

Relationship between Pre-Operative Breast Magnetic Resonance Imaging-Detected Additional Cancer and Survival Outcomes: A Retrospective Multi-Center Study

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Purpose: To determine the additional cancer detection yield of pre-operative magnetic resonance imaging (MRI) in women with invasive breast cancer that was occult on mammography and ultrasonography (US), identify women with likelihood to develop MRI-detected additional cancer (MDAC), and compare long-term outcomes between patients without pre-operative MRI and those with pre-operative MRI or MDAC.

Materials and Methods: This retrospective multi-institutional study was conducted between January 2010 and December 2012. Among 2,104 women who had undergone surgery for invasive breast cancer, pre-operative MRI examinations of 1,808 women were reviewed for the presence of MDAC. Logistic regression analysis was conducted to determine factors associated with MDACs. We identified patients with unilateral breast cancer who underwent breast-conserving surgery (BCS) with radiation therapy and compared disease-free survival (DFS) between patients with and without pre-operative MRI and between patients with MDACs and without MRI, using Cox proportional hazards model and Kaplan-Meier curve analyses.

Results: Of 1,808 patients, 174 (9.6%) had MDAC. Multivariate analysis showed that invasive lobular cancer (ILC) (odds ratio: 2.522, 95% confidence interval [CI]: 1.281, 4.647; $P = .005$) and premenopausal status (odds ratio, 1.471; 95% CI: 1.063, 2.054; $P = .022$) were independently associated with higher probability of MDAC. Patients with pre-operative MRI or MDAC were not significantly associated with better DFS as compared to those without MRI ($P = .229$ and $.693$, respectively).

Conclusion: ILC and premenopausal status were associated with greater likelihood of pre-operative MRI to detect MDAC. However, pre-operative MRI had no significant impact on DFS.

Index words: Breast; Breast Cancer; Magnetic resonance imaging; Prognosis; Survival

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Introduction

Due to its extremely high sensitivity, breast magnetic resonance imaging (MRI) has been widely used to evaluate breast cancer (1, 2). This technique is used before surgery to determine the extent of disease, assist in surgical planning, and assess the need for neoadjuvant systemic therapy (3–5). Pre-operative breast MRI is growing in popularity because it can detect occult disease that might be undetected or overlooked by traditional breast imaging (3–5). The reported incidence of additional MRI-detected disease varies between 3% and 34% in the ipsilateral breast and between 3% and 24% in the contralateral breast (6, 7). Therefore, breast MRI seems to be beneficial for patients; it allows more complete staging and can be used to guide optimized resection and tailor adjuvant systemic treatment. Nevertheless, randomized clinical trials, systematic reviews, and meta-analyses have consistently failed to show that pre-operative MRI improves surgical outcomes, breast cancer recurrence rates, or survival (8–14).

For this reason, several authors have suggested that pre-operative MRI should only be used when it is likely to provide additional information (15–18). Iaconi et al. (19) analyzed the characteristics of 73 MRI-detected multicentric cancers and reported that many of the MRI-detected additional cancers were larger or more invasive compared with index cancers, indicating the possible clinical relevance of the additional, unsuspected, multicentric cancer visualized through MRI alone. Considering the relatively low incidence of MRI-detected additional cancers, especially in combination with conventional mammography and US, survival advantage from MRI could be masked if survival outcomes are compared between MRI vs. no-MRI groups, as previously reported. However, no studies have focused on survival outcomes in patients with MRI-detected additional cancers (MDACs) that were occult on mammography and ultrasonography (US).

Therefore, the purpose of the present study was as follows: (1) To determine the additional cancer detection yield of pre-operative MRI in women with invasive breast cancer that was occult on mammography and US, (2) identify a subgroup of women who are likely to develop MDAC, and (3) compare long-term outcome between patients with pre-operative MRI and those without pre-operative MRI and between patients with MDACs and those without pre-operative breast MRI in a relatively large cohort.

Materials and Methods

Patients and treatment

For purpose of this retrospective observational study, we recruited patients from two tertiary academic hospitals (Samsung Medical Center and Gyeongsang National University Hospital) between January 2010 and December 2012. The Institutional Review Boards of both hospitals approved the study and waived the requirement for informed consent.

The inclusion criteria were as follows: (1) Availability of pre-operative bilateral mammography and whole-breast US within a month before surgery in each hospital, (2) initial unilateral breast malignancy with final pathological diagnosis of invasive breast cancer, and (3) women whose final margins were negative, defined as no ink on tumor. The exclusion criteria were as follows: (1) MRI performed after the diagnosis of cancer by vacuum-assisted or excisional biopsy, (2) MRI performed in patients treated with neoadjuvant chemotherapy (NAC), (3) existing malignancy in another organ (metastasis or primary malignancy), and (4) patients who did not receive adjuvant treatment despite indication. We also excluded patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer who did not receive treatment with trastuzumab during the study period. Finally, 2,104 women (mean age, 50 years; age range, 23–90 years)

were included in the present study. Among them, 1,808 (85.9%) patients underwent MRI while 296 (14.1%) patients did not.

