds), editor. Diseases of the Breast (2nd ed.). Philadelphia: Lippincott Williams & Wilkins; 2000. pp. pp 731-748.

4. Pierce S, Recht, A, Lingos, TI, Abner, A, Vicini, F, Silver, B, Herzog, A, Harris, JR. Long-term radiation complications following conservative surgery (CS) and radiation therapy (RT) in patients with early stage breast cancer. *Int. J Radiation Oncology Biol. Phys.* 1992;23: 915-923.

5. Shapiro C, Recht, A. Late effects of adjuvant therapy for breast cancer. *J Natl Cancer Inst Monogr* 1994;16:101-112.

6. Pierce L, Oberman, H., Strawderman, M., Lichter, A. Microscopic extracapsular extension in the axilla: is this an indication for axillary radiotherapy? *Int J Radiat Oncol Biol Phys* 1995;33:253-259.

7. Schnitt S, Connolly, JL. Processing and evaluation of breast excision specimens: A clinically oriented approach. *Am J Clin Pathol* 1992;98:125-137.

8. Holland R, Connolly, J., Gelman, R. et al. The presence of an extensive intraductal component following a limited excision correlates with prominent residual disease in the remainder of the breast. *J Clin Oncol* 1990;8:113-118.

9. Schnitt S, Connolly JL, Khettry U, et al:. Pathologic findings on re-excision of the primary site in breast cancer patients considered for treatment by primary radiation therapy. *Cancer* 1987;59:675-681.

10. Solin L, Fowble, B, Martz, K, et al:. Results of re-excisional biopsy of the primary tumor in preparation for definitive irradiation of patients with early stage breast cancer. *Int J Radiat Oncol Biol Phys* 1986;12:I721-725.

11. Ngai J, Zelles, GW, Rumore, GJ, et al:. Breast biopsy techniques and adequacy of margins. *Arch Surg* 1991;126:1343-1347.

12. Vicini F, Beron, P, Wimbish, K, et al. Value of mammographic and pathologic findings in predicting the adequacy of tumor excision in breast cancer patients treated with breast-conserving therapy. *Radiology* 1993;189 (P):214 (Abstr.).

13. Peterse J. The predictive value of an extensive intraductal component for residual tumor. Findings in 168 cases of reexcision after tumorectomy (Abstr.). 5th EORTC Breast Cancer Working Conference. Leuven, Belgium; 1991.

14. Morimoto T, Okazaki, K, Komaki, K, et al:. Cancerous residue in breast-conserving surgery. *J Surg Oncol* 1993;52:71-76.

15. Recht A, Houlihan MJ:. Conservative surgery without radiotherapy in the treatment of patients with early-stage invasive breast cancer: a review. *Ann Surg* 1995;222:9-18.

16. Ribeiro G, Dunn, G, Swindell, R, et al:. Conservation of the breast using two different radiotherapy techniques: interim report of a clinical trial. *Clin Oncol* 1990;2:27-34.

17. Ribeiro G, Magee, B, Swindell, R, et al:. The Christie Hospital breast conservation trial: an update at 8 years from inception. *Clin Oncol* 1993;5:278-283.

18. Magee B YE, Swindell R:. Patterns of breast relapse following breast conserving surgery and radiotherapy (Abstr.). *Br J Cancer* 1998;78 (suppl. 2):24.

19. Polgar C, Major T, Mangel LC, et al:. Sole HDR-brachytherapy after breast conserving surgery: 4 year results of a pilot study and initial findings of a randomized Phase III trial (Abstr.). *Radiother Oncol* 2000; 55 (suppl. 1):31.

20. Fentiman I, Poole, C, Tong, D, et al:. Iridium implant treatment without external radiotherapy for operable breast cancer: a pilot study. *Eur J Cancer* 1991;27:447-450.

21. Pacini P MS, Cionini L, et al:. Exclusive interstitial brachytherapy after conservative surgery for breast cancer (Abstr.). *Eur J Cancer* 1994;30A (suppl. 2):S77.

