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Preoperative Single-Fraction Partial Breast Radiotherapy – A Novel Phase I Dose-Escalation Protocol with Radiation Response Biomarkers

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Summary

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Prior Presentations: Portions of this work were presented at the 2013 International Society for Magnetic Resonance in Medicine, the 2013 American Association of Physicists in Medicine, the 2013 San Antonio Breast Cancer Symposium and the 2013 and 2014 American Society for Radiation Oncology Annual Meeting. A manuscript addressing detailed MRI findings has been submitted to the Journal of Technology in Cancer Research and a manuscript outlining radiation delivery techniques is in press at Practical Radiation Oncology.

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This phase I dose-escalation trial evaluates the feasibility of single-dose preoperative partial breast irradiation delivered with external beam techniques in early stage breast cancer patients. No acute dose-limiting toxicity was observed at 15, 18, or 21Gy. Paired pre- and post-radiation imaging and tumor biopsies offer unique insight into the biology of breast cancer radiation response.

Purpose—Women with biologically favorable early stage breast cancer are increasingly treated with accelerated partial breast radiation (PBI). However, treatment-related morbidities have been linked to the large post-operative treatment volumes required for external beam PBI. Relative to external beam delivery, alternative PBI techniques require equipment that is not universally available. To address these issues, we designed a phase I trial utilizing widely available technology to 1) evaluate the safety of a single radiation treatment delivered preoperatively to the small-volume, intact breast tumor and 2) identify imaging and genomic markers of radiation response.

Methods—Women 55 or older with clinically node negative, ER+ and/or PR+, HER2-, T1 invasive carcinomas or low-intermediate grade in situ disease ≤2cm were enrolled (n=32). Intensity-modulated radiotherapy was used to deliver 15 Gy (n=8), 18 Gy (n=8), or 21Gy (n=16) to the tumor with a 1.5cm margin. Lumpectomy was performed within 10 days. Paired pre- and post-radiation MRI images and patient tumor samples were analyzed.

Results—No dose-limiting toxicity was observed. At a median follow-up of 23 months, there have been no recurrences. Physician-rated cosmetic outcomes were good/excellent and chronic toxicities were grade 1-2 (fibrosis, hyperpigmentation) in patients receiving preoperative radiation only. Evidence of dose-dependent changes in vascular permeability, cell density, and expression of genes regulating immunity and cell death were seen in response to radiation.

Conclusions—Preoperative single-dose radiotherapy to intact breast tumors is well-tolerated. Radiation response is marked by early indicators of cell death in this biologically favorable patient cohort. This study represents a first-step towards a novel PBI approach. Preoperative radiation should be tested in future clinical trials as it has the potential to challenge the current treatment paradigm and provide a path forward to identify radiation response biomarkers.

Introduction

Partial breast irradiation (PBI) is increasingly utilized in the treatment of early stage breast cancer. As data supporting the efficacy and tolerability of PBI continue to accumulate, this conceptual approach has been incorporated into national radiation guidelines and deemed acceptable for use outside of a clinical trial in carefully selected patients[1]. A number of techniques are available for treatment delivery, ranging from a single intra-operative treatment to one week of twice daily treatments. In fact, a phase III trial focused only on brachytherapy PBI delivery techniques completed enrollment in 2009 with 1300 patients (GEC-ESTRO; NCT00402519). In addition, early reports are emerging from two randomized trials (ELIOT, TARGIT) testing a single-fraction of radiation delivered in the operating suite directly to the tumor bed[2,3]. However, with the exception of external beam PBI, every technique requires specialized training or equipment that, relative to linear accelerator-based options, are not as widely available to all radiation oncology practitioners. As a result, in a recent interim analysis of the phase III NSABP B-39/RTOG 0413 partial

breast trial, external beam PBI was utilized in 72.9% of patients randomized to the PBI arm[4].

However, suboptimal outcomes have been reported with post-operative external beam PBI. Hepel and colleagues reported high rates of grade 3-4 soft tissue fibrosis (8.3%) in 60 patients treated with external beam techniques[5]. Jagsi and colleagues closed their study after only 34 patients secondary to high rates of unacceptable cosmesis after only 2.5 years[6]. Both authors linked these adverse outcomes to the sizeable treatment volumes required to target a post-operative surgical seroma plus appropriate margin. Although other institutional series and phase II trials[7-10], as well as the randomized NSABP B-39/RTOG 0413 trial[4] have reported low rates of long-term toxicity the Canadian phase III trial (RAPID) also noted adverse cosmetic outcomes (29% PBI versus 17% whole breast, $p<0.001$) at 3 years [11], suggesting that the results of external beam PBI could be improved upon.

