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Preoperative Breast MRI in the Surgical Treatment of Ductal Carcinoma In Situ

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■ **Abstract:** Accurate determination of the size or extent of ductal carcinoma in situ (DCIS) by imaging is uncertain, and incomplete resection of tumor results in involved margins in up to 81% of cases. This study examined the accuracy of magnetic resonance imaging (MRI) for assessment of DCIS size, and evaluated the effect of preoperative breast MRI on achievement of tumor-free surgical margins after breast-conserving surgery (BCS). One-hundred and fifty-eight female patients with DCIS were identified from a prospective database: 60 patients (62 cases) had preoperative breast MRI, and 98 patients did not have MRI. The accuracy of tumor size assessed by MRI was determined by comparison with histopathologic size. All patients underwent BCS initially. The rate of involved margins after resection was compared in MRI and no-MRI groups. The overall correlation between MRI size and histopathologic size was high ($p < 0.0001$). MRI assessment of size was significantly more accurate when DCIS was high grade ($p < 0.0001$) or intermediate grade ($p = 0.005$) versus low grade ($p = 0.187$). The rate of tumor-involved margins was not significantly different in MRI and no-MRI groups (30.7% and 24.7%, respectively; $p = 0.414$). The rate of mastectomy was significantly higher in the MRI group than the no-MRI group (17.7% versus 4.1%; $p = 0.004$). These findings indicate that MRI can detect DCIS, especially when lesions are high or intermediate grade, but that MRI does not accurately predict the size of DCIS. In this study, MRI did not improve the surgeon's ability to achieve clear margins following BCS. ■

Key words: ductal carcinoma in situ, MRI, tumor margin

Ductal carcinoma in situ (DCIS) accounts for approximately 25% of breast malignancies that are diagnosed in the United States, with 32.5 per 100,000 women affected each year (1). The rate of inadequate or tumor-involved specimen margins after initial definitive breast-conserving surgery (BCS) for DCIS has been reported to be as high as 81% (2).

Ductal carcinoma in situ is typically detected as microcalcifications on screening mammography. It is known, however, that mammography may underestimate extent of DCIS because of its inability to detect noncalcified disease (3). Larger tumor size is a predictor of re-excision for tumor-involved margins in both invasive breast cancer and DCIS, and predicts the likelihood of local relapse (4,5).

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Magnetic resonance imaging (MRI) is a good predictor of tumor size in invasive breast cancer in close to 100% of cases (6,7). Past studies have suggested that MRI is less reliable in the detection of DCIS than in invasive breast cancers. Early studies, in particular, cite variable sensitivities ranging from 33% to 100% (8–11). However, more recent studies have shown perhaps an improved MRI detection of DCIS with sensitivities ranging from 73% to 100% (2,12–15), suggesting that technique and interpretation have improved over time.

The goal of this study was to evaluate the accuracy of preoperative MRI as compared with histopathologic evaluation for assessment of DCIS size. In addition, we sought to determine whether or not preoperative MRI was linked to higher rates of tumor-free surgical margins for patients undergoing BCS.

PATIENTS AND METHODS

Female patients over 18 years of age, diagnosed with DCIS and treated at the John Wayne Cancer Institute between December 2002 and June 2009,

were identified from a prospectively maintained database. This was a single-institution review, and all patients were treated by surgical staff of the John Wayne Cancer Institute. All patients underwent BCS as the initial surgical procedure; if margins were involved, then further excision or mastectomy was undertaken. Patients were excluded if they were found to have invasive or microinvasive disease. Patients who did not undergo operation at the John Wayne Cancer Institute were also excluded, as were women whose initial surgical procedure was mastectomy.

Of the 183 patients identified from the database, 158 were eligible for study. Of these, 60 patients underwent preoperative breast MRI; two of these patients had bilateral DCIS (Table 1). Breast MRI was performed after core biopsy, but before segmental resection.

This study was approved by the John Wayne Cancer Institute Institutional review board (IRB).

