Phase II Trial of Lumpectomy and Partial Breast Proton Therapy for Early Stage Breast Cancer

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Radiation Medicine Proton Therapy

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Phase II Trial of Lumpectomy and Partial Breast Proton Therapy for Early Stage Breast Cancer

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Schema

Surgery	**Proton Therapy**	**Systemic Therapy**
Lumpectomy and axillary dissection or sentinel lymph node biopsy.	Proton therapy to tumor bed. Dose = 40 CGE in 10 fractions.	Chemotherapy and/or hormonal therapy as needed per treating oncologist.

Eligibility (see section 3.0 for details)

- Invasive ductal, medullary, papillary, colloid or tubular histologies or ductal carcinoma in-situ (DCIS)
- Stages Tis, T1 or T2 (tumors < or = 3 cm)
- Negative surgical margins (>2mm)
- Negative sentinel node biopsy or three or fewer histologically involved axillary nodes on axillary node dissection. No extra-capsular extension
- No previous chemotherapy for breast cancer
- No collagen vascular disease
- No prior malignancy except non-melanoma skin cancer (unless disease free > 5 years)
- No patients who are pregnant or lactating

Sample Size: 50 patients

1.0 Introduction

General

Breast cancer is the most common site of cancer for women worldwide and has an enormous impact on the health of women. In the United States, approximately 210,000 new cases of breast cancer are estimated in 2003. Each year, approximately 40,000 women die of the disease, making it the second leading cause of cancer death in women.[1]

Rationale for Whole Breast Irradiation

To date, there have been six large prospective randomized trials that have shown that the locoregional control and survival rates achieved with breast-conserving therapy are comparable to modified radical mastectomy in patients with early stage breast cancer.[2-7] The major advantages of breast conserving therapy are reduced emotional/psychological trauma and superior cosmetic outcome. The disadvantage is that this involves a more complex, prolonged treatment requiring 5-7 weeks of external beam radiation therapy.

Rationale for Partial Breast Irradiation

The rationale for whole breast irradiation following lumpectomy is to reduce the breast recurrence rate by eliminating residual foci of cancer in the tumor bed and to treat presumed occult multicentric disease in remote areas of the breast. However, the majority (67-100%) of ipsilateral breast recurrences after breast conservation therapy are in the same quadrant of the initial tumor.[8-11] In fact, 80-90% of breast recurrences after breast conservation therapy occur in the immediate vicinity of the lumpectomy scar.[10, 12] Upon review of multiple randomized trials and retrospective studies comparing lumpectomy alone versus lumpectomy and whole breast irradiation, it is apparent that there is no difference in remote breast recurrence (<4%). [7,10,13,33]

NSABP B-06 analyzed 1851 patients with Stage I/II breast cancer randomized to total mastectomy, lumpectomy, or lumpectomy and whole breast irradiation. The breast recurrence rate in lumpectomy alone was 43% in contrast to a 10% breast failure rate for patients receiving lumpectomy and whole breast irradiation.[13] The EORTC 22881/10882 Trial analyzed 5318 Stage I/II breast cancer patients who underwent lumpectomy with negative margins and axillary lymph node dissection, followed by 50 Gy to the whole breast. They were randomized to receive no boost versus a 16 Gy tumor bed boost. Local recurrence was 7.3% vs. 4.3% at 5 years (no boost versus boost), a 41% reduction in local recurrence.[14] Thus it appears that delivering additional treatment to the tumor bed significantly reduces the chance of local tumor recurrence.

The next question that follows is if the whole breast irradiation can be eliminated altogether with delivery of a high dose of radiation limited only to the site at highest risk for recurrence. By confining treatment to a limited volume of breast tissue adjacent to the lumpectomy cavity, it may allow delivery of higher doses to high risk areas, potentially reducing acute and chronic toxicity, thus improving the quality of life in patients. In addition, the smaller target volumes may allow hypofractionated treatment schedules, which would decrease the time and inconvenience of breast conservation therapy,

eliminate scheduling problems with systemic chemotherapy, and potentially improve outcome by reducing delay to local therapy.

Trials Investigating Partial Breast Irradiation

Investigations of partial breast irradiation have, in fact, been performed, with excellent early results. Primarily Phase I, II and a few Phase III studies have been initiated using: high dose rate (HDR) brachytherapy, low dose rate (LDR) brachytherapy, external beam radiotherapy, and intra-operative radiotherapy.[15-32] A hypofractionated treatment scheme has been used in all cases. Local recurrence rate has been <10% in all studies except two, which had poor selection criteria.[25,26,29] When evaluated, cosmetic results have been rated Good/Excellent in >75% of the patients treated.