22. King T, Bolton, JS, Kuske, RR, et al. Long-term results of wide-field brachytherapy as the sole method of radiation therapy after segmental mastectomy for Tis,1,2 breast cancer. *Am J Surg* 2000;180:299-304.

23. Kuske R, Bolton, JS, Fuhrman, G, et al. Wide volume brachytherapy alone for select breast cancers: the ten year experience of the Ochsner Clinic. Int J Radiat Oncol Biol Phys 48 (suppl. 3). Vol 296 (Abstr.); 2000.

24. Vicini F, Chen, PY, Fraile, M, et al:. Low-dose-rate brachytherapy as the sole radiation modality in the management of patients with early-stage breast cancer treated with breast-conserving therapy: preliminary results of a pilot trial. *Int J Radiat Oncol Biol Phys* 1997;38:301-310.

25. Vicini F, Kini, VR, Chen, P, et al:. Irradiation of the tumor bed alone after lumpectomy in selected patients with early-stage breast cancer treated with breast conserving therapy. *J Surg Oncol* 1999;70:33-40.

26. Vicini F, Kestin, LL, Edmundson, GK, et al:. Dose-volume analysis for quality assurance of interstitial brachytherapy for breast cancer. *Int J Radiat Oncol Biol Phys* 1999;45:803-810.

27. Vicini FA, Baglan KL, Kestin LL*, et al.* Accelerated Treatment of Breast Cancer. *J Clin Oncol* 2001;19:1993-2001.

28. Wazer DE, Lowther D, Boyle T*, et al.* Clinically evident fat necrosis in women treated with high-dose-rate brachytherapy alone for early-stage breast cancer. *International Journal of Radiation Oncology*Biology*Physics* 2001;50:107-111.

29. Lawenda BD, Taghian AG, Kachnic LA*, et al.* Dose-volume analysis of radiotherapy for T1N0 invasive breast cancer treated by local excision and partial breast irradiation by low-dose-rate interstitial implant. *International Journal of Radiation Oncology*Biology*Physics* 2003;56:671-680.

30. Hughes K, Schnaper, LA., Berry, D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 Years of age or older with early breast cancer. *N Engl J Med* 2004;351:971-977.

31. Chu K, Turner, RR, Hansen, NM, et al. Do all patients with sentinel node metastasis from breast carcinoma need complete axillary node dissection? *Ann Surg* 1999;229:536-541.

32. Noguchi S MK, Inaji H, et al. Clonal analysis of predominantly intraductal carcinoma and precancerous lesions of the breast by means of polymerase chain reaction. *Cancer Res* 1994;54:1849-1853.

33. Lagios M, Margolin, F., Westdahl, P. et al. Mammographically detected duct carcinoma in situ: Frequency of local recurrence following tylectomy and prognostic effect of nuclear grade on local recurrence. *Cancer* 1989;63:619-624.

34. Wong J, Gadd, MA, Gelman, R, et al. Wide excision alone for ductal carcinoma in situ(DCIS) of the breast. Proc Am Soc Clin Oncol. San Antonio, texas; 2003. p. (Abstract #44).

35. Hetelekidas S, Collins, L, Silver, B, et al. Predictors of local recurrence following excision alone for ductal carcinoma in situ. *Cancer* 1999;85:427-431.

36. Hiramatsu H, Bornstein, B, Recht, A, et al. Local recurrence after conservative surgery and radiation therapy for ductal carcinoma-in-situ: the possible importance of family history. *Cancer J Sci Am* 1995;1:55-61.

37. Vicini F, Kestin, LL, Goldstein NS, et al. Relationship between excision volume, margin status, and tumor size with the development of local recurrence in patients with ductal carcinoma-in-situ treated with breast-conserving therapy. *J Surg Oncol* 2001;76:245-254.

38. Fourquet A, Sigal-Zafrani, B, Clough, KB. Breast-conserving surgery plus radiation therapy in ductal carcinoma in situ: the Institut Curie experience:. In: Silverstein MJ RA, Lagios MD (eds), editor. Ductal Carcinoma In Situ of the Breast (2nd ed.). Philadelphia: Lippincott William & Wilkins; 2002. pp. pp 365-372.