Mammography, ultrasonography, and magnetic resonance imaging

Conventional mammography was performed in all patients. Craniocaudal and mediolateral oblique views were obtained in all cases. Further views or spot magnification views were performed as indicated. All mammograms were acquired using two full-field digital mammography units (Senographe 2000D; GE Healthcare, Milwaukee, WI, USA; and Selenia; Hologic Inc., Bedford, MA, USA). Whole-breast US was performed by board-certified radiologists specializing in breast imaging. US images were acquired using high-end equipment such as Philips unit (iU22; Philips Medical Systems, Bothell, WA). Breast MRI was performed with patients in prone position using a 1.5-T or 3-T scanner (Achieva; Philips Medical Systems, Best, Netherlands, Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany and Ingenia; Philips Medical Systems, Best, Netherlands) and a dedicated breast coil. MRI examination consisted of axial, turbo spin-echo, T1- and T2-weighted sequences, as well as an axial, three-dimensional, dynamic, contrast-enhanced sequence. In dynamic contrast enhancement, 0.1mmol/kg bolus of gadobutrol (Gadovist; Bayer Healthcare Pharmaceutical, Berlin, Germany) was injected, followed by 20-mL saline flush. Contrast-enhanced images were acquired at 30, 90, 150, 210, 270, and 330 s after injection of contrast material. All images were interpreted according to the American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS) (20). All mammograms and US examinations were performed before MRI was obtained. Typically, all imaging examinations were performed at <2 weeks before surgery.

Imaging analysis for evaluating effect of MRI-detected additional cancers

Two experienced breast imaging radiologists (ESK and HYC with 13 and 10 years of experience respectively) reviewed all MRI examinations for the presence of multifocal, or multicentric disease in cases that were occult on mammography and US. In accordance with prior studies (18, 19, 21), multifocal disease was identified in case of additional sites of malignancy within the same breast quadrant as of index cancer, or index cancer which was underestimated by more than 2 cm using mammography or US, as revealed by MRI. Multicentric disease was identified in case of additional sites of malignancy within a different quadrant of the ipsilateral breast or at > 4-cm distance from index lesion. All MRI findings that appeared suspicious on the basis of morphological or kinetic analysis were compared to the corresponding pathological reports from core-needle or surgical biopsy. The sizes of index cancer and MDAC were determined using the radiology report. The breast MRI findings in MDAC were described as focus, mass, or non-mass enhancement according to the BI-RADS lexicon (20).

Clinicopathological data analysis

Final histopathological results of surgical specimens in cases of index cancer were reviewed to determine the following: histologic grade, and expression status of the estrogen receptor (ER), progesterone receptor (PR), and HER2. Tumors with HER2 scores of 3+ (strong homogeneous staining) were considered as positive. In case of 2+ score (moderate complete membranous staining in $\geq 1\%$ of tumor cells), silver *in situ* hybridization (SISH) was used to determine whether HER2 was amplified. Specimens were considered as ER-positive if $\geq 1\%$ of the tumor cells showed nuclear staining at immunohistochemistry analysis (22).

Breast cancers were divided into three molecular subtypes based on the immunohistochemical or SISH findings regarding ER, PR, and HER2: Hormone receptor-positive (hormone receptor-positive and HER2 negative), HER2-positive (HER2-positive and any hormone receptor status), and triple-negative (hormone receptor- and HER2-negative). For convenience, pathological diagnoses were divided into three groups: invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), and others.

Patients' medical records were reviewed to collect clinical data such as age, menopausal status, personal history of cancer, and surgery type. In this study, the endpoint was disease-free survival (DFS). DFS was defined as the time from the date of surgery to that of first recurrence of the disease, date of death, date last known to have no evidence of disease, or date of the most recent follow-up. Disease recurrence was identified in case of either breast cancer recurrence (local, regional, or distant) or new primary contralateral breast cancer (invasive or ductal carcinoma *in situ*; DCIS). Information regarding patient follow-up and recurrence status was obtained from the patients' medical records. Patients without recurrence at last follow-up or those lost to follow-up were treated as censored observations in the analysis.