To address these issues, we designed a novel phase I dose-escalation trial of single-dose preoperative radiation treatment in carefully selected favorable risk patients. This technique has numerous potential advantages: 1) it can be delivered with widely available radiation techniques; 2) the target volume is a small intact breast tumor and its adjacent tissue rather than a large postoperative seroma which significantly decreases the uninvolved breast tissue receiving high radiation doses; 3) more accurate targeting of the areas of subclinical disease surrounding the tumor may be possible, 4) smaller treatment volumes are amenable to dose escalation which can further accelerate treatment and improve accessibility for patients, and 5) the pre-operative approach provides a novel opportunity to study breast cancer radiation response. Our goal was to determine the feasibility, toxicity, and maximally tolerated dose (MTD) of this approach.

Material and Methods

Eligibility Criteria

Patients 55 or older with cT1N0 invasive carcinomas or low/intermediate grade ductal carcinoma in situ ≤2cm were enrolled after providing informed consent, on our Institutional Review Board (Pro00015617) approved study. Patients were estrogen receptor (ER) positive and/or progesterone receptor (PR) positive, HER2- with no evidence of lymphovascular invasion (LVI) on diagnostic biopsy. Neoadjuvant therapy was prohibited.

Pre-Treatment Imaging

A treatment planning breast magnetic resonance imaging (MRI) was performed in the XXXX Department of Radiation Oncology (n=21) or at a diagnostic MRI (n=11) facility. Most patients were scanned in the prone position (n=30) on a dedicated 4-Channel Breast Coil (GE Healthcare or Hologic (Bedford, MA)) with arms up. Two patients were scanned supine with a 4-Channel Torso Array Coil (GE Healthcare). T1 and T2-weighted imaging, and dynamic contrast enhanced (DCE) images were obtained on a scanner with at least 1.5 Tesla magnet strength for characterization of the target volume. Diffusion weighted images (DWI) were acquired when feasible.

A planning CT scan (GE Light-speed RT, GE Medical System, Milwaukee, WI) was then conducted in the same position as the treatment planning MRI using a prone breast board (CDR systems Inc, Calgary, Alberta, Canada) or a BodyFix® (Elekta Oncology System, Stockholm, Sweden) supine board.

Treatment Planning

The breast tumor, or gross tumor volume (GTV), and the titanium diagnostic biopsy clip (required for protocol entry) were identified on the treatment planning MRI in BrainLAB iPlan (BrainLAB, Heimstetten, Germany) or Eclipse (Varian Medical Systems, Palo Alto, CA) with the assistance of an expert breast radiologist (typically XX). T1 post-contrast MRI images were utilized to identify the area of enhancing tumor while T2 MRI images, as well as those without fat subtraction, helped to distinguish tumor from post-biopsy change. MR images were then fused with the CT planning images using manual rigid-body registration to align the biopsy marker and surrounding soft tissues.

A 1.5 cm uniform expansion margin was applied around the GTV to account for microscopic disease spread and create the clinical target volume (CTV). Data correlating tumor extent on MRI with pathologic disease extent was utilized to select the CTV width[12].. The advantages of in situ targeting were felt to overcome the decrease in absolute volume of tissue treated with a 1.5cm preoperative margin as compared to a 1.5-2cm postoperative margin. The rationale for this has been described previously[13]. An additional 0.3 cm margin was applied to allow for minor variation in patient positioning and generate the planning target volume (PTV). The first 5mm of subcutaneous of tissue from the external body surface was excluded from the CTV and PTV. The skin was defined in this protocol as a 3mm layer from the external body surface. Breasts, heart, and lungs were segmented according to institutional standard and reflecting the guidelines of NSABP B39/RTOG 0413.

Four to seven beam co-planar or non-co-planar intensity-modulated therapy (IMRT) techniques were used to generate the radiation plan. Dose was prescribed to cover at least 95% of the CTV. Normal tissue constraints were developed using the NSABP/RTOG PBI trial and available hypofractionation literature [14] as a guide [Supplemental Table 1]. Additional treatment planning and delivery details are reported in a separate manuscript[15].