MRI Technique, Specifics, and Analyses

Magnetic resonance imaging examination of all cases was performed on a GE Signa Excite (11.0) 1.5 Tesla magnet using a dedicated four-channel In Vivo breast coil. All studies were obtained with axial signal acquisition of both breasts using compound imaging VIBRANT technique. Fat-saturated T1 and T2 sequences were performed, followed by serial T1 imaging after injection of 15-mL Omniscan (287 mg/ mL; GE Healthcare, Princeton, NJ). Postprocessing included subtraction imaging in conjunction with CADstream software analysis, and sagittal and coronal reconstructions. Findings considered suspicious included enhancing masses and focal nonmass enhancement. Nonmass lesions suspicious for DCIS were characterized as ductal, segmental or regional. Early (''wash-in'') and delayed (''wash-out'') enhancement kinetics were assessed, as well as peak enhancement, measured as a percentage compared with background at 90 seconds.

Radiologists interpreting MRI studies were not blinded to other imaging studies, core biopsy or excisional biopsy histopathology results.

Table 1. Table Comparing Demographics of Patients who did and did not Receive Preoperative Breast MRI

Demographic variables	Preoperative MRI (*n*)	No preoperative MRI (*n*)	p-values
Year of diagnosis			
2002–2004	1	48	p = 0.001
2005–2006	9	41	
2007–2009	50	9	
Age (mean years)	55 ± 9	62 ± 14	p = 0.001
DCIS lesion size on histopathology (mean cm)	2.78 ± 2.56	2.09 ± 1.89	p = 0.055
ER positive tumor	74.6%	75%	p = 0.954

Histopathologic Review

Histopathologic size of DCIS was the standard against which MRI assessment was compared. During BCS, efforts were made to excise all DCIS completely, and all excised tissue was analyzed and sectioned at 3-mm intervals. When the neoplasm was confined to a single section, lesion size was based on the greatest distance measured between ducts involved. When DCIS was detected in multiple histologic sections, size was measured in all sections and lesion size was based on the greatest distance measured. When multifocality was detected, the size of the largest lesion was used. Although histopathologic size of DCIS was based on the BCS specimen, if re-excision for involved margins was necessary, pathologists used the newly excised biopsy cavity as a landmark for additional size estimation.

All patients had undergone diagnostic biopsy to investigate mammographic abnormalities. All, but three patients underwent stereotactic core biopsy; three patients had excisional biopsy because stereotactic core needle biopsy could not be performed. In all three cases, incomplete removal of tumor required additional definitive excision (BCS).

In addition to size, tumors removed during BCS were analyzed for low, intermediate and high nuclear grade. The presence or absence of comedo necrosis was documented, as was the presence or absence of tumor estrogen receptors. Margins were classified as clear (tumor >1 mm from the specimen edge) or involved (tumor <1 mm from the specimen edge).

Statistical Analysis

Associations between categorical variables were analyzed using Fisher's exact test and chi-square analysis. Continuous variables were compared between groups using Student's *t*-test and Wilcoxon rank sum test. A Pearson correlation coefficient was used to examine the correlations of two continuous variables. A p-value less than or equal to 0.05 was considered to be statistically significant. Stepwise multivariate logistic regression analysis was performed to identify the significant predictors of mastectomy and to determine variables

predictive of involved tumor margins. Statistical analysis was performed using SAS 9.13 (SAS, Cary, NC).

RESULTS

Mean (± standard deviation) age was 60 ± 12 years overall: 55 ± 9 years (range, 35–78 years) in the MRI group and 62 ± 14 years (range, 38–93 years) in the no-MRI group ($p < 0.001$). Estrogen receptor expression, available for 143 cases, was not significantly different between the MRI group (44 of 59, or 74.6%) and the no-MRI group (63 of 84, or 75%). The rate of tumor necrosis also was not different between MRI (43 of 62, or 69.4%) and no-MRI (64 of 98, or 65.3%) groups. High-grade DCIS was significantly associated with necrosis ($p < 0.0001$).