39. Solin L, Fourquet, A, Vicini, FA, et al. Salvage treatment for local recurrence after breast-conserving surgery and radiation as initial treatment for mammographically detected ductal carcinoma in situ of the breast. *Cancer* 2001;91:1090-1097.

40. Baglan KL, Sharpe MB, Jaffray D*, et al.* Accelerated partial breast irradiation using 3D conformal radiation therapy (3D-CRT). *International Journal of Radiation Oncology*Biology*Physics* 2003;55:302-311.

41. Remouchamps VM, Letts N, Yan D*, et al.* Three-dimensional evaluation of intra- and interfraction immobilization of lung and chest wall using active breathing control: A reproducibility study with breast cancer patients. *International Journal of Radiation Oncology*Biology*Physics* 2003;57:968-978.

42. Weed D, Wong J, Yan D*, et al.* The validity of clips as a radiographic surrogate for the biopsy cavity in image-guided accelerated partial breast irradiation. *International Journal of Radiation Oncology*Biology*Physics* 2003;57:S308.

43. Recht A, Edge, S., Solin, LJ et al. Postmastectomy Radiotherapy: Guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001;19:1539-1569.

44. Rosenstein BS, Lymberis SC, Formenti SC. Biologic comparison of partial breast irradiation protocols. *International Journal of Radiation Oncology*Biology*Physics* 2004;60:1393-1404.

45. Perera F, Engel, J, Holliday, R et al. Local resection and brachytherapy confined to the lumpectomy site for early breast cancer: A pilot study. *J Surg Oncol* 1997;65:263-268.

46. Kuske R, Winter, K., Arthur, D., et al. A phase I/II trial of brachytherapy alone following lumpectomy for select breast cancer: Toxicity analysis of Radiation Therapy Oncology Group 95-17. *Proceeding of ASTRO.Int J Radiat Oncol Biol Phys* 2002;54 (suppl).

47. Arthur DW KD, Zwicker RD, et al. Partial breast brachytherapy after lumpectomy: low dose rate and high dose rate experience. *Int J Radiat Oncol Biol Phys.* 2003;56:681-689.

48. Polgar C, Sulyok, Z., Fodor, J. et al. Sole brachytherapy of the tumor bed after conservative surgery for T1 breast cancer: Five-year results of a phase I-II study and initial findings of a randomized phase III trial. *J Surg Oncol* 2002;80:121-129.

49. Polgar C, Major T, Fodor J*, et al.* High-dose-rate brachytherapy alone versus whole breast radiotherapy with or without tumor bed boost after breast-conserving surgery: Seven-year results of a comparative study. *International Journal of Radiation Oncology*Biology*Physics* 2004;60:1173-1181.

50. Keisch M, Vicini F, Kuske RR, et al. Initial clinical experience with the MammoSite breast brachytherapy applicator in women with early-stage breast cancer treated with breast-conserving therapy. *Int J Radiat Oncol Biol Phys.* 2003;55:289-293.

51. Veronesi U, Orecchia R, Luini A, et al. A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated. *Eur J Cancer* 2001;37:2178-2183.

52. Magee B, Swindell, R, Harris, M. Prognostic factors for breast recurrence after conservative breast surgery and radiotherapy: results from a randomised trial. *Radioth and Oncol* 1996;39:223-227.

53. Vicini FA, Remouchamps V, Wallace M*, et al.* Ongoing clinical experience utilizing 3D conformal external beam radiotherapy to deliver partial-breast irradiation in patients with early-stage breast cancer treated with breast-conserving therapy*1. *International Journal of Radiation Oncology*Biology*Physics* 2003;57:1247-1253.

54. Formenti SC, Truong MT, Goldberg JD*, et al.* Prone accelerated partial breast irradiation after breast-conserving surgery: Preliminary clinical results and dose-volume histogram analysis. *International Journal of Radiation Oncology*Biology*Physics* 2004;60:493-504.

55. Silverstein MJ, Poller DN, Waisman JR, et al. Prognostic classification of breast ductal carcinoma-in-situ. *Lancet* 1995;345:1154-1157.