Treatment

Patient positioning was confirmed with on-board kV and cone-beam CT imaging, using the biopsy clip as a fiducial marker. Radiation was prescribed as described below and delivered in a single fraction. Within 10 days of radiation, lumpectomy and sentinel lymph node evaluation, if indicated, were completed in standard fashion. A negative margin of 2mm was required. Post-operative conventional radiotherapy (46-50Gy in 1.8-2.0Gy/fraction) was administered to patients not satisfying eligibility criteria following surgical resection (n=3). Systemic therapy was prescribed at the discretion of the treating medical oncologist [Table 1].

Study Endpoints

Patients were enrolled consecutively in cohorts of eight to a dose of 15Gy, 18Gy or 21Gy in order to determine the maximum tolerated dose of preoperative partial breast radiotherapy. An additional eight patients were planned at the final dose level for further analysis of safety and efficacy. Patients were assessed 3-4 weeks after radiation for acute grade 3 or 4 toxicity. Any toxicity possibly, probably, or definitely related to radiation was considered dose-limiting (DLT). Escalation was prohibited if two or more DLTs were encountered in any eight patient dose cohort. In the event that no DLT was encountered, 21Gy was defined a priori as the recommended phase II dose given the efficacy and limited toxicity seen at this dose in randomized trials evaluating intraoperative radiation[2,3]. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, was used to score and grade acute and chronic treatment-related toxicity.

Cosmetic outcomes were assessed by both physician and patient at baseline and again at 6 months, 1, 2, and 3 years utilizing the NSABP B39/RTOG 0413 cosmesis evaluation scale.

Radiation Response Imaging Analysis

When feasible between radiation treatment and surgical resection, patients underwent a second MRI in order to assess radiation response. K^{trans} (volume transfer constant between blood plasma and extravascular-extracellular space), v_e (extravascular-extracellular space fraction), semi-quantitative iAUC (initial area under contrast agent concentration curve) and ADC (apparent diffusion coefficient) were evaluated in patients with paired pre- and post-radiation MRI imaging (n=15). The Wilcoxon signed-rank test was used to assess the relative changes of each parameter in each area of interest (GTV, CTV and PTV) following radiotherapy. A correlation test was used to examine the linear dependence of relative parameter change on radiation dose. $p<0.05$ was considered statistically significant.

Gene Expression Analysis

Formalin-fixed, paraffin-embedded (FFPE) pre- and post-treatment paired diagnostic biopsy and lumpectomy samples were used to assess changes in gene expression. FFPE RNA extraction and labeling was performed using the RNeasy FFPE kit from Qiagen, and the SensationPlus™ FFPE Amplification and Labeling Kit (Affymetrix, Inc. catalog # 902312). All total RNA samples were assessed for quality using a NanoDrop ND8000 Spectrophotometer for absorbance ratios, and the Agilent Bioanalyzer 2100 for RIN scores. Whole transcriptome expression analysis was evaluated with HTA 2.0 arrays (Affymetrix, Inc. catalog # 902162).

Gene level expression estimates were obtained with Affymetrix Expression Console software (v.1.3) using RMA-Sketch workflow. Differential expression for paired samples was evaluated using the Bioconductor limma package with correction for multiple comparisons[16]. Genes with FDR adjusted p-values (q-values) less than 0.05 were selected as differentially expressed in response to radiation. This set of genes was then tested for radiation dose effect using linear regression of the log2 fold change over dosage received. Those genes with regression p-values less than 0.0005 and q-values less than 0.25 were selected as having dose effect. Gene set analysis (GSA) was performed with the R package

GSA using “two class paired” problem type and 100,000 permutations to estimate false discovery rates. The gene set collection used is “all GO (gene ontology) gene sets” which contains 1454 gene sets in total.

Results

Patients

Between August 2010 and March 2013, 32 patients were enrolled [Table 1]. The median breast volume was 1590 cm^3 (range 3293-3733) while the median target volume (CTV) was 43cm^3 (range 20-66). Due to the large discrepancy between target and normal breast tissue volumes, the median amount of breast receiving prescription dose was only 4% of the total breast volume. Furthermore, due to the highly conformal nature of the radiation techniques [Figure 1], only 14% of the breast received half of the prescription dose. The mean heart dose was less than 0.1Gy for the entire cohort and the highest maximum dose was 1Gy. Radiation doses to the lungs, thyroid and brachial plexus were negligible. The median maximum skin dose (as a proportion of prescription dose: 77.5% (51.7-97.6%)) approached the prescribed dose in some patients. However, the median dose to a 1cc skin volume fell to only 59.8% (41.1-84.2%) while the 10cc median dose was only 37.7% (25.5-53.9%).

