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BREAST

# Long-term survival outcomes in invasive lobular carcinoma patients with and without preoperative MR imaging: a matched cohort study

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## Abstract

**Objective** To investigate and compare the effect of preoperative breast magnetic resonance (MR) imaging on recurrence-free survival (RFS) and overall survival (OS) outcomes among patients with invasive lobular carcinoma (ILC).

**Methods** A total of 287 ILC patients between January 2005 and December 2012 were included. One hundred twenty (41.8%) had undergone preoperative breast MR imaging (MR group) and 167 (58.2%) had not (no MR group). Two groups were matched for 21 covariates in terms of patient demographics, tumor characteristics, and clinical features. We compared unmatched variables between the patients with and without breast MR imaging using the chi-square or Student's *t* test. Comparisons of matched data were performed with McNemar's test or test of symmetry for categorical variables and paired *t* test for continuous variables. The RFS and OS outcomes were compared using the Kaplan-Meier estimates. MR effects were estimated after adjusting for significant potential confounders of specific outcomes in the multivariable modeling.

**Results** In the matched cohort, no statistically significant association was observed between MR imaging and total recurrence (hazard ratio [HR], 1.096; $p = 0.821$), loco-regional recurrence (HR, 1.204; $p = 0.796$), contralateral breast recurrence (HR, 0.945; $p = 0.952$), or distant recurrence (HR, 1.020; $p = 0.973$). MR imaging was associated with improved OS with 51% reduction, but not significantly (HR, 0.485; $p = 0.231$). Analysis with multivariable Cox regression model indicated that MR imaging was not significant independent factor for better RFS (HR, 0.823; $p = 0.586$) or improved OS (HR, 0.478; $p = 0.168$).

**Conclusion** Preoperative MR imaging is not significant prognostic factor and produces no apparent recurrence or survival outcome benefits in ILC patients.

**Key Points**

- *Preoperative breast MR imaging in invasive lobular carcinoma was associated with a better overall survival with 51% reduction, but not statistically significant.*
- *Preoperative breast MR imaging does not show significant prognostic value in invasive lobular carcinoma as there is no apparent benefit in terms of recurrence or survival outcomes.*

**Keywords** Lobular carcinoma · Magnetic resonance imaging · Recurrence · Survival · Breast neoplasm

**Abbreviations**

| | |
|---|---|
| ILC | Invasive lobular carcinoma |
| MR | Magnetic resonance |
| BCS | Breast-conserving surgery |
| RFS | Recurrence-free survival |
| OS | Overall survival |

## Introduction

Invasive lobular carcinoma (ILC) is the second most common histopathological subtype of breast cancer and accounts for approximately 5–15% of all breast cancer [1]. Because of

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the infiltrative nature of ILC, it is difficult to diagnose clinically and it has a high false-negative rate [2]. ILC also has an increased propensity for multifocal, multicentric, and bilateral distribution. The ability of ILC to elude early detection often manifests as a presentation of more advanced stage disease than invasive ductal carcinoma [3, 4]. Indeed, because preoperative magnetic resonance (MR) helps to measure the tumor extent more accurately and detect multifocal, multicentric, and occult foci not seen on conventional imaging [5, 6], several studies [1, 7, 8] looked specifically at outcomes of MR in ILC. In terms of the mastectomy rate and need for reoperation, two of these three studies [1, 7] found that outcomes were improved with the use of preoperative MR. A retrospective study found that preoperative MR identified new ipsilateral (11%) and contralateral (7%) lesions and influenced surgical management in 23 patients (25%), of which 20 (22%) were felt to be justified [7]. Mann et al have also shown in a retrospective cohort study that MR reduces the reoperation rate (9%) after initial breast-conserving surgery (BCS) compared with 27% in those with no preoperative MR [1].

Several studies [6, 9, 10] have insisted that preoperative MR imaging in breast cancer has no significant benefit on long-term outcomes, but confounding variables were present as these studies did not control for the baseline characteristics of patients. Two matched studies [11, 12] found no improvement on loco-regional recurrence or disease-free survival, whereas the other two matched studies [13, 14] described a limited benefit in contralateral breast cancer occurrence. However, no previous studies, whether using matched or unmatched populations, have investigated the role of preoperative breast MR imaging in specific ILC histologic subtype.

The purpose of our current study was to compare the effects of preoperative breast MR imaging on recurrence-free survival (RFS) and overall survival (OS) outcomes among patients with a newly diagnosed ILC subtype. To evaluate the impact of preoperative MR imaging on long-term outcomes, we controlled for various clinicopathological and radiological variables and created a balanced cohort with and without MR imaging. In addition, we sought to identify the prognostic factors and the relevance of preoperative MR imaging for long-term outcomes in ILC.