56. Boyages J, Recht, A., Connolly, J. et al. Early breast cancer: predictors of breast recurrence for patients treated with conservative surgery and radiation therapy. *Radiother Oncol* 1990;19:29-35.

57. Acs G LT, Rebbeck TR, et al. Differential Expression of E-Cadherin in lobular and ductal neoplasms of the breast and its biologic and diagnostic implications. *Am J Clin Pathol* 2001;115:85-98.

58. Goldstein N. Does the level of E-Cadherin expression correlate with the primary breast carcinoma infiltration pattern and type of systemic metastases? *Am J Clin Pathol* 2002;118:425-434.

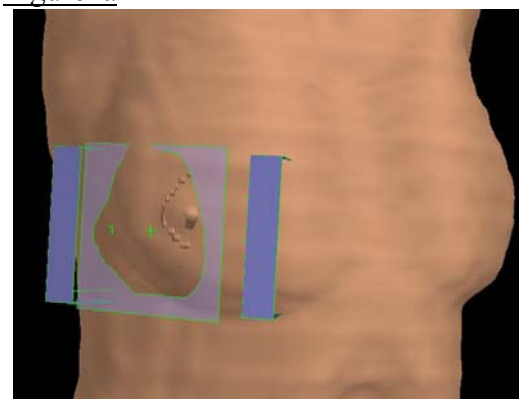
Appendix 1

Examples of Treatment Planning

The radiation oncologist will outline the tumor bed or seroma, and add a margin of 1.5-2 cm superiorly, inferiorly, medially, and laterally to create the planning target volume (PTV). The anterior border of the PTV will be at 5 mm below the skin surface; the posterior border will be at the anterior surface of the chest wall. No attempt will be made to include the entire length of the excision scar.

The margins to be given around the excision volume will be determined in relation to the maximum diameter of the tumor bed. If the maximum diameter of the tumor bed or seroma is 4 cm or less, then 2-cm margins around it should be used. If the maximum diameter is larger than 4 cm, then 1.5-cm margins should be used. It is preferred that the PTV volume does not exceed 30-35% of the breast volume. If it does, patient could potentially wait for 1-3 weeks till the seroma decreases in size and another plan is initiated. It is also preferred that the non-target breast tissue does not receive more than 50% of the prescribed dose.

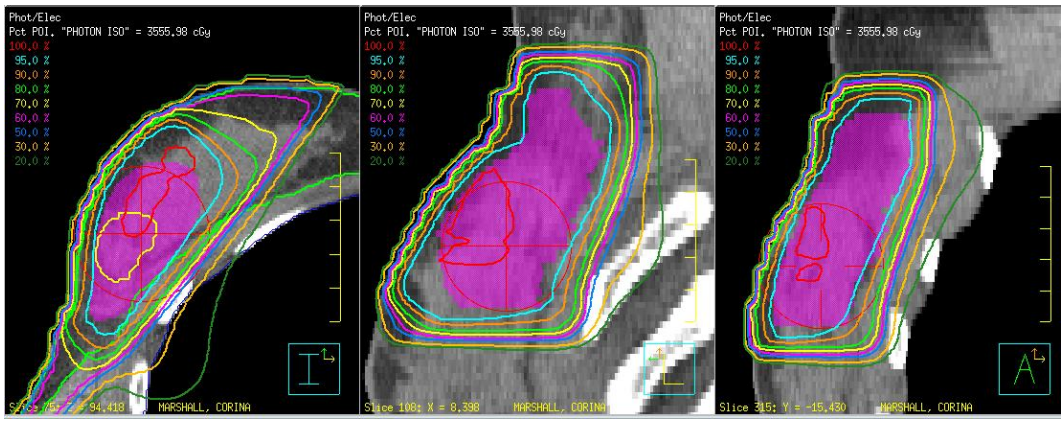
Figure1a



Additional margin beyond the PTV to the field edges will be added as required to achieve full dose (100%) to the PTV. Blocks or multileaf collimators should be used to define the treatment area.