Clinical Outcomes

Eight patients received 15Gy, eight 18Gy, and 16 received 21Gy. No acute dose-limiting grade 3 or 4 radiation-related toxicities were seen. No wound dehiscence was observed. Median follow-up is 23 months (range 11-37; excluding one patient who died in a motor-vehicle accident at 2 months of follow-up). Toxicities attributed to radiation are reported in Table 2. Side effects were largely mild and consistent with expected sequelae of surgical and/or radiation therapy. Fibrosis occurred in 77% of patients; most were grade 1. Dermatitis and breast pain were also common.

According to study protocol, 3 patients received post-operative external beam radiotherapy. This was due in one case to DCIS extending over >2cm, a positive lymph node in another, and a mixed ductal/metaplastic tumor in the final patient. Two grade 3 chronic toxicities were seen in a patient from this group who was diagnosed post-treatment with a connective tissue disorder. Another patient with diabetes developed a post-operative wound infection and all three had fair/poor cosmetic outcomes [Supplemental Figure 1].

In contrast, all patients receiving preoperative therapy alone had good or excellent physician-reported cosmetic outcomes at each time point [Figure 2]. All patients remain without evidence of disease.

MRI Imaging and Radiation Response

Fifteen of 32 patients had interpretable post-operative MR imaging. Among those who underwent both pre- and post-treatment MRI, the iAUC decreased significantly in the PTV ($p<0.006$) and CTV ($p<0.006$) volumes suggesting an increase in the post-radiation vascular permeability [Figure 3]. In contrast, v_e significantly increased in both the PTV and CTV ($p<0.05$) consistent with decreased cellular density. The impact of radiation appears to be

dose-related with greater relative changes associated with increasing radiation dose in all parameters (rADC, $iAUC_{6min}$, K^{trans}, and v_e) and nearly all areas of interest (GTV, CTV, PTV).

Changes in Gene Expression after Radiation

Twenty-six patients had pre- and post-operative FFPE tissue pairs for analysis of gene expression. Principal component analysis revealed marked separation of samples before and after radiation with minimal overlap [Figure 4A]. After selecting genes whose expression levels varied with radiation, we were able to identify a subset of 27 genes with evidence of significant dose-dependent changes. Increasing dose appears to primarily induce rather than repress gene expression [Figure 4B/C] and this cohort was enriched for modulators of the inflammatory and immune response such as CD48, LST1, LY86, LY96, AIF1, and CCR1 [Figure 4D]. Specifically, increased expression of AIF1, or allograft inflammatory factor 1, has been observed in response to vascular trauma[17]. The dose-dependent induction of AIF was conserved across multiple probe sets and is consistent with the MRI data described above suggesting early vascular trauma. CD48, a plasma membrane immunoglobulin, is intimately involved in immune signaling and has been reported to act as a regulator that inhibits the malignant transformation of stem cells[18]. Finally, CCR1, a G-protein coupled plasma membrane receptor, is a known mediator of host immune response with a potential role in the induction of apoptotic cell death[19].

Gene set analysis utilizing all genes exhibiting significant change in response to radiation further identifies programmed cell death as a pathway of major significance in the radiation response of these tumors [Induction of Apoptosis By Intracellular Signals: p=4.00E-05, FDR 0.0418, Apoptosis Go: p=0.00388, FDR 0.0418; Programmed Cell Death: p=.00416, FDR 0.0418; Supplemental Table 2].

Discussion

External beam radiotherapy has emerged as the most accessible and thus, most common method of PBI delivery in the United States. Long-term toxicity and cosmesis results with this technique are conflicting but in the largest randomized report to date, suboptimal cosmetic outcomes were noted[11]. Though the cause has not been clearly identified, multiple reports have implicated generous post-operative treatment volumes in this process[20]. The size of the post-operative seroma relative to the actual tumor size makes it unlikely that large and consistent reductions could be achieved post-operatively to address this issue. Target volumes in the post-operative setting typically range from 9-26% of the whole breast receiving prescription dose and 34-49%[20] receiving half of prescription dose. This is due, in part, to the larger margins required to account for geographic target uncertainty post-resection and daily reproducibility with fractionated radiation in the supine position.