## Materials and methods

### Patients

This retrospective study from a single tertiary center was approved by institutional review board, and the informed consent requirement was waived. By using a search program, we identified 329 consecutive patients who were newly diagnosed with ILC by biopsy or surgical excision between January 2005 and December 2012 and underwent subsequent treatment. Among these cases, we excluded 42 patients for the following reasons: were treated with neoadjuvant systemic therapy ($n = 16$), had initial stage IV disease ($n = 4$), was male patient ($n = 1$), had double primary cancer ($n = 1$), and patient information or data on tumor characteristics were incomplete ($n = 20$). A final total of 287 patients (age range 31–82 years; mean age, 49.8 years) were thus included in the analysis. Of these 287 cases, 120 had undergone preoperative breast MR imaging and were assigned to the MR group. The remaining 167 patients had not undergone preoperative breast MR imaging and comprised the no MR group. Subset population overlaps with previous study that dealt with the association between MR imaging and short-term outcomes in 603 patients with ILC, which included patients with less than 5-year follow-up [15].

### MR technique

Patients underwent dynamic contrast-enhanced MR imaging with either a 1.5-T or 3-T scanner (Magnetom Avanto or Skyra, Siemens Healthineers; Achieva, Philips Healthcare) using a dedicated breast coil. Imaging protocols included a T2-weighted sequence and a dynamic contrast-enhanced fat-suppressed axial three-dimensional T1-weighted sequence that consisted of unenhanced and at least three contrast-enhanced acquisitions. For axial T2-weighted imaging, a fast spin-echo sequence with fat suppression was used ([repetition time/echo time (TR/TE), 6700/74 ms; field of view (FOV) 300 × 300 mm; matrix size, 448 × 448; and slice thickness, 5 mm] for the 1.5-T scanner and [TR/TE, 1100/131 ms; FOV, 341 × 210 mm; matrix size, 416 × 256; and slice thickness, 1.5 mm] for the 3-T scanner).

Dynamic contrast-enhanced images were obtained with fast low-angle shot volume interpolated breath-hold examination (FLASH VIBE) pulse sequences ([TR/TE, 5.2/2.4 ms; FOV 340 × 340 mm; matrix size, 384 × 384; slice thickness, 0.9 mm] for the 1.5-T scanner and [TR/TE, 5.6/2.5 ms; FOV 360 × 360 mm; matrix size, 360 × 360; slice thickness, 0.9 mm] for the 3-T scanner). Contrast material (0.2 ml/kg body weight; Magnevist; Schering or 0.1 mmole/kg gadoterate meglumine; Dotarem; Guerbet) was injected using an MR-compatible power injector (Spectris; Medrad).

### Histopathologic analysis

Tumor diameter, histologic grade or pathologic staging, lymphovascular invasion, and expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) were evaluated on the basis of surgical histologic findings. Antibodies against ER (1:200 dilution; Leica Biosystems), HER2 (1:8 dilution; Ventana Medical Systems) were used in immunohistochemical analysis. ER positivity was scored using an Allred score [16]. The

tumor was considered positive for ER or PR if the Allred score was > 2. HER2 status was determined initially by immunohistochemical analysis and scored on a 0–3 scale. Tumors with scores of 2 were further evaluated by silver in situ hybridization.

### Postoperative evaluations and follow-up

After curative treatment, all patients were examined annually with bilateral mammography and ultrasound to detect any loco-regional or contralateral breast recurrence. The follow-up interval was calculated from the date of surgery to the last date of follow-up or to any event occurrence or death. RFS was defined as the interval between the date of surgery and the date on which cancer recurrence was first detected. Patients without evidence of an event were censored on the date of the most recent follow-up. Recurrence sites included loco-regional (limited to the ipsilateral breast or chest wall and/or the axillary, internal mammary, infraclavicular, or supraclavicular lymph nodes), contralateral breast, or distant (metastases to other parts of the body). OS was defined as the time from the date of breast cancer diagnosis to the date of death from any cause, last date known to be alive, or the date of the most recent follow-up.

### Variable selection

For each of the women in our study cohort with ILC who had not undergone preoperative MR imaging (the no MR group), 21 covariates were matched to women who had undergone preoperative MR imaging (MR group) in terms of patient demographics, tumor characteristics, and various clinical features. These covariates were as follows: (1) age at the time of diagnosis of ILC; (2) age at first menstruation; (3) menopausal status; (4) childbirth; (5) use of contraception; (6) hormone-replacement therapy; (7) past history of breast cancer; (8) family history of breast cancer; (9) mammographic parenchymal density (fatty or dense); (10) pathological staging based on the American Joint Committee on Cancer, 7th edition (I, II, or III) [17]; (11) histologic grade (I, II, or III); (12) pathologic node (negative or positive); (13) lymphovascular invasion; hormonal receptor status (negative or positive), including (14) estrogen receptor (ER), (15) progesterone receptor (PR), and (16) human epidermal growth factor receptor 2 (HER2); (17) pathologic tumor size; and type of treatment, including (18) surgery type (breast conservation or mastectomy), (19) adjuvant chemotherapy, (20) adjuvant endocrine therapy, and (21) adjuvant radiation therapy.