Any combinations of photon beams of energy 6 MV or higher, with or without the addition of electrons of any energy, may be used for treatment provided the dosimetric requirements of adequately treating the planning target volume and homogeneity are met. Although ***mixed energy (photons and electrons) are encouraged*** in order to minimize the exposure of the lung to radiation. Proton radiation using one, two or three fields or more may also be used provided adequate PTV coverage. Intensity-modulated radiotherapy (IMRT) may be used. The example below (Figure 1a and b) is a three-field mixed photon/electrons approach (medial and lateral tangents and en face electrons), with a daily dose of 4 Gy prescribed to the PTV.

Figure1b



Partial Breast Irradiation using IMRT

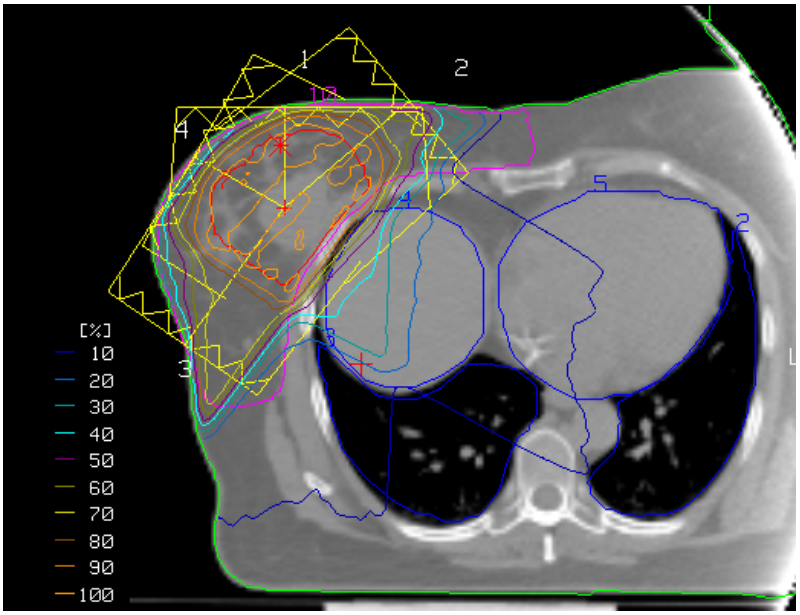


Figure 2: Example treatment plan for an IMRT Partial Breast plan.

IMRT plans were generated using the Helios inverse treatment planning system. For this representative plan (see Figure 2), a 4 field, 6 MV IMRT plan was generated. Two of the beam angles were chosen at typical medial and lateral tangent beam angles (50 and 215 degrees). Typically, IMRT fields are offset by at least 15 degrees to best utilize the optimized fluence patterns. For this case, AP and RAO beams were also used to increase target conformality, but at the risk of increasing the dose to the lung, liver and heart. The choice of beam angles will be patient specific, based on the location of the tumor and the dose tolerance for organs at risk.

The following structures should be contoured for all patients by the physician:

1. Whole breast
2. Seroma
3. Ipsilateral lung
4. Contralateral lung
5. Heart
6. Nipple

Ensure a DVH (with volumes expressed as % total) is submitted and the Dosimetry forms is completed using the DVH data of the following:

1. Ipsilateral lung.
2. Contralateral lung
3. Heart
4. PTV
5. Breast minus PTV
6. Seroma

After the contouring by the physician (on a GE Advantage Sim workstation), data is then transferred to the treatment planning system. The GTV was automatically expanded in three dimensions by 1.5-2.0 cm to create a clinical target volume (CTV). The CTV was then manually edited to eliminate any volume expansion outside the healthy breast contour. Since the setup and organ motion requirements for partial breast irradiation were not determined prior to this dosimetry study, there was no further target expansion to create a planning target volume (PTV). Therefore the CTV and PTV were the same in this planning exercise.