The histopathologic size of DCIS in the MRI group (mean 2.09 ± 1.89 cm; range, 0.2–10 cm; $p = 0.055$) was significantly different from the histopathologic size of DCIS in the no-MRI group (mean 2.78 ± 2.56 cm; range, 0–10 cm) (Table 1). As shown in Table 2, univariate analysis revealed that MRI assessment of tumor size was more accurate in high-grade and intermediate-grade DCIS as compared with low-grade lesions. Among DCIS of all grades, mean tumor size was 2.15 ± 2.24 cm (range, 0–9 cm) by MRI assessment and 2.78 ± 2.56 cm (range, 0–10 cm) by histopathologic evaluation. Although MRI and histopathologic measurements of DCIS size were closely correlated ($r = 0.76$; $p < 0.0001$), their accuracy was not. The correlation between MRI and histopathologic size measurement is illustrated in Figure 1. We found that MRI underestimated or overestimated true histopathologic size in 70.7% of cases: underestimation occurred by 30% in 53.5% of cases, and histopathologic size was overestimated by 30% in 17.2% of cases (Fig. 1).

The rate of tumor-involved margins after BCS did not significantly differ between the no-MRI group and the MRI group (24.7% and 30.7%, respectively, $p = 0.414$). Patient age, preoperative MRI, histopathologic tumor size, MRI tumor size, grade, ER status, and presence of necrosis were analyzed for their association with margin status. Univariate analysis showed that high-grade tumors were more likely to be associated with positive margins (34.5%) than were low-grade or intermediate-grade tumors (18.9%) ($p = 0.028$). Larger histopathologic tumor size also increased the likelihood of margin involvement ($p < 0.0001$); mean histopathologic tumor size was 3.89 cm in patients with tumor-involved margins, as compared with 1.82 cm in patients with clear margins. In stepwise logistic regression analysis, only histopathologic size remained a significant predictor of margin status for all patients (odds ratio [OR] 1.522; 95% CI 1.268–1.826; $p < 0.0001$), and high-grade lesions became a significant predictor of positive margins only within the MRI group ($p = 0.039$).

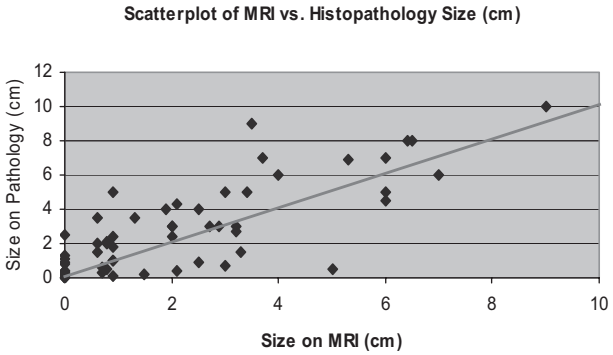

Figure 1. Scatter plot of MRI versus histopathology size measurements.

Table 2. Correlation Between MRI size and Histopathologic size in Different Tumor Grades

		Mean tumor size (cm)		
Tumor grade	Number of cases	MRI	Histopathology	p-value
All Grades	62	2.15	2.78	<0.0001
Low	7	1.40	0.46	0.187
Intermediate	21	1.98	2.29	0.005
High	34	2.48	3.63	<0.0001

The rate of mastectomy after attempted BCS was significantly lower in patients who did not undergo preoperative MRI (4.1% versus 17.7%; $p = 0.004$) (Table 3). In both groups, women who had mastectomy tended to be younger (<50 years) than those who did not have mastectomy, but this was not statistically significant ($p = 0.125$). On multivariate analysis of the combined MRI and no-MRI groups, both histopathologic size (OR 1.483; 95% CI 1.164–1.891; $p = 0.0014$) and margin tumor involvement (OR 4.190, 95% CI 1.147–15.300; $p = 0.030$) were significant predictors of mastectomy. When the MRI group was separately studied, only histopathologic size predicted an increased mastectomy rate (OR 1.41, 95% CI 1.091–1.831; $p = 0.009$).