In contrast, preoperative targeting of the intact tumor with single-fraction delivery allows for treatment of a well-circumscribed, dramatically reduced target volume. In our study, identification of the tumor as a target was feasible and resulted in only 4% of the whole breast receiving prescription dose and 14% receiving half of prescription dose. With short follow-up, our single-fraction approach was well-tolerated despite skin doses that routinely

approached the dose prescribed. No patient experienced acute dose-limiting toxicity up to 21Gy. Furthermore, chronic toxicity and cosmetic outcomes at 2 years appear comparable to standard whole-breast treatment.

Long-term follow-up with larger patient cohorts will be needed to determine if this approach has comparable safety and efficacy to fractionated radiation. However, the precedent exists for the single-dose approach with multiple intra-operative series demonstrating high rates of local control. Two large randomized European equivalence trials (ELIOT, TARGIT A) have compared intra-operative radiation only to whole breast treatment[2,3] in a more diverse patient population than included in this study. Both trials found a statistically significant reduction in local recurrence for patients receiving whole breast versus intraoperative treatment (5 year ipsilateral breast tumor recurrence rate (IBTR) of 4.4% with 0.4% in ELIOT; 4-year IBTR 3.3% versus 1.3% in TARGIT-A), but the small absolute differences in both studies are unlikely to be clinically meaningful in the context of careful patient selection and low overall recurrence rates seen in the modern era.

The use of a targeted preoperative approach has been explored by other investigators. Researchers at the University of Maryland enrolled women with early stage breast cancer on a clinical trial evaluating the impact of preoperative partial breast irradiation on pathologic complete response (NCT01014715). Bondiau et al. conducted a phase I study testing 5 dose levels of focused radiotherapy delivered during preoperative chemotherapy in high-risk patients that may not otherwise have been candidates for breast conservation[21]. Surgery and conventional post-operative radiotherapy followed neoadjuvant chemoradiotherapy. Total dose ranged from 19.5Gy to 31.5Gy (10.5Gy/fraction). Only 1 grade 3 or greater treatment-related toxicity was measured over a period of 8 months. This is in contrast to the fair/poor cosmetic outcomes noted in our patient cohort when preoperative and postoperative radiotherapy was combined, despite presumably smaller target volumes. However, comorbid conditions in our group would have also increased the risk of complications associated with conventional therapy. Alternatively, it may be that the fractionation of the preoperative dose in the French series helped to decrease complication rates.

One especially exciting aspect of the preoperative approach is the potential to enhance our understanding of breast cancer radiation biology. Our MRI findings suggest that vascular permeability is increased and cellular density decreased. In concert with gene expression findings suggesting initiation of inflammatory/immune response and programmed cell death, radiation appears to induce a vigorous response that may be partially mediated through host immunity. If confirmed in larger cohorts and tied to clinical outcomes in future studies, these genes have the potential to act as radiation response biomarkers as well as therapeutic targets to enhance radiation sensitivity in more resistant tumors[22]. Furthermore, these data show the power of integrating functional imaging and gene expression in the assessment of tumor response to radiation[23,24].

Our preliminary data suggests that though the preoperative approach is feasible, well-tolerated and generates novel and interesting correlative data, it is not without limitations. The number of patients treated in this phase I trial is small and the follow-up is still short. Clinical outcomes will need to be verified in a larger patient cohort with many years of

follow-up. Furthermore, the specifics of this technique may benefit from further optimization. For example, we anticipate that the small treatment volumes in this study will reduce long-term complications. However, the large single-dose may offset the benefits of volume reduction long-term. A fractionated preoperative approach may provide a more optimal complement to the small target volume. In addition, larger treatment margins may be required to sterilize all microscopic disease. Modern studies correlating MRI and pathology findings suggest that for many cases there is general agreement to within 0.5cm. Overestimation remains common (33%) but the most worrisome finding for a preoperative technique, underestimation of tumors, was noted in only 15%[12]. In another study, 93% of patients had no invasive disease more than 10mm's beyond that identified on MRI[25]. We used a generous margin in this series, but at present, the optimal margin has not been established. In future studies, increases in the margin size would be feasible without approaching post-operative volumes.