Statistical methods

The present study was conducted in two stages. First, we evaluated the frequency of MDAC and determined the conditions correlated with MDAC among all 1,808 patients with pre-operative MRI. Patient characteristics, including clinicopathological findings (age at diagnosis, pathological type, histologic grade, ER, PR, HER2, molecular subtype, T stage, N stage, clinical stage, tumor size, and menopausal status) and mammographic breast density were compared between patients with and without MDAC. Univariate logistic regression

analysis was conducted to determine the factors associated with MDAC. Multivariate logistic regression analysis was performed to determine the independent features associated with MDACs. Variables with P-values < .05 were included in multivariate logistic regression model.

As second stage, with regard to effect of pre-operative MRI on survival outcome, we wanted to evaluate the effect of MRI and MDAC independent of the influence of tumor burden itself or surgery type. Therefore, we limited inclusion to patients with unilateral breast cancer who underwent breast-conserving surgery (BCS) with radiation therapy. We compared survival outcomes between patients with and without pre-operative MRI; subsequently, as subgroup analysis, survival outcomes of patients with MDAC were compared with those without pre-operative MRI. Univariate Cox proportional hazards model was used to analyze the effects of pre-operative MRI and MDAC on DFS. Kaplan-Meier curves were used to analyze survival between patients with and without MRI and between patients with MDAC and without MRI. Log-rank tests were used to compare differences in survival between the two groups. Multivariate Cox proportional hazards model was used to assess the difference of DFS under consideration of confounding variables.

Two-tailed P-values of < .05 were considered as significant. All statistical analyses were performed by a dedicated statistician using R Statistical Software (version 3.2.4; R Foundation for Statistical Computing, Vienna, Austria).

Results

Additional cancers detected using magnetic resonance imaging

Among 2,104 patients who underwent breast cancer surgeries during study period, 1,808 (85.9%) underwent breast MRI. Breast MRI examinations were performed using a 1.5-T (n = 1,032, 57.1%)

or 3.0-T scanner ($n = 776$, 42.9%). Among total 1,808 patients who underwent MRI, 1,349 (74.6%) underwent BCS, while the remaining 459 (25.4%) underwent mastectomy. Through MRI, 174 (9.6%) of the 1,808 patients were confirmed with additional cancer that was occult on mammography and US. Of these 174 additional cancers, 96 (55.2%) were multifocal and 78 (44.8%) were multicentric from index cancer and all lesions were asymptomatic. Median age of the patients with MDAC was 48 years (range, 29–77 years). Pathological diagnoses of MDAC were as follows: DCIS (80 patients; 46.0%), IDC (85 patients; 48.9%), ILC (seven patients; 4.0%), and other (two patients; 1.1%). Other pathologies were mucinous carcinoma in one patient and tubular carcinoma in one patient. Mean size of the invasive lesion was 9.4 mm (range, 3–40 mm). In cases of separate lesions ($n = 112$), five (4.5%) cancers presented as foci, 77 (68.8%) as masses, and 30 (26.8%) as non-mass enhancements. Table 1 shows the characteristics of the patients according to the presence of MDAC, as well as univariate logistic regression analysis for potential associated factors. MDACs were significantly associated with ILC ($P = 0.003$), and pre-menopausal status ($P = .015$). There was no significant difference in terms of mammographic breast density ($P = .332$). In multivariate analysis, higher probability of MDAC was independently associated with ILC (odds ratio: 2.522, 95% confidence interval [CI]: 1.281, 4.647; $P = .005$) and pre-menopausal status (odds ratio: 1.471, 95% CI: 1.063, 2.054; $P = .022$) (Table 2).

Effect of MRI-detected additional cancers on survival outcome

Among 2,108 patients, we identified 1,543 patients with unilateral breast cancer who underwent unilateral BCS followed by radiation therapy. Patient, mammographic density, and tumor characteristics are shown in Table 3. In total of 1,349 patients with pre-operative MRI, 92 (6.8%) patients

showed MDAC.

Mean follow-up time was 64.7 months (range, 7–92 months). There were 101 recurrences in 101 patients (22 local, 14 regional, 16 contralateral breasts, 49 distant), with mean time-to-recurrence of 37.0 months (range, 6–80 months). There were three recurrences within the first 6 months' follow-up, possibly due to residual disease.