The dose prescription used in the treatment planning optimization was 32 Gy or 36 Gy or 40 Gy in 4 Gy/fx BID. For the inverse planning optimization, dose constraints were placed on the target and healthy structures. The Helios treatment planning system allows maximum, minimum, and DVH dose constraints to be utilized. For the PTV, the minimum dose constraint was set to 90% of the prescribed dose, while the maximum dose constraint was set to 110% of the prescribed dose. In addition, 90-95% of the PTV volume was to be covered by the prescribed dose. Since the lung and liver were nearly adjacent to the PTV, the maximum dose constraint used for these structures was 90% of the prescription dose. DVH dose constraints were used to further limit the dose to these organs (e.g. 20% of the liver should not receive more than 5 Gy, and 10% of the right lung should not receive more than 5 Gy). Furthermore, the maximum dose to the heart was set at 5 Gy. Numerical weights are assigned to prioritize the dose constraints for each organ. For this planning example, the target was given the highest priority to ensure optimal target dose coverage. The treatment planning system then optimizes the beam fluences based on the desired dose constraints and priorities, and may achieve a better or worse result than specified in the dose constraints. Several optimization sessions may therefore be needed to achieve the desired result by modifying the requested dose constraints and/or the beam orientation.

Appendix 2

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
SKIN	None	Slight atrophy; Pigmentation change; Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; Slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; Field contracture > 10% linear measurement	Necrosis

From: Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 31:1341-1346, 1995; incorporated into CTC version 2.0, April 30, 1999

Definition of Fat Necrosis

Fat necrosis typically causes a painless mass located superficially in the breast, accompanied by retraction or dimpling of the overlying skin. The skin may be thickened clinically and radiologically. Fat necrosis is firm and relatively circumscribed on palpation. Mammography usually reveals a spiculated, often poorly defined mass that may contain punctate or large, irregular calcifications. Attachment to the skin, dimpling, and thickening of the skin are often evident. Less frequently, the lesion consists of a circumscribed, oil-filled, partly calcified cyst. Early in its development, fat necrosis has the appearance of hemorrhage in indurated fat. After several weeks, the affected area becomes demarcated, forming a distinct yellow-gray and focally reddish tumor. Cystic degeneration may develop in the center of such a lesion, resulting in a cavity that contains oily fluid or necrotic fat. Calcification frequently develops in the cyst wall. Biopsy may be required to distinguish fat necrosis from recurrence.

Appendix 3

Cosmetic Scoring System

Excellent: little or no observable change

Good: minimal but identifiable changes

Fair: significant results of radiotherapy noted

Poor: severe normal tissue sequelae

From: Harris JR, Levene MB, Svensson G, Hellman S. Analysis of cosmetic results following primary radiation therapy for Stages I and II carcinoma of the breast. Int J Radiat Oncol Biol Phys 5:257-261, 1979

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER℠

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

Breast Oncology Unit
55 Fruit Street, Cox Building
100 Blossom Street
Boston, MA 02114
Tel.: 617-726-7559, Fax: 617-726-3603
Radiation Appts.: 617-726-8662
Breast Center Appts.: 617-724-4800
Email: ataghian@partners.org

Alphonse G Taghian, M.D., Ph.D.
Associate Professor of Radiation Oncology
Harvard Medical School
Chief of Breast Service
Department of Radiation Oncology
Massachusetts General Hospital

Date

[Patient Name]
[Patient Address]

Dear [Patient Name]:

Thank you for your continued participation in the Partial Breast Irradiation study.

I am writing today to inform you of a few changes that we have made to this study. First, we have decided to eliminate the unilateral diagnostic mammograms since we have seen no evidence to show benefit of this additional 6 month screening. Therefore, the study now only requires standard yearly bilateral mammograms. You will continue with your follow-up visits every 6 months; however, the only mammograms required will be bilateral yearly mammograms. Secondly, we have decided to extend the duration of our long term follow-up visits and mammograms from 10 to 15 years. These are your routine visits with your provider. We would like to continue to assess all patients for changes in breast appearance up to 15 years following the completion of their treatment with partial breast irradtion.

Please feel free to contact me at 617-726-6500 or the research coordinator, Marissa Frongillo at (617) 724-7578, with any questions you might have regarding this change.

Thank you,

A. Taghian

Alphonse Taghian, M.D., Ph.D.