Conclusion

This is the first report of an innovative, preoperative approach to PBI, which demonstrates clear feasibility in women with low risk, early stage breast cancer. The technique captures the appeal of a single-dose approach without incurring additional equipment costs or logistic complexities. Importantly, this approach also improves upon the inaccuracies and large treatment volume requirements of post-operative targeting. Short-term outcomes have been favorable, with toxicities at lower or expected rates than those reported with conventional external beam radiotherapy. Tumor response to radiation is marked by early radiologic and genomic indicators of immune response and cell death.

This study is a first and hypothesis-generating step towards a transformative PBI approach. Preoperative radiation should be tested in future clinical trials as it has the potential to challenge the current treatment paradigm and provide a path forward to identify radiation response biomarkers. Such efforts will inform the design of the next generation of trials evaluating preoperative radiation and biologically driven radiation therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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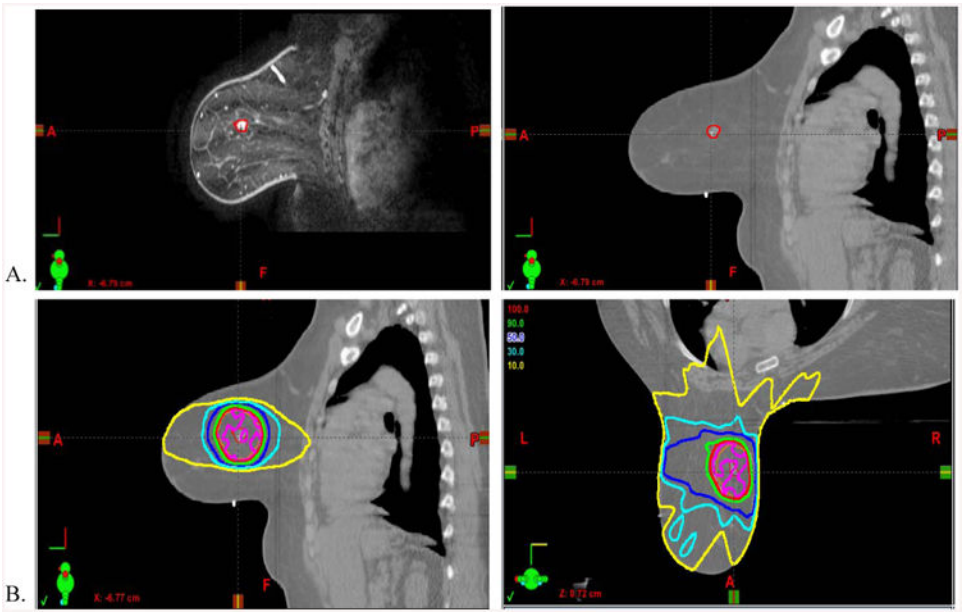

Figure 1.

Preoperative radiation to the intact tumor. Sagittal view (A) of a prone treatment planning MRI (left) and CT (right). (B) Sagittal (left) and axial (right) treatment planning images with dose distribution in the same patient.

A.

Time Point	Patient-Reported Cosmetic Outcome	Physician-Reported Cosmetic Outcome
Baseline (n=29)	28 excellent/good 1 fair/poor	29 excellent/good
6 months (n=28)	28 excellent/good	27 excellent/good 1*
12 months (n=28)	28 excellent/goood	27 excellent/good 1*
24 months (n=15)	14 excellent/good 1 fair/poor	15 excellent/good
36 months (n=4)	4 excellent/good	4 excellent/good

*missing data

B.

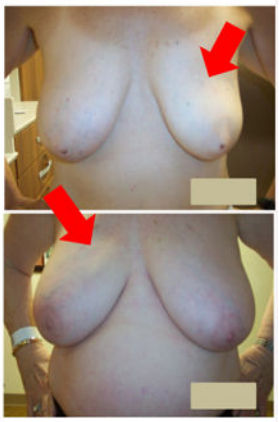

Figure 2.

Cosmetic outcomes for single-dose, definitive pre-operative partial breast irradiation. (A) Patient and physician-reported cosmetic outcomes in patients treated with preoperative radiation only. (B) Two women with more than 3 years of follow-up. Red arrows highlight the region of lumpectomy.

