



## **MRI In Breast Cancer: Is Seeing Always Believing?**

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### **Monica Morrow, MD**

Chairman, Department of Surgical Oncology  
G. Willing Pepper Chair in Cancer Research  
Fox Chase Cancer Center, Philadelphia, Pennsylvania

The following summarizes Dr. Morrow's presentation.

### **Summary**

- Breast-conserving therapy (BCT) is now a well-established technique with long-term follow-up in multiple prospective, randomized trials.
- The clinical indications for mastectomy are relatively few, e.g., patients who cannot receive breast irradiation, either secondary to pregnancy or prior radiotherapy to the breast; the inability to reduce the tumor burden to a subclinical level where it can be controlled with radiation; and the inability to achieve negative margins.
- Previous studies suggest that for women with stage 1 disease, contraindications to BCT were present only in about 10%. That percentage increased to 30% for women with DCIS and stage 2 disease.<sup>1</sup>
- In determining the role of MRI in selecting patients for BCT, we need to identify what clinical benefits this study provides. At issue is the "garden variety patient with breast cancer," not the rare cases of women with gene mutations.

### **Conventional Imaging**

- Earlier studies suggest that the bar is set relatively high for improving patient selection on the basis of an additional imaging modality, i.e., MRI. For example, in a study of 263 women with DCIS or stage 1 and 2 cancers, evaluated with relatively "primitive" mammography, 216 were considered candidates for BCT. Of these, the conversion rate to mastectomy was only 3%.<sup>2</sup>

## MRI Performance Studies

- Single-institution studies indicate that MRI will detect additional cancer in from 10% to 33% of patients with unicentric breast cancer identified by physical exam and mammography (Table 1).

**Table 1. Studies of MR in Women with Breast Cancer**

| <u>Author</u> | <u>Year</u> | <u>n</u> | <u>% additional cancer</u> |
|---------------|-------------|----------|----------------------------|
| Harms         | 1993        | 29       | 34                         |
| Boetes        | 1995        | 61       | 15                         |
| Mumtaz        | 1997        | 92       | 11                         |
| Fisher        | 1999        | 336      | 16                         |
| Drew          | 1999        | 178      | 23                         |
| Esserman      | 1999        | 58       | 10                         |
| Liberman      | 2003        | 70       | 19                         |
| Furman        | 2003        | 76       | 13                         |
| Bedrosian     | 2003        | 267      | 15                         |

- Similar results were found in a multi-institutional study involving 426 women with primarily invasive breast cancer treated at 14 sites in the U.S. and Europe. About half of the patients had palpable cancers (1.8 cm median diameter). Only 14% of the women had pure DCIS.<sup>3</sup>
- Of the 426 women, 103 had additional MRI abnormalities >2 cm from the primary tumor. Of these 103 abnormalities, 78 were biopsied and 56 additional cancers were found, representing 10% of the entire study population.<sup>3</sup>
- Data from the University of Pennsylvania MRI center addresses how these additional lesions may impact clinical management. In this series of 267 diverse patients (T1 to T4 lesions), about a quarter of the women (N = 69) had additional disease identified by MRI. Of those 69 women, 44 underwent a mastectomy that they would not otherwise have had without the MRI exam. Eleven patients underwent a wider excision, and the final 5% had a separate excisional biopsy. In this study, where all of these lesions were not confirmed by pretreatment biopsy, only 71% could be pathologically verified as cancer.<sup>4</sup>
- In another recent study of MRI clinical outcomes, Berg studied 121 women with cancer who underwent pretreatment MRI.<sup>5</sup> Of these women, 12% went on to have what was termed an unnecessary mastectomy, often as the patient's choice upon being told that she had an MRI abnormality. Almost half of these women had MRI findings such as are illustrated in presentation slide 12.
- Studies by Morrow et al corroborate this finding that women often choose to undergo mastectomy when they fear recurrence. (See presentation slide 13.) Thus, identification of multiple benign abnormalities on MRI and the high-false positive rate carries with it significant clinical consequences.