### Statistical analysis

We compared unmatched variables between the patients with and without breast MR imaging using the chi-square or Student's *t* test. The patients in each group were then balanced with propensity score matching method using measured covariates to control confounders at a ratio of 1:1. We additionally analyzed using inverse probability weighting to adjust for confounding variables. Comparisons of matched data were performed with McNemar's test or test of symmetry for categorical variables and paired *t* test for continuous variables.

The primary endpoint of our study was the comparison of the RFS and OS outcomes between the MR and no MR group. A Cox proportional hazards model analyzed the independent effect of preoperative MR on the RFS and OS for the balanced data. The RFS and OS were compared between the two groups using the Kaplan-Meier estimates. To investigate the significant prognostic factors and the relevance between MR receipt and long-term outcomes, variables with a $p$ value $< 0.20$ in the univariable analysis were entered as input variables for a multivariable Cox proportional hazards model using backward elimination in unmatched data. MR effects were estimated after adjusting for the effects of variables which are significant potential confounders for specific outcomes in the multivariable modeling. A $p$ value $< 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) software version 23.0 (SPSS).

## Results

### Demographics

Of the 287 women, 41.8% (120 of 287) had a preoperative MR and 58.2% (167 of 287) did not. Prior to propensity score matching, the MR group tended to be younger, premenopausal, have dense breast tissue, and not receiving hormone replacement therapy (Table 1). With regard to treatment type, no difference was observed between the surgical method, receipt of chemotherapy and endocrine or radiation therapy between the no MR imaging and MR imaging groups. After matching, 104 pairs of patients were allocated to the no MR imaging and MR imaging groups, respectively, and the 21 possible confounding variables were well balanced between these groups (Table 1).

### Survival analysis

The median RFS was 74 months (range, 4–146 months), and the median OS was 78 months (range, 8–147 months). Before matching, 24 patients showed recurrences among the 167 no MR cases, including 7 loco-regional, 5 contralateral breast, and 12 distant recurrences. Thirteen patients showed recurrences among the 120 MR cases, including 4 loco-regional, 2 contralateral breast, and 7 distant recurrences (Table 2).