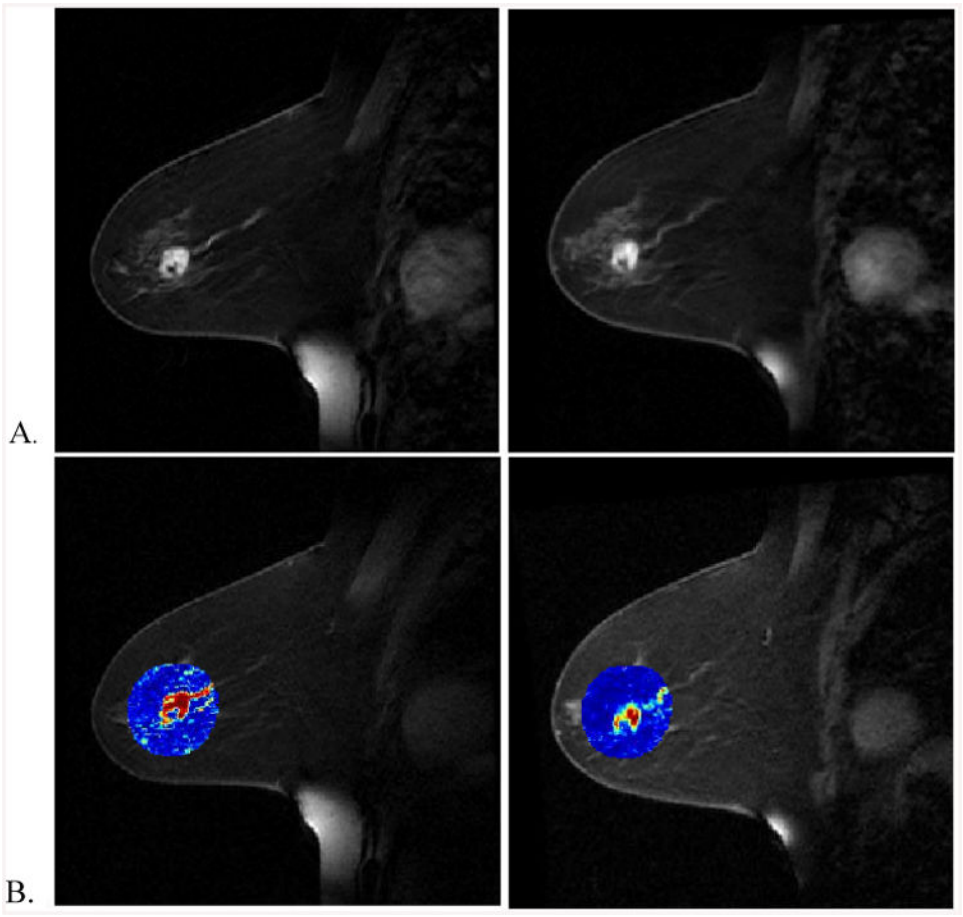

Figure 3.
Paired pre and post-radiation MRI images demonstrate evidence of increased vascular permeability. (A) Pre- (left) and post-treatment (right) DCE-MRI images. (B) Pre- (left) and post-treatment (right) images highlighting contrast agent distribution with the planning target volume.