- Other clinical consequences of MRI are apparent in the Berg study.<sup>5</sup> In the 96 women considered candidates for BCT on the basis of a conventional evaluation, MRI examination revealed that 29 (30%) patients had larger areas of cancer than were initially expected and they therefore underwent more extensive lumpectomies. In 20 of these 29 women, the extent of disease was overestimated, resulting in excessive uplifting and shrinkage of the treated breast due to excessive sacrifice of normal breast tissue.

### **Local Recurrence**

- As a result of improvements in mammography, more detailed pathologic evaluation of margins, and the routine use of adjuvant systemic therapy, local recurrence rates have plummeted.
- Studies by Holland show that 40% of additional pathologic tumor foci are located at a distance >2 cm from the known primary tumor and are not being surgically resected in the majority of cases treated with conventional American lumpectomy.
- Distribution studies suggest that MRI-detected tumors and pathologically detected tumors are the same cancer. In studies by Holland, 95% were within 4 cm of the primary tumor.
- In two other MRI studies by Berg and Liebermann, 87% and 73% of these tumors, respectively, are located within 4 cm or within the same quadrant as the primary tumor.
- There has been one direct comparison, which looked at the correlation of serial subgross sectioning and MRI findings in 99 women who underwent mastectomy. Investigators found that the sensitivity of MRI for detecting pathologic foci of disease was about 81%. The positive predictive value was 68%. Note that there was no difference in this study in positive predictive value, between MRI and mammography, and the benefit of MRI was limited to women with dense breasts.
- A retrospective case control study by Morrow et al matched women with pure infiltrating lobular cancer or mixed ductal and lobular cancer to women with pure infiltrating ductal cancer on the basis of stage, year of diagnosis and menopausal status. Investigators found that lobular cancers tended to be slightly larger than ductal cancers, and therefore there was a small difference in eligibility for BCT. However, if they looked at patients selected for BCT by physical exam, diagnostic mammography, and ultrasound of the primary tumor site, the failure rate (9%) was identical.
- The investigators also looked at the number of surgeries needed to achieve negative margins on univariate analysis. There was a significant difference here in favor of ductal cancer, with only 21% of women with ductal cancer requiring >2 excisions compared to 25% of those in the lobular group. The absolute difference of 4% fails to justify the routine use of MRI in all women with lobular cancer, and after adjustment for tumor size and patient age, no difference in the number of excisions on the basis of histology was observed.

## Clinical Outcomes

- Published studies fail to demonstrate a difference in the incidence of local failure in women with infiltrating lobular versus infiltrating ductal carcinoma, although a study by Kurtz shows a trend with no statistical value.
- In a large study of 4,000 lobular cancers versus 45,000 ductal cancers, we see no difference in 5-year disease-free survival.
- Pathology tells us that apparently localized breast cancer is in fact multifocal or multicentric in anywhere from a third of cases to as many as 63% of cases. MRI now allows us to detect some but not all multifocal cancers.
- However, for patients selected for treatment on the basis of mammography and clinical exam, local failure rates are <10%. Most of these foci of clinically and mammographically occult carcinoma are controlled by radiotherapy.

## Conclusions

- The potential benefits of MRI are a decreased rate of local recurrence and an increased likelihood of achieving negative margins with a single operation. To date, these remain scientifically unproven. These have been observed.
- The potential risks of MRI are an increased likelihood of mastectomy, increased number of breast biopsies, and increased cost.
- At present clinical evaluation and diagnostic mammography, tools available in all breast practices throughout the U.S. and the world, identify women who require mastectomy with a high degree of accuracy.
- The routine use of MRI outside of a clinical trial is not appropriate until actual evidence of clinical benefit to the patients has been clearly demonstrated.

## Selected References

1. Morrow M. *J Am Coll Surg*, 1998.
2. Morrow M, et al. *Surgery* 1995.
3. Schnall et al. *ASCO* 2004.
4. Bedrosian. *Cancer*. 2003.
5. Berg. *Radiology*. 2004.