Phase I, II and III studies conducted at the National Institute of Oncology in Hungary have some of the longest follow-up data to date. Forty-five patients with T1 breast cancer were enrolled in the Phase I-II study and underwent lumpectomy followed by HDR brachytherapy 7 x 4.33 Gy or 7 x 5.2 Gy to the tumor bed. With a median follow-up of 57 months, the local recurrence rate was 4.4%. The 5-year probability of cancer-specific, relapse-free and local recurrence-free survival was 90.0%, 85.9%, and 95.6%, respectively. The phase III study was subsequently performed with an additional 126 patients randomized to receive 50 Gy WBRT or HDR brachytherapy 7 x 5.2 Gy to the tumor bed alone. With a median follow-up of 30 months, this study also confirms excellent locoregional tumor control of 100% in both arms. The 3-year probability of cancer-specific and relapse-free survival was essentially equivalent, 98.1% and 98.4% in the WBRT group and 100% and 94.4% in the HDR brachytherapy group.[18]

Several institutions have been evaluating accelerated partial breast irradiation using 3D conformal external beam radiotherapy.[15,29,30] A concern of EBRT is that the breast is a moving target that may require larger volumes of normal breast tissue to be irradiated to avoid a geographic miss. William Beaumont Hospital has been studying this, with careful evaluation of breast motion using standard free-breathing virtual scans compared with CT scans obtained at the end of normal inhalation (NI) and exhalation (NE). They found that 5 mm of margin was sufficient to fully account for breast motion, with minimal use of immobilization devices (alpha cradle). Sixteen patients were treated using a CTV of 1.5 cm plus 1 cm for breathing motion/set-up uncertainty. A dose of 34-38.5 Gy was delivered in 10 fractions BID over 5 days using a 4-5 noncoplanar beam arrangement. With a median follow-up of 8 months, toxicity has been mild, consisting of mild fatigue, mild breast tenderness and mild to moderate erythema/dry desquamation.[15] The RTOG also has a proposed Phase I/II protocol to evaluate 3D CRT confined to the lumpectomy site in Stage I/IIA breast carcinoma.

Rationale for Partial Breast Irradiation with Protons

Proton therapy has several advantages over other forms of radiotherapy for performing partial breast irradiation. Proton therapy would eliminate the additional surgical procedure required for brachytherapy. In addition, it is likely to improve dose homogeneity within the target volume, which may improve cosmetic results and reduce the risk of symptomatic fat necrosis associated with brachytherapy which has been reported to be as high as 40%. In comparison to three-dimensional conformal radiation therapy, the inherently superior depth dose characteristics (Bragg peak) would minimize the integral dose delivered to surrounding normal tissues, particularly the lung and heart. We anticipate that this will result in decreased toxicity and less risk of radiation induced malignancy.

2.0 Objectives

2.1 To evaluate the technical feasibility of delivering partial breast irradiation with proton beam.

2.2 To evaluate the acute and long term toxicity associated with partial breast proton therapy.

2.3 To evaluate the cosmetic results with partial breast proton therapy

2.4 To determine the local tumor control and survival associated with partial breast proton therapy.

3.0 Eligibility Criteria

3.1 Histologic evidence of invasive carcinoma (except lobular carcinoma) or ductal carcinoma-in-situ.

3.2 Primary tumor < or = 3 cm.

3.3 AJCC stage 0, I, or II

3.4 Patients with invasive carcinoma must have an axillary node dissection or sentinel lymph node biopsy. If the sentinel node is positive an axillary node dissection must be performed. A minimum of 6 nodes must be pathologically reviewed. No more then 3 nodes may contain metastatic carcinoma and there can be no evidence of extra-capsular extension. Axillary staging is not required for DCIS.