**Table 1** Baseline characteristics of the unmatched and matched study patients

| Variables | Unmatched patients | | | | Propensity score-matched patients | | | | Inverse probability weighting | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | No MR group ($N = 167$) | MR group ($N = 120$) | $p$ value[b] | Standardized difference[c] | No MR group ($N = 104$) | MR group ($N = 104$) | $p$ value[b] | Standardized difference[c] | No MR group ($N = 167$) | MR group ($N = 120$) | Standardized difference |
| Age at diagnosis (years)[a] | 50.6 ± 8.9 [range, 32–82] | 48.6 ± 7.0 [range, 31–68] | 0.036[b] | 0.257 | 49.4 ± 8.2 [range, 32–82] | 48.5 ± 7.2 [range, 31–68] | 0.425 | 0.111 | 49.9 ± 8.7 [range, 32–82] | 50.0 ± 7.8 [range, 31–68] | 0.015 |
| 1st menstruation age (years)[a] | 14.1 ± 1.8 [range, 10–22] | 14.0 ± 1.6 [range, 11–19] | 0.660 | 0.053 | 14.0 ± 1.6 [range, 10–22] | 14.1 ± 1.7 [range, 11–19] | 0.966 | 0.006 | 14.0 ± 1.7 [range, 10–22] | 14.0 ± 1.6 [range, 11–19] | 0.023 |
| Postmenopausal | 72 (43.1) | 36 (30.0) | 0.032[b] | 0.275 | 35 (33.7) | 32 (30.8) | 0.767 | 0.062 | 63 (37.8) | 47 (39.1) | 0.028 |
| Childbirth | 159 (95.2) | 110 (91.7) | 0.330 | 0.143 | 99 (95.2) | 99 (95.2) | 1.000 | < 0.001 | 156 (93.3) | 113 (93.9) | 0.024 |
| Use of contraceptives | 12 (7.2) | 9 (7.5) | 1.000 | 0.012 | 10 (9.6) | 9 (8.7) | 1.000 | 0.033 | 12 (7.2) | 9 (7.5) | 0.006 |
| Hormone replacement | 25 (15.0) | 7 (5.8) | 0.025[b] | 0.303 | 8 (7.7) | 7 (6.7) | 1.000 | 0.037 | 19 (11.1) | 13 (10.7) | 0.013 |
| Past history of breast cancer | 4 (2.4) | 8 (6.7) | 0.138 | 0.206 | 3 (2.9) | 3 (2.9) | 1.000 | < 0.001 | 7 (4.1) | 5 (3.9) | 0.012 |
| Family history of breast cancer | 21 (12.6) | 9 (7.5) | 0.234 | 0.169 | 6 (5.8) | 8 (7.7) | 0.782 | 0.077 | 17 (10.4) | 13 (10.7) | 0.01 |
| Dense breast tissue | 101 (60.5) | 93 (77.5) | 0.004[b] | 0.374 | 73 (70.2) | 78 (75.0) | 0.534 | 0.108 | 110 (66.0) | 78 (64.6) | 0.029 |
| Pathologic stage 2 or 3 | 96 (57.5) | 61 (50.8) | 0.319 | 0.134 | 54 (51.9) | 59 (56.7) | 0.578 | 0.097 | 92 (54.9) | 66 (55.3) | 0.008 |
| Histologic grade 3 | 19 (11.4) | 11 (9.2) | 0.819 | 0.076 | 7 (6.7) | 10 (9.6) | 0.631 | 0.133 | 17 (10.2) | 12 (10.3) | 0.078 |
| LN metastasis | 58 (34.7) | 41 (34.2) | 1.000 | 0.012 | 34 (32.7) | 37 (35.6) | 0.770 | 0.061 | 57 (34.1) | 40 (33.4) | 0.014 |
| Lymphovascular invasion | 11 (6.6) | 7 (5.8) | 0.990 | 0.031 | 5 (4.8) | 7 (6.7) | 0.766 | 0.083 | 10 (6.2) | 7 (5.8) | 0.010 |
| ER-positive | 151 (90.4) | 114 (95.0) | 0.225 | 0.177 | 98 (94.2) | 98 (94.2) | 1.000 | < 0.001 | 154 (92.5) | 112 (93.0) | 0.022 |
| PR-positive | 132 (79.0) | 100 (83.3) | 0.448 | 0.110 | 83 (79.8) | 85 (81.7) | 0.860 | 0.049 | 135 (80.7) | 95 (79.4) | 0.032 |
| HER2-positive | 11 (6.6) | 7 (5.8) | 0.990 | 0.031 | 7 (6.7) | 7 (6.7) | 1.000 | < 0.001 | 11 (6.6) | 6 (5.2) | 0.062 |
| Tumor size (mm) | 24.3 ± 16.0 [range, 1–90] | 24.7 ± 20.3 [range, 1–100] | 0.873 | 0.019 | 24.1 ± 17.1 [range, 1–90] | 25.3 ± 20.4 [range, 1–100] | 0.646 | 0.064 | 24.4 ± 16.6 [range, 1–90] | 23.9 ± 19.5 [range, 1–100] | 0.025 |
| Mastectomy | 80 (47.9) | 48 (40.0) | 0.227 | 0.160 | 44 (42.3) | 43 (41.3) | 1.000 | 0.019 | 75 (45.0) | 51 (42.7) | 0.045 |
| Adjuvant radiation | 101 (60.5) | 85 (70.8) | 0.092 | 0.219 | 69 (66.3) | 74 (71.2) | 0.550 | 0.104 | 108 (64.8) | 81 (67.1) | 0.048 |
| Adjuvant chemotherapy | 96 (57.5) | 73 (60.8) | 0.655 | 0.068 | 59 (56.7) | 62 (59.6) | 0.779 | 0.059 | 98 (58.5) | 67 (56.1) | 0.048 |
| Adjuvant endocrine therapy | 158 (94.6) | 114 (95.0) | 1.000 | 0.018 | 99 (95.2) | 101 (97.1) | 0.718 | 0.100 | 159 (95.5) | 116 (96.4) | 0.044 |

Data in parentheses indicate the percentages

*ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *LN* lymph node

[a] Data are means ± standard deviation

[b] $p$ values less than 0.05 were considered to indicate a statistically significant difference using Student's $t$ test for continuous variables and chi-square test for categorical variables. Comparisons of matched data were performed with McNemar's test or test of symmetry for categorical variables and paired $t$ test for continuous variables

[c] Absolute standardized differences were obtained to evaluate the balance of matched variables. An absolute standardized difference of less than 0.15 was considered to indicate a balanced variable

In the propensity score-matched cohort, no statistically significant association was observed between preoperative breast MR imaging