



Magnetic Resonance Imaging (MRI) Identifies Multifocal and Multicentric Disease



in Breast Cancer Patients Eligible for the NSABP B-39/RTOG 0413 Partial Breast Irradiation (PBI) Trial

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INTRODUCTION

OVERVIEW OF THE NSABP B-39/RTOG 0319 TRIAL:

- Trial tests whether partial breast irradiation to the lumpectomy site plus a margin provides local tumor control comparable to whole-breast radiotherapy (WBI)
- Eligible patients have stage 0, I,II cancers no larger than 3 cm in size and no more than 3 positive lymph nodes

RATIONALE FOR NSABP B-39/RTOG 0319 TRIAL:

- First, PBI proponents argue that the “majority of recurrences” occur at the tumor bed
- Second, although histopathological studies have demonstrated the existence of multicentric disease [Rosen, *et al.*] in breast cancer patients, the biological importance of these additional areas of disease is not known

CLINICAL DATA TO SUPPORT RATIONALE:

- The proportion of in-quadrant failures varies from 83% to 100% with an average around 90% [Vaidya, *et al.*]
- The biological importance of additional areas of disease identified by histopathology has been questioned because similar survival rates were observed for patients treated with quadrantectomy plus radiation as those treated with quadrantectomy alone [Veronesi, *et al.*]

WHY IS THERE RESISTANCE TO PBI IN RADIOTHERAPY COMMUNITY?

- Breast conserving therapy (BCT) has a 94% local tumor control rate at 10 years for patients with Stage I,II cancer [Veronesi, *et al.*]; most PBI trials are reported with significantly shorter follow-up
- With such a high treatment success rate, many radiotherapists are resistant to deviating from the standard of care treatment by enrolling patients on a PBI trial
- One main concerns identified at our institution was the lack of information about potential disease elsewhere in the breast that would have been sterilized by WBI

STUDY HYPOTHESIS:

- To address these concerns, we hypothesized that MRI and confirmatory biopsies would identify patients not suitable for PBI compared to modern mammography & clinical exams
- MRI has higher sensitivity than mammography and thus can detect disease that is clinically and/or mammographically occult [Lalonde, *et al.*]
- Thus, MRI could help identify patients with concurrent invasive disease in the ipsilateral and/or contralateral breasts
- Elimination of these patients from PBI trials would increase the statistical power of the trials and would ensure that patients with concurrent disease receive the proper therapeutic management

MATERIALS & METHODS

PATIENTS INCLUDED IN THE MRI STUDY:

- Since 2002, MRI has been routinely and *non-selectively* used at our institutions for breast cancer staging
- We identified 69 patients with staging MRI between June, 2002 and August, 2005 who met entry criteria for NSABP B-39 based on mammography, ultrasonography, and initial pathologic criteria
- Although NSABP B-39 allows for the participation of patients with DCIS disease, our study focused only on patients with primary invasive disease

MAMMOGRAPHY, ULTRASOUND, & PATHOLOGY ANALYSIS:

- The initial screening mammography, ultrasonography, and biopsy pathology reports were retrospectively reviewed to determine whether the patient met entry criteria for inclusion in NSABP B-39
- Upon initial examination, each patient had:
 1. A unifocal invasive lesion no greater than 3cm in size with negative pathological margins
 2. No more than 3 positive lymph nodes
 3. No extra-capsular nodal extension

ANALYSIS OF MRI STAGING DATA:

- MRI and final pathology were then reviewed to determine whether MRI identified secondary invasive lesions or intraductal disease
- Secondary disease was classified according to location:
 1. Within the same quadrant (multifocal)
 2. In a different quadrant and at least 3 cm away (multicentric)
 3. In the contralateral breast
- All secondary lesions found by MRI were pathologically proven invasive carcinoma or ductal carcinoma in situ and would have rendered the patient ineligible for NSABP B-39
- Furthermore, the additional invasive or intraductal disease was *not identified* by the initial mammography, ultrasonography, or clinical exams

WOULD STRICTER PBI ELIGIBILITY CRITERIA AFFECT INCIDENTAL CANCER DETECTION RATE?