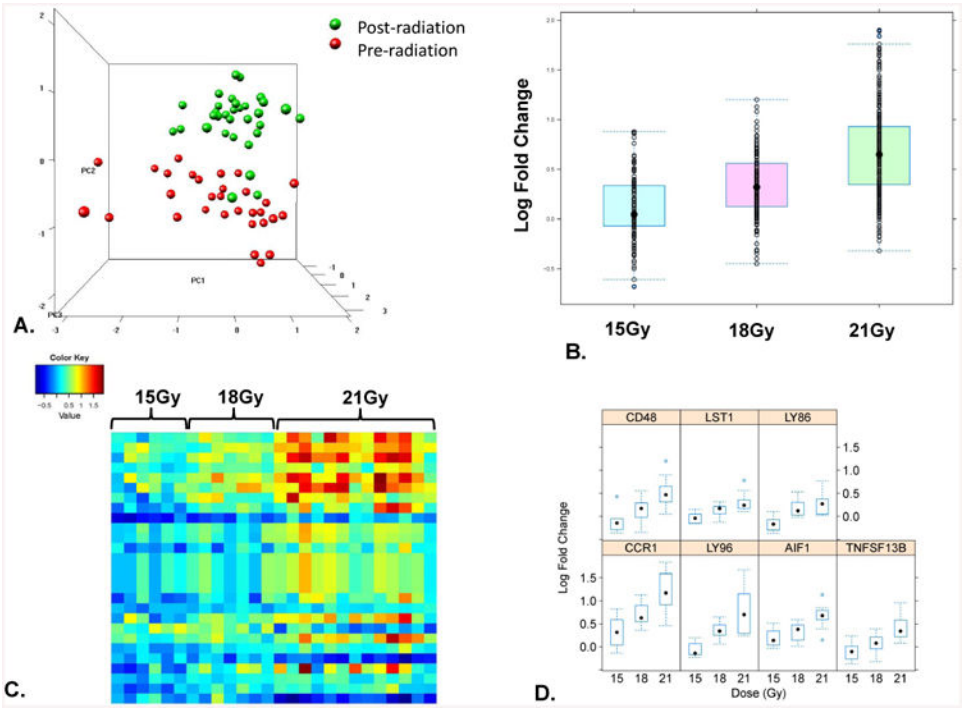

Figure 4.

Changes in gene expression following radiation in early-stage favorable breast tumors (ER +). (A) Principal component analysis suggests that gene expression profiles following radiation are significantly and consistently distinct from that noted prior to radiation. (B) The primary effect of increasing dose is to enhance, rather than repress, gene expression in the subset of 27 genes experiencing significant and dose-related change with radiation. (C) The impact of radiation on relative gene expression increases (n=24 of 27) with each incremental increase in dose. (D) The cohort of genes demonstrating significant dose-response is enriched for modulators of immunity and inflammation.

Table 1
Characteristics of Patients Treated with Preoperative Partial Breast Irradiation

Characteristic	N (%)
Age (years)	
Median (range)	66 (55-78)
Race	
White	30 (94)
Black	2 (6)
Body Mass Index	
≤ 25	7 (22)
25 < BMI < 30	14 (44)
≥30	11 (34)
Histologic type	
Ductal	24 (75)
Ductal carcinoma in situ (DCIS)	7 (22)
Invasive, other	1 (3)
Clinical Tumor Size*	
DCIS	7 (22)
T1a	4 (13)
T1b	14 (44)
T1c	7 (22)
Pathologic Tumor Size	
DCIS	
<2 cm	5 (16)
≥ 2 cm	1 (3)
T1a	4 (13)
T1b	10 (32)
T1c	12 (38)
Nodal status	
N0	25 (78)
N1	1 (3)
Nx	6 (19)
Receptor Status	
ER+/PR+	29 (91)
ER+/PR-	3 (9)
Adjuvant Systemic Therapy	
Endocrine therapy, alone	23 (72)
Endocrine and Chemotherapy	2 (6)

Characteristic	N (%)
Neither Endocrine nor Chemotherapy	7 (22)

* reflects the largest tumor diameter identified on physical exam or any breast imaging modality

Table 2

(A) Acute toxicity (90 days or less) possibly, probably, or definitely related to radiation. (B) Chronic toxicity possibly, probably, or definitely related to radiation. CTCAE: Common Terminology Criteria for Adverse Events.

(A)						
CTCAE Toxicity Term	**Total**		**Grade 1**		**Grade 2**	
	n	**%**	**n**	**%**	**n**	**%**
Breast pain	7	23%	5	16%	2	6%
Dermatitis	12	39%	9	29%	3	10%
Fatigue	2	6%	2	6%	0	0%
Fibrosis	7	23%	7	23%	0	0%
Infection	1	3%	0	0%	1	3%
Seroma	10	32%	10	32%	0	0%
Skin ulceration	1	3%	1	3%	0	0%

(B)								
CTCAE Toxicity Term	**Total**		**Grade 1**		**Grade 2**		**Grade 3**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Breast atrophy	5	16%	2	13%	2	6%	1	3%
Breast pain	6	19%	4	16%	2	6%	0	0%
Dermatitis	6	19%	5	3%	1	3%	0	0%
Fatigue	1	3%	1	58%	0	0%	0	0%
Fibrosis	22	71%	18	0%	3	10%	1	3%
Infection	1	3%	0	0%	1	3%	0	0%
Lymphedema	1	3%	0	3%	1	3%	0	0%
Pruritus	1	3%	1	6%	0	0%	0	0%
Seroma	3	10%	2	19%	1	3%	0	0%
Skin hyperpigmentation	7	23%	6	0%	1	3%	0	0%
Skin infection	1	3%	0	6%	1	3%	0	0%
Telangiectasia	2	6%	2	0%	0	0%	0	0%