DISCUSSION

Since its use as an investigational diagnostic tool in 1982, the use of breast MRI for preoperative planning

for management of invasive breast cancer has been controversial (16). Over the years, with improved MRI interpretation and biopsy techniques, preoperative breast MRI has become more widely used. MRI identification of tumor depends on the presence of enhancement caused by tumor-induced angiogenesis (17). An increased density of microvasculature will increase blood flow, thereby causing contrast enhancement. In addition, tumor-induced microvasculature often demonstrates structural abnormalities which give rise to leakage of the contrast agent. This leads to the characteristic malignant contrast enhancement known as washout phenomenon (18).

Magnetic resonance imaging of DCIS often does not exhibit the same characteristics seen with invasive cancers (19). Previous studies have found that MRI findings suspicious for DCIS include nonmass enhancement, especially in a ductal or segmental/linear pattern, and variable perfusion patterns including delayed washout, plateau, and persistent kinetics (20).

Magnetic resonance imaging reportedly detects high-grade and intermediate-grade DCIS more accurately than low-grade DCIS (14,21); our findings confirmed a very strong correlation between MRI size and histopathologic size in these lesions. Given the small number of patients with low-grade DCIS in this study, further conclusions regarding low-grade DCIS lesions and MRI size-estimation accuracy cannot be made.

Mammography has been shown to be inaccurate for determination of DCIS size. In a large retrospective study of 2564 DCIS patients, Thomas *et al.* found that preoperative imaging with mammography underestimated the extent of disease in 30% of patients undergoing BCS (3). They concluded that this underestimation of disease extent resulted in a requirement for further surgery. Similarly, in a retrospective analysis of 86 cases of histologically proven pure DCIS, Santamaria *et al.* noted that mammography alone underestimated the extent of DCIS by 18.6%, and that MRI underestimated the extent of DCIS by 31.4% (12). However, when both mammography and breast MRI were used, the extent of DCIS was underestimated by only 8%. In a large prospective observational study, Kuhl *et al.* found that 48% of DCIS was missed by mammography, but detected on MRI (13). This variability in ability to accurately measure DCIS extent was also demonstrated in a recent retrospective cohort study by Allen *et al.* (15). In that study, there were fewer tumor-involved margins among patients who underwent preoperative MRI compared with those who did not (21.2% versus 30.8%). However, this finding was not statistically significant.

Tumor-involved margins after BCS for DCIS range from 20% to 81% (2,3,14,22–25) and continue to be a source of frustration, cost, and concern. Importantly, tumor-involved margins have been found to be one of the strongest predictors of local recurrence (22,26–28). Studies reporting correlation of MRI and histopathologic size must also report accuracy as correlation may be seen even if size estimate is inaccurate. In our study, though tumor size assessment by MRI strongly correlated with histopathologic size, preoperative MRI did not reduce the rate of tumor-involved margins. The size of DCIS was the strongest predictor of tumor-involved margins.

The goal of the present study was to evaluate the effect of MRI on the surgical treatment of DCIS. As previously noted Allen, *et al.*, found that MRI may assist in surgical planning (15). Several other studies have been published in the literature that specifically address the impact of MRI and margin status in breast cancer (both in situ and invasive) and are summarized in Table 4. Two of the retrospective studies found very low rates of re-excision/involved tumor margins in patients who had preoperative MRI, but they did not compare rates of re-excision/involved tumor margins with patients who did not receive a preoperative MRI (Grobmyer 2008 and Hollingsworth 2008) (29,30). In one recent retrospective study, preoperative MRI was found to result in reduced re-excision rates

Table 3. Relationship Between Patient age, Preoperative Breast MRI, and Final Surgical Treatment. The Percentage of Patients who Received Either BCS or Mastectomy is Given in Parentheses

Final surgical treatment	MRI assessment of tumor size		p-value
	no-MRI (n = 98 cases)	MRI (n = 62 cases)	
BCS			
<50 years	20 (90.9%*)	14 (74%*)	NS
50–64 years	28 (93%*)	28 (90%*)	NS
>65 years	46 (100%*)	9 (75%*)	NS
Overall	94 (95.9%)	51 (82.3%)	NS
Mastectomy			
<50 years	2 (9.1%*)	5 (26%*)	NS
50–64 years	2 (7%*)	3 (10%*)	NS
>65 years	0	3 (25%*)	NS
Overall	4 (4.1%)	11 (17.7%)	0.004

NS, not significant.
*Percentage of all cases in this age group.