- Clinical data has shown that age, tumor size, and nodal status are linked to local tumor control rates [Mirza, *et al.*]
- As a result, at our institution PBI is being considered for patients with our own internal protocol guidelines:
 1. Unifocal stage I invasive carcinoma \leq 2 cm
 2. No positive nodes
- Data from the 69 patients were re-analyzed for this smaller subset of patients to determine whether employment of stricter inclusion guidelines would reduce the incidence of multifocal, multicentric, or contralateral disease missed by mammography, ultrasonography, and clinical exams

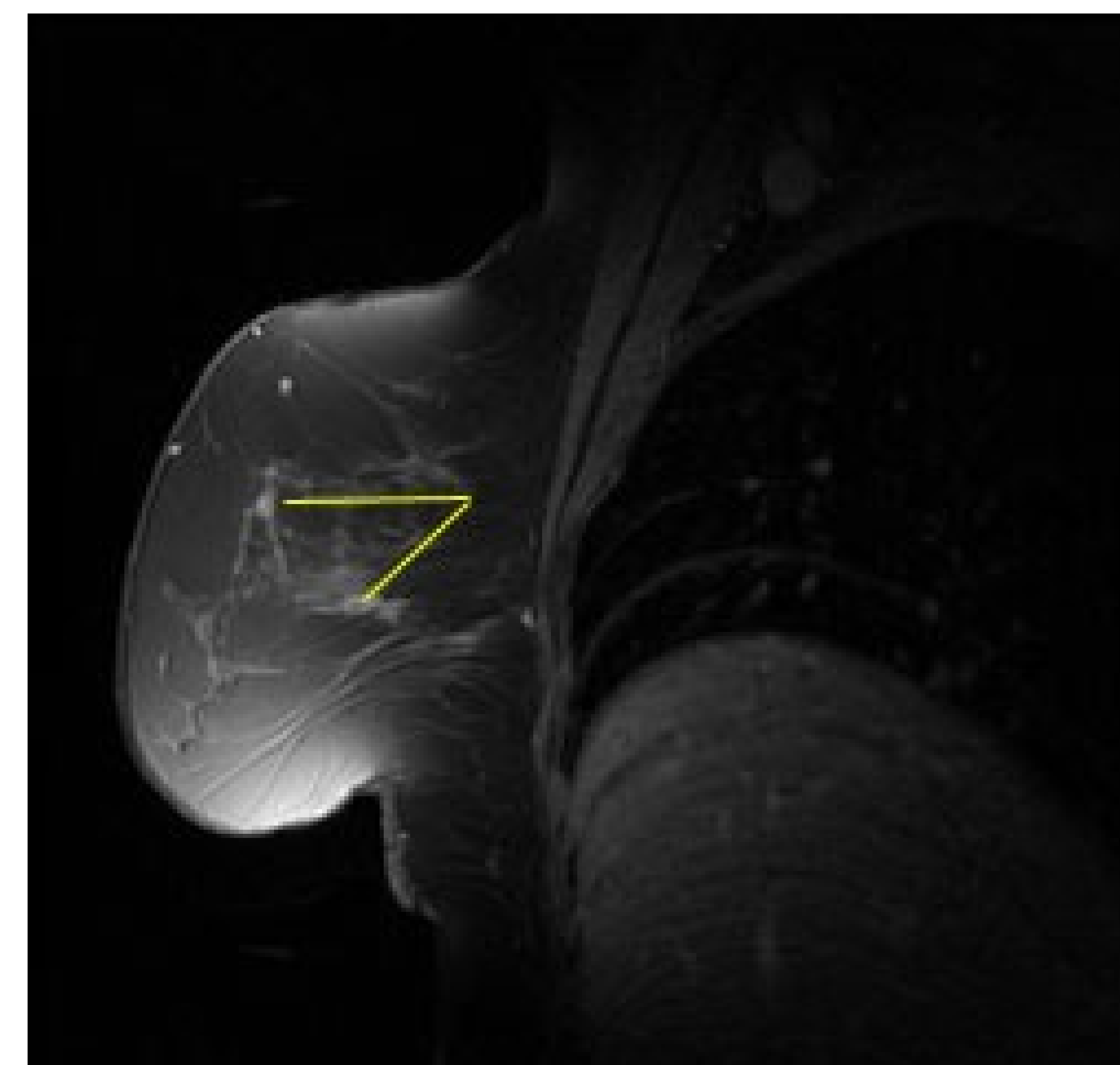


Figure 1. Incidental invasive lesion identified by MRI on the same sagittal slice as the initial cancer