To evaluate effect of pre-operative MRI on survival outcome, we compared patients' characteristics according to the use of MRI (Table 3). There were significant differences of histologic grade, HER2 status, and molecular subtype between the two groups according to the use of MRI. First, we performed univariate Cox proportional hazards model for recurrence to evaluate effect of pre-operative MRI on survival outcome. The hazard ratio for recurrence in patients with pre-operative MRI compared with those without MRI was 0.695 (95% CI: 0.407, 1.186; $P = .182$). Kaplan-Meier curve analysis showed that survival in patients with MRI was slightly better, without statistical significance ($P = .180$) (Fig. 1). To control for the effect of other variables, we performed multivariate Cox proportional hazard model with some confounding variables (Table 4). As confounding variables, T stage, N stage, histologic grade, and molecular subtype were selected which were significant in the Cox proportional hazard regression model for recurrence. Results revealed that the following parameters were significantly associated with worse DFS outcome: N1 stage (DFS hazard ratio: 1.662, 95% CI: 1.048, 2.637; $P = .031$), N2 stage (DFS hazard ratio: 3.111, 95% CI: 1.626, 5.952; $P = .001$), grade 2 tumor (DFS hazard ratio: 2.180, 95% CI: 1.097, 4.335; $P = .026$), grade 3 tumor (DFS hazard ratio: 2.716, 95% CI: 1.246, 5.921; $P = .012$), and triple-negative subtype (DFS hazard ratio: 2.592, 95% CI: 1.520, 4.419; $P < .001$) (Table 4). However, pre-operative MRI had no significant impact on DFS ($P = .229$).

Similarly, we performed univariate Cox

Table 1. Univariate Analysis of Factors Associated with MRI-Detected Additional Cancer

Variable	Pre-operative MRI (n = 1,808)			P-value
	MDAC (-) (n = 1,634)	MDAC (+) (n = 174)	Odds ratio (95% CI)	
Age				
< 50	838 (51.3%)	102 (58.6%)	Ref	0.066
≥ 50	796 (48.7%)	72 (41.4%)	0.743 (0.540, 1.018)	
T stage				
1	1006 (61.6%)	103 (59.2%)	Ref	0.739
2	563 (34.5%)	61 (35.1%)	1.058 (0.755, 1.472)	
3	58 (3.5%)	8 (4.6%)	1.347 (0.581, 2.745)	
4	7 (0.4%)	2 (1.1%)	2.791 (0.412, 11.725)	
N stage				
0	1052 (64.4%)	104 (59.8%)	Ref	0.415
1	418 (25.6%)	48 (27.6%)	1.162 (0.804, 1.656)	
2	98 (6.0%)	13 (7.5%)	1.342 (0.697, 2.395)	
3	66 (4.0%)	9 (5.2%)	1.379 (0.626, 2.713)	
Stage				
1	755 (40.2%)	78 (44.8%)	Ref	0.960
2	691 (42.3%)	72 (41.4%)	1.009 (0.719, 1.412)	
3	188 (11.5%)	24 (13.8%)	1.236 (0.747, 1.978)	
Index cancer pathological type				
IDC	1473 (90.1%)	153 (87.9%)	Ref	0.003
ILC	47 (2.9%)	13 (7.5%)	2.663 (1.356, 4.892)	
Others	114 (7.0%)	8 (4.6%)	0.676 (0.298, 1.326)	
MBD*				
1+2	460 (28.2%)	43 (24.7%)	Ref	0.332
3+4	1172 (71.8%)	131 (75.3%)	1.196 (0.840, 1.733)	
Histologic grade				
1	500 (30.6%)	54 (31.0%)	Ref	0.679
2	712 (43.6%)	83 (47.7%)	1.079 (0.754, 1.556)	
3	422 (25.8%)	37 (21.3%)	0.812 (0.521, 1.253)	
Estrogen receptor status				
Negative	382(23.4%)	30(17.2%)	Ref	0.068
Positive	1252(76.6%)	144(82.8%)	1.465 (0.986, 2.244)	
Progesterone receptor status				
Negative	478 (29.3%)	43 (24.7%)	Ref	0.209
Positive	1156 (70.7%)	131 (75.3%)	1.260 (0.886, 1.825)	
HER2 status				
Negative	1377 (84.3%)	146 (83.9%)	Ref	0.900
Positive	257 (15.7%)	28 (16.1%)	1.028 (0.659, 1.549)	
Molecular subtype				
HR-positive	1142 (69.9%)	129 (74.1%)	Ref	0.869
HER2-positive	257 (15.7%)	28 (16.1%)	0.964 (0.616, 1.462)	
Tripe-negative	235 (14.4%)	17 (9.8%)	0.640 (0.366, 1.053)	

Continued

Table 1. Continued

Variable	Pre-operative MRI (n = 1,808)			P-value
	MDAC (-) (n = 1,634)	MDAC (+) (n = 174)	Odds ratio (95% CI)	
Menopausal status				
Post-menopausal	722 (44.2%)	60 (34.5%)	Ref	
Pre-menopausal	912 (55.8%)	114 (65.5%)	1.504 (1.088, 2.098)	0.015
Index tumor size (mm)	20.89 ± 13.37	22.21 ± 16.12	1.007 (0.990, 1.022)	0.405

*Two patients in MDAC (-) group could not be assessed due to interstitial mammoplasty.

Note: Unless otherwise noted, data are numbers of patients, with percentages in parentheses.