3.5 Surgical clips will be placed outlining margins of lumpectomy cavity.

3.6 Lumpectomy margins negative by at least 2 mm and/or negative reexcision

3.7 No evidence of distant metastasis.

3.8 No evidence of extensive intraductal component.

3.9 No patients with multicentric ipsilateral carcinoma or contralateral carcinoma.

3.10 No prior radiation therapy to the breast or chest wall.

3.11 No prior malignancy except non-melanoma skin cancer unless disease free for > 5 years.

3.12 No patients who are pregnant or lactating.

3.13 No patients with history of collagen vascular disease.

3.14 No prior chemotherapy for breast cancer

4.0 Pretreatment Evaluation

4.1 History and physical examination.

4.2 Bilateral mammogram.

4.3 Chest x-ray.

4.4 CBC and serum chemistries with liver function tests.

4.5 Bone scan if alk phos is elevated or if there are symptoms of bone metastasis

4.6 Abdominal CT if liver function test are abnormal.

4.7 Breast MRI (optional)

5.0 Radiation Therapy

5.1 Radiation therapy will start within 4 weeks of surgical resection

5.2 Immobilization and treatment planning CT scan of the chest.

5.3 Treatment Planning

5.3.1 Outline tumor bed using surgical clips and clinical information

5.3.2 Add 1 cm in all directions to create clinical target volume (CTV) excluding chest wall and skin.

5.3.3 Create multi-field treatment plan with the 90% isodose covering the CTV while the skin surface receives no more then 70%.

5.4 Dose, Fractionation and Treatment

5.4.1 40 CGE will be delivered to the CTV in 10 equal fractions over ten treatments days.

5.4.2 At least 2 fields will be treated each day.

5.4.3 Orthogonal localization radiographs to be taken prior to each treatment with surgical clips used as localizing markers.

6.0 Surgical Therapy

6.1 Excisional biopsy (lumpectomy) will be done per established surgical standards. Surgical clips will be placed to outline the surgical cavity (i.e. deep, superior, inferior, right, left).

6.2 Axillary lymph node sampling or sentinal lymph node biopsy will be done per surgeon's preference.

7.0 Systemic Therapy

7.1 Chemotherapy and/or hormonal therapy may be given following the completion of proton therapy as recommended by the treating oncologist.

8.0 Patient Assessments

8.1 Study Parameters

Assessment	Pre TX	1 Mo Post TX	6 MO Post TX then every 6 months	6 MO Post TX then annually
H & P	X	X	X*	
Disease Status	X	X	X*	
Toxicity Assessment	X	X	X*	
Mammo	X			X
CBC & LFT	X	As indicated	As indicated	As indicated
Bone scan or CT scan	As needed	As indicated	As indicated	As indicated
Photos	X			X
Cosmesis Assess. (MD&Pt.)			X	X
Chest X-ray	X			X

* Until year 5 at which time complete assessment will be conducted annually

8.2 Definitions for Cosmetic Outcomes

Cosmetic outcome will be graded by the study subject, radiation oncologist, and surgical oncologist periodically following treatment according to section 8.1. The grading scale will be as follows:
Excellent – the treated breast, when compared to the untreated breast, shows minimal or no changes in shape or size. There may be minimal subcutaneous fibrosis or scarring.

Good – there are mild changes in the size and shape of the treated breast. Scarring within the breast causes mild alterations

in breast shape.

Fair – there is a clear difference in the size and/or shape of the treated breast that involves ¼ or less of the treated breast.

Poor – marked changes in the treated breast that involves more then ¼ of the breast.

8.3 Photographs

Photographs will be taken of the post-surgical breast and periodically following proton therapy per section 8.1. These will be used to document cosmetic outcome. Photos will include a "close up" view of the treated breast with the subjects arms raised over the head and a photo of both breasts with the subjects hands on hips. Photographs will not include the subjects' face.

9.0 Statistics and Data Management

9.1 Initially 25 subjects will be enrolled into this trial. After a toxicity evaluation is completed and felt to be acceptable, 25 additional subjects will be enrolled for a total of 50 subjects.

An additional 50 subjects will be enrolled under the new eligibility criteria defined in the April 4, 2008 revision.

9.2 All acute toxicities will be scored according to the NCI Common Toxicity Criteria v2.0. Late toxicity will be scored per RTOG guidelines. Any toxicities with a threshold of Grade 3 or above will be reported as an adverse event. Frequencies of toxicities will be tabulated and compared to published reports.

9.3 Frequency and type of recurrence (local, regional, distant) will be tabulated and compared to prior studies.

9.4 Data Management and Publications

Treatment records and study data will be collected, stored and maintained in the department of radiation medicine. Data

analysis and publications will be performed under the direction of the study principal investigators. All presentations, posters, abstracts and manuscripts that include data from this study will be reviewed and approved by the study PI's prior to presentation or submission.

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