Table 4. Effect of Breast MRI on Incomplete Tumor Excision or Margin Status in BCS: Review of the Literature

First author	Type of study	Number of total cases	Tumor-involved margins or re-excision rates			Type of breast cancer
			MRI	no-MRI	p-value	
Turnbull, 2010 (34)	RCT	1623	19% (re-excision rate)	19%	0.77	Both DCIS and invasive cancers
Allen, 2010 (15)	Retrospective	98	21.2% (involved margins)	30.8%	0.41	DCIS only
Grobmyer, 2008 (29)	Retrospective	79	10% (re-excision rate)	All patients had MRI	–	Both DCIS and invasive breast cancers
Bleicher, 2009 (31)	Retrospective	577	21.6% (involved margins)	13.8%	0.20	Both DCIS and invasive breast cancers
Hollingsworth, 2008 (30)	Retrospective	603	8.8% (re-excision rate)	All patients had MRI	–	Both DCIS and invasive breast cancers
Hwang, 2009 (32)	Retrospective	472	11.8% (re-excision rate)	13.3%	0.50	Invasive breast cancer
Mann, 2010 (37)	Retrospective	267	9% (re-excision rate)	27%	0.010	Invasive lobular carcinoma
Pengel, 2009 (33)	Prospective Nonrandomized	349	13.8% (incomplete tumor excision rate)	19.4%	0.17	Invasive breast cancer

for involved margins (Allen 2010) (15). However, these findings are not consistent in the literature, as Bleicher *et al.* found that those who had preoperative MRI had a higher rate of tumor-involved margins compared with those who did not have MRI. (31–34,37). The COMICE (Comparative Effectiveness of MRI in Breast Cancer) trial was the only randomized trial on preoperative breast MRI that has been published in the literature. The authors evaluated surgical margin status in patients who underwent preoperative breast MRI for early breast cancer. In this economic analysis, patients with either non-invasive or invasive breast cancer were randomly assigned to receive either MRI or no further imaging. In this study of over 1600 women, reoperation rates were identical in MRI versus no-MRI patients (34). The authors concluded that MRI might not be necessary to reduce repeat operation rates in patients with early, newly diagnosed breast cancer. Though the nonrandomized trial by Pengel *et al.* did not reveal an overall significant difference in re-excision rates with preoperative MRI, it should be noted that when they stratified surgical outcome by histologic subtype, they did find that the incompletely excised infiltrating ductal carcinoma was significantly associated with absence of MRI (33).

The MONET (MR Mammography of Nonpalpable BrEast Tumors) randomized clinical trial is underway, with the purpose of investigating whether MRI will improve breast cancer management for nonpalpable tumors; results from this Netherlands trial are not yet available (35).

Whether or not preoperative MRI results in an increased mastectomy rate remains unclear. In a recent large meta-analysis of 10 prospective and 7 retrospective studies, Houssami *et al.* found that MRI staging overall was associated with more extensive breast surgery (36). MRI in the present study was significantly associated with an increased mastectomy rate; however, women who had MRI tended to have larger tumors ($p = 0.055$) and were younger ($p < 0.001$), which may also have influenced the mastectomy rate.

Despite the high correlation between MRI size and histopathologic size measurement of DCIS, MRI appears to have overestimated or underestimated the tumor size in over 70% of patients, thus revealing a low level of true accuracy in size estimation. In the present study, MRI did not favorably impact the surgeon's ability to achieve clear margins and may not be of value to this end in patients with DCIS.

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