MDAC = MRI-detected additional cancer, CI = confidence interval, IDC = invasive ductal cancer, ILC = invasive lobular cancer, MBD = mammographic breast density, HR = hormone receptor, HER2 = human epidermal growth factor receptor 2

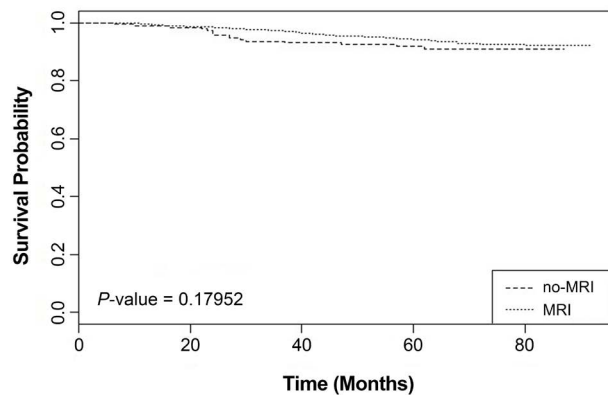


Fig. 1. Kaplan-Meier survival analyses in patients treated with breast-conserving surgery and radiation therapy according to pre-operative MRI-detected additional cancer among all patients (n = 1,543).

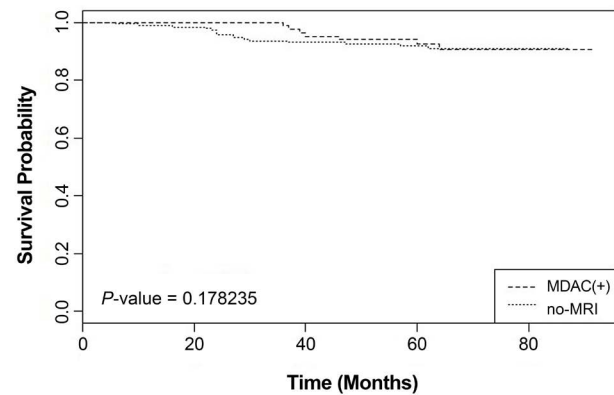


Fig. 2. Kaplan-Meier survival analyses in patients with MRI-detected additional cancer and those without pre-operative MRI (n = 286).

proportional hazard model to evaluate effect of MDAC on survival outcome. As compared to patients without pre-operative MRI, hazard ratio of recurrence in patients with MDAC was 0.882 (95% CI: 0.363, 2.141; $P = .781$). In Kaplan-Meier curve, patients with MDAC showed better survival than those without MRI, however, there was no statistical significance in the case of DFS ($P = .178$) among all patients (n = 286) (Fig. 2). To control for other variables that might affect DFS, we performed multivariate Cox proportional hazard model with some confounding variables (Table 4). As confounding variables, T stage, N stage, histologic grade, and molecular subtype were selected which were significant in Cox proportional hazard regression model for recurrence. In multivariate Cox proportional hazards model, N2 stage (DFS hazard

ratio: 7.012, 95% CI: 1.848, 26.604; $P = .004$) and N3 stage (DFS hazard ratio: 5.427, 95% CI: 1.394, 21.120; $P = .015$) were independently associated with worse DFS (Table 5). However, patients who received additional treatment due to MDAC did not show significantly better DFS compared to those without pre-operative MRI (DFS hazard ratio: 0.806, 95% CI: 0.277, 2.342; $P = .693$).

Discussion

In our results, 174 of 1,808 patients (9.6%) had MDAC that was occult on mammography and US. In multivariate analysis, higher probability of MDAC was independently associated with ILC (odds ratio, 2.522; 95% CI: 1.281, 4.647; $P = .005$) and premenopausal status (odds ratio, 1.471; 95%

CI: 1.063, 2.054; $P = .022$). Regarding survival outcomes, patients with pre-operative MRI were not significantly associated with better DFS as compared to those without MRI. In addition, patients with MDAC failed to show better survival compared with those without pre-operative MRI.

Several studies have determined cases with indication for pre-operative MRI to detect additional cancers. As a result, high mammographic density (16–18), pre-menopausal status (17, 18), and lobular pathology (16–18, 23) are frequently associated with high likelihood of MDAC in pre-operative MRI. In general, our results corroborated previously reported findings. In our multivariate analyses, only ILC and premenopausal status were associated with MDAC. High mammographic density was not associated with MDAC in either univariate or multivariate analyses, possibly due to high mammographic density characteristic in most Asian women which may have resulted in no significant difference between the two groups. In our study, 9.6% of patients showed MDACs, which was a relatively low rate. We routinely perform mammography and US as part of our hospital's pre-operative imaging procedure. We suspect that our practice partially explains the relatively low rate of MDAC in our study.

Based on these prior results, many authors have insisted that pre-operative MRI should only be used in these subsets of women. In a recent study, Iaconi et al. (19) analyzed the characteristics of 73 MRI-detected multicentric cancers. In their results, 17 of the 73 cancers (23%) were larger than index cancer, which may have changed disease-staging; 27 of the 73 cancers (37%) differed from index cancer in terms of invasion, grade, and/or receptor status. Furthermore, in two of the 73 patients (3%), the MDAC was invasive and index cancer was DCIS, possibly changing the patient's treatment options or prognosis. Based on these observations, they concluded that the additional, unsuspected, multicentric cancer seen only on MRI

was likely to be clinically relevant (19). However, these studies focusing on MDAC did not evaluate survival benefits of pre-operative MRI and MDAC management.

Fisher et al. (24) first reported that the ipsilateral breast tumor recurrence rate among patients who had undergone pre-operative MRI was significantly lower than that among patients who had not undergone pre-operative MRI (1.2% vs. 6.8%, respectively; $P < .001$); since then, there have been many studies evaluating survival difference by pre-operative MRI use. For example, Solin et al. (25) reported no difference in local failure between the MRI or no-MRI groups (3% vs. 4%; $P = .51$). In an individual patient-data meta-analysis of four studies with 3,180 affected breasts of 3,169 patients, pre-operative MRI did not reduce the risk of local or distant recurrence (10). Sung et al. (26) recently reported the effect of pre-operative MRI on outcomes in 348 patients with early breast cancer. With median follow-up of 8 years, there was no difference in locoregional recurrence rate or DFS between the MRI and no-MRI groups. However, this methodology might mask any real benefit of pre-operative MRI. In our daily practice, most pre-operative MRI scans give no further significant information when combined with conventional mammography and US. Therefore, we compared survival outcomes between patients with MDAC

Table 2. Multivariate Logistic Regression Analysis of Factors Associated with MRI-Detected Additional Cancer

Variables	Odds ratio	95% CI	P-value
Index cancer pathological type			
DC	Ref		
ILC	2.522	1.281, 4.647	0.005
Others	0.667	0.295, 1.311	0.282
Menopausal status			
Post-menopausal	Ref		
Pre-menopausal	1.471	1.063, 2.054	0.022

Note: IDC = invasive ductal cancer, ILC = invasive lobular cancer CI = confidence interval.

Table 3. Characteristics of Patients Treated with Breast-Conserving Surgery and Radiation Therapy According to Pre-Operative MRI

Variables	Pre-operative MRI			P-value
	Yes (n = 1,349)		No (n = 194)	
	MDAC (+) (n = 92)	MDAC (-) (n = 1257)	All	
Age				0.547
< 50	47 (51.1%)	638 (50.8%)	685 (50.8%)	
≥ 50	45 (48.9%)	619 (49.2%)	664 (49.2%)	
T stage				0.633
1	66 (71.7%)	855 (68.1%)	921 (68.3%)	
2	25 (27.2%)	393 (31.3%)	418 (31.0%)	
3	0 (0.0%)	8 (0.6%)	8 (0.6%)	
4	1 (1.1%)	1 (0.1%)	2 (0.2%)	
N stage				0.795
0	64 (69.6%)	890 (70.8%)	954 (70.7%)	
1	24 (26.1%)	281 (22.4%)	305 (22.6%)	
2	0 (0.0%)	58 (4.6%)	58 (4.3%)	
3	4 (4.3%)	28 (2.2%)	32 (7.0%)	
Stage				0.659
1	53 (57.6%)	665 (52.9%)	718 (53.2%)	
2	34 (37.0%)	502 (39.9%)	536 (39.7%)	
3	5 (5.4%)	90 (7.2%)	95 (7.0%)	
Pathology				0.826
IDC	86 (93.5%)	1138 (90.5%)	1224 (90.7%)	
ILC	3 (3.3%)	30 (2.4%)	33 (2.5%)	
Others	3 (3.3%)	89 (7.1%)	92 (6.8%)	
Mammographic density*				0.296
1 + 2	21 (22.8%)	350 (27.9%)	371 (37.5%)	
3 + 4	71 (77.2%)	905 (72.1%)	976 (72.5%)	
Histologic grade§				0
1	29 (31.5%)	414 (33.1%)	443 (32.8%)	
2	45 (48.9%)	510 (40.6%)	555 (41.1%)	
3	18 (19.6%)	333 (26.5%)	351 (26.0%)	
Estrogen receptor status				0.833
Negative	16 (17.4%)	294 (23.4%)	310 (23.0%)	
Positive	76 (82.6%)	963 (76.6%)	1039 (77.0%)	
Progesterone receptor status				0.476
Negative	24 (26.1%)	368 (29.3%)	392 (29.1%)	
Positive	68 (73.9%)	889 (70.7%)	957 (70.9%)	
HER2 status				0
Negative	76 (82.6%)	1082 (86.1%)	1158 (85.8%)	
Positive	16 (17.4%)	175 (13.9%)	191 (14.2%)	
Molecular subtype				0.001
HR-positive	67 (72.8%)	884 (70.3%)	951 (70.5%)	
HER2-positive	16 (17.4%)	175 (13.9%)	191 (14.2%)	
Triple-negative	9 (9.8%)	198 (15.8%)	207 (15.3%)	

Continued

Table 3. Continued

Variables	Pre-operative MRI				P-value
	Yes (n = 1349)		No (n = 194)		
Menopausal status					0.588
Postmenopausal	34 (37.0%)	560 (44.6%)	594 (44.0%)	90 (46.4%)	
Premenopausal	58 (63.0%)	697 (55.4%)	755 (56.0%)	104 (53.6%)	
Recurrences					0.384
No	85 (92.4%)	1179 (93.8%)	1264 (93.7%)	178 (91.8%)	
Yes	7 (7.6%)	78 (6.2%)	85 (6.3%)	16 (8.3%)	
Recurrence location (n = 85)					0.255
Local	2 (28.6%)	14 (17.9%)	16 (16.8%)	6 (37.5%)	
Regional	3 (42.9%)	10 (13.5%)	13 (15.3%)	1 (6.3%)	
Distant	1 (14.3%)	40 (54.1%)	41 (48.2%)	8 (50.0%)	
Contralateral	1 (14.3%)	14 (18.9%)	15 (17.7%)	1 (6.3%)	

*Two patients could not be assessed due to interstitial mammoplasty in MDAC (-) group. †In no-MRI group, 15 patients were not available. Note: MDAC = MRI-detected additional cancer, IDC = invasive ductal cancer, ILC = invasive lobular cancer, HR = hormone receptor.

Table 4. Multivariate Analysis of Factors Associated with Disease-Free Survival (DFS) Between Patients with or without Pre-Operative MRI

Variables	Hazard ratio	95% CI	P-value
Pre-operative MRI			
No	Ref		
Yes	0.707	0.401, 1.244	0.229
T stage			
1	Ref.		
2	0.971	0.629, 1.497	0.893
3	2.846	0.646, 12.531	0.167
4	0.000003092	0, Inf	0.995
N stage			
0	Ref		
1	1.662	1.048, 2.637	0.031
2	3.111	1.626, 5.952	0.001
3	2.072	0.852, 5.040	0.108
Tumor grade			
1	Ref		
2	2.18	1.097, 4.335	0.026
3	2.716	1.246, 5.921	0.012
Molecular subtype			
HR-positive	Ref		
HER2-positive	1.127	0.592, 2.145	0.716
Triple-negative	2.592	15.20, 4.419	< 0.001

Note: DFS = disease-free survival, HR = hormone receptor, HER2 = human epidermal growth factor receptor 2, CI = confidence interval.

Table 5. Multivariate Analysis of Factors Associated with Disease-Free Survival (DFS) Between Patients with MRI-Detected Additional Cancer or without Pre-Operative MRI

Variables	Hazard ratio	95% CI	P-value
Pre-operative MRI			
No-MRI	Ref		
MDAC (+)	0.806	0.277, 2.342	0.693
T stage			
1	Ref		
2	0.505	0.176, 1.443	0.204
3	NA	NA	NA
4	0.000001613	0, Inf.	0.998
N stage			
0	Ref		
1	1.461	0.453, 4.712	0.526
2	7.012	1.848, 26.604	0.004
3	5.427	1.394, 21.12	0.015
Histological grade			
1	Ref		
2	0.952	0.264, 3.439	0.940
3	1.875	0.538, 6.537	0.324
Molecular subtype			
HR-positive	Ref		
HER2-positive	3.089	0.865, 11.031	0.082
Triple-negative	1.523	0.442, 5.248	0.505

Note: MDAC = MRI-detected additional cancer, DFS = disease-free survival, HR = hormone receptor, HER2 = human epidermal growth factor receptor 2, NA = not available.

with potential maximal advantage of pre-operative MRI and those without pre-operative MRI without tumor excision despite the possibility of additional cancer. However, despite this approach, pre-operative MRI had no significant impact on survival outcome. In an ideal study to determine effect of MDAC on survival outcome, patients with MDAC should be prospectively randomized into groups of patients with and without plan of treatment for MDAC and survival outcomes should be compared between the two groups. However, this methodology is almost impossible because of the large number of patients required and ethical issue. Therefore, our major goal was not to evaluate direct effect of MDAC on survival outcome but the impact of pre-operative MRI compared with that of patients with MDAC.

Previous and present study suggest that adjuvant chemotherapy, endocrine therapy, and radiation therapy inhibit the progression of early stage cancers that are undetected by conventional imaging (10, 12). Biological characteristics of tumors are more important in local control, and complete excision of all cancers may not be necessary. These results suggest that cancer detected by MRI alone has low malignant potential, and low treatment impact on outcome has low biological or clinical relevance (29). Thus, the role of pre-operative MRI must be changed so that it does not direct the surgeon to resect all radiologically detectable disease.

The current study has several limitations. First, although it was one of the largest analyses to date to evaluate pre-operative MRI in primary breast cancer, a larger population would have ensured a more robust and dedicated analysis. In particular, the number of patients without MRI was relatively small. Consequently, the expected number of patients with potential MDAC under condition of undergoing pre-operative MRI would be so small to show significant survival difference. Therefore, we are planning multi-institutional study to address this issue with large no-MRI group. Second, this was a retrospective study. However, all patients

were managed prospectively based on their MRI findings. Decision for performing pre-operative MRI was entirely dependent on the hospital. Pre-operative MRI has already been generalized at one study hospital while just begun at the other during study period. Therefore, it is likely that there was no significant bias with regard to decision to undergo pre-operative MRI. Third, during the study period, trastuzumab was barely reimbursed by national health insurance but could be used freely by one study hospital participating in multiple international clinical trials, which explains our finding of significantly differences in HER2 status and molecular subtype between patients with and without MRI. However, because we excluded patients who did not receive treatment with adequate adjuvant treatment including trastuzumab, these biased treatment variables may not have affected our results. Fourth, we did not include the contralateral lesion in our analyses for convenience, which may have underestimated the merit of pre-operative MRI. Fifth, we did not include other risk factors such as family history or BRCA mutation.

In conclusion, ILC and premenopausal status were associated with a greater likelihood that pre-operative MRI would detect MDAC that was occult on mammography and US. However, pre-operative MRI had no significant impact on DFS even when compared between patients with MDAC and those without pre-operative MRI. Our results suggested that instead of the role of pre-operative MRI to improve survival outcome by eradicating additional cancer, pre-operative MRI enables accurate diagnosis or increased surgeon's convenience.

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수술전 유방 자기공명영상에서 발견된 추가암과 생존 결과와의 관계: 후향적 다기관 연구

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목적: 유방촬영술과 초음파에서 보이지 않는 침윤성 유방암 환자에서 수술전 유방 자기공명영상(MRI)에서 추가 암 진단을 결정하고, 자기공명영상에서 진단된 추가암 (MDAC)이 생길 가능성이 있는 여성을 확인하며, 또한 수술전 자기공명영상에 없는 환자들과 수술전 자기공명영상 및 MDAC를 가진 환자들 사이의 장기 결과를 비교하기 위해서이다.

대상 및 방법: 본 후향적 다기관 연구는 2010년 1월과 2012년 12월 사이에 이루어졌다. 침윤성 유방암에 대한 수술을 받은 2,104명의 여성 중 1,808명의 수술전 MRI 검사를 검토하여 MDAC의 존재를 확인했다. MDAC와 연관된 인자들을 분석하기 위해 로지스틱 회귀 분석을 시행하였다. 편측 유방암에 대해 유방보존술과 방사선 치료를 시행한 환자들을 확인하여, 수술전 유방 MRI를 시행한 군과 시행하지 않은 군 사이 및 MDAC가 있는 군과 수술전 유방 MRI를 시행하지 않은 군 사이의 무병생존 (DFS)을 콕스 비례 위험 모형과 카플란 마이어 곡선 분석을 이용하여 비교하였다.

결과: 1,808명의 환자 중에서, 174명 (9.6%)가 MDAC를 가졌다. 다변량 분석 결과 침윤성 소엽암 (오즈비: 2.522, 95% 신뢰 구간: 1.281, 4.647; $P = .005$)과 폐경전 상태 (오즈비: 1.471; 95% 신뢰구간: 1.063, 2.054; $P = .022$)가 MDAC의 높은 가능성과 독립적으로 상관 관계가 있었다. 수술전 MRI 또는 MDAC를 가진 환자들은 더 나은 DFS와 의미 있는 상관 관계를 보이지 않았다 (각각 $P = .229$ 와 $.693$).

결론: 침윤성 소엽암과 폐경전 상태는 수술전 MRI에서 MDAC를 진단하기 위한 높은 가능성과 관계가 있었다. 그러나, 수술전 MRI는 DFS에 의미 있는 영향을 미치지 않았다.

Index words: Breast; Breast Cancer; Magnetic resonance imaging; Prognosis; Survival

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