RESULTS

MRI IDENTIFIES INCIDENTAL LESIONS:

- Table I demonstrates that MRI identified secondary disease in 13% of patients analyzed
- The 95% confidence interval (CI) of 6.1% - 23.2%, demonstrates that this percentage is significantly different from zero
- Even in this limited sample size, MRI identified a significant number of secondary disease compared to mammography, ultrasonography, and clinical exams
- Multifocal disease was identified in 7.2% of patients, multicentric disease in 4.3% of patients, and contralateral disease in 1.4% of patients

STRICTER PBI CRITERIA DO NOT ALTER INCIDENTAL LESION DETECTION RATE:

- 52% of all patients would have met the more stringent inclusion criteria for PBI at our institution
- MRI identified secondary disease in 11.1% of these patients (95% CI: 3.1% - 26.1%)
- The percentage distributions of multifocal and multicentric disease were not significantly different with the use of more stringent PBI eligibility criteria
- Thus, altering the PBI criteria by tumor size and nodal status did not change the rates of secondary disease identified by MRI

3D MRI STAGING HELPS CLINICAL MANAGEMENT OF PATIENT:

- MRI exams of 2 patients correctly identified a single primary lesion, which had been identified as two separate lesions by the mammography exams
- MRI also found primary invasive lesions in 3 patients in which mammography did not detect any mass but merely detected suspicious calcifications
- Finally, MRI did prompt biopsies in 3 patients that were histopathologically negative (i.e., a 4.3% false positive rate)

DISCUSSION

MRI IDENTIFIES INCIDENTAL LESIONS THAT WOULD NOT HAVE BEEN INCLUDED IN PBI TREATMENT:

- Our results show that MRI identified frequent secondary lesions, not otherwise found by standard screening or clinical exams (i.e., incidental lesions)
- The incidental lesions reported on in this study would not have been included in either the surgical or the PBI radiation field

- In fact, our data provides evidence that so-called ipsilateral “recurrences” away from the tumor bed following even WBI could simply have been incidental lesions that were present at the time of initial diagnosis
- The ipsilateral tumor recurrence (ITR) rate would have increased had these patients been included in a PBI trial

MRI STAGING SHOULD BE USED TO ASSESS PBI ELIGIBILITY:

- At our institution, MRI is used routinely for breast cancer staging because it has been shown to have higher sensitivity than mammography [Lalonde, *et al.*]
- MRI has also been shown to detect incidental cancer in women at a significantly higher rate than mammography examination [Schnall, *et al.*]
- Our data demonstrate that MRI should be used to assess PBI eligibility in order to minimize out-of-field failures and to reduce the potential difference in ipsilateral tumor control rates between PBI and WBI (by which smaller tumors may have been sterilized)
- Moreover, MRI assessment for PBI eligibility could allow PBI trials to reach the “upper-limit” of ITC rates
- Since PBI essentially treats the affected “quadrant” of the breast, tumor control rates could be expected to be less than or at best equal to those of quadrantectomy surgery alone [Veronesi, *et al.*]

MRI COULD MINIMIZE OUT-OF-QUADRANT FAILURES IN PBI TRIALS:

- As a result of the retrospective nature of this study, these data represent a minimum of multifocal and multicentric disease that exist in the population eligible for the NSABP study
- Other investigators [Schnall, *et al.* and Berg, *et al.*] have shown that MRI detects incidental lesions at a 6-11% higher rate than standard screening and clinical exams
- Our results demonstrate that 3D image guidance such as MRI should be strongly considered to assess PBI eligibility in order to minimize out-of-quadrant failures
- MRI staging would also give a PBI clinical trial more power to succeed and to correlate well with the long term failure patterns seen in the quadrantectomy data from the Milan series

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Table 1. MRI Identifies Multifocal, Multicentric, Contralateral Disease

	NSABP B-39 / RTOG 0319 PBI Criteria [N/Total (%)]	The University of Chicago PBI Criteria [N/Total (%)]
Patient Mean Age (years)	57	57
Patient Age Range (years)	34-87	35-80
All Invasive Secondary Lesions	9/69 (13.0%)	4/36 (11.1%)
Multifocal Secondary Disease	5/69 (7.2%)	2/36 (5.6%)
Multicentric Secondary Disease	3/69 (4.3%)	2/36 (5.6%)
Contralateral Secondary Disease	1/69 (1.4%)	0/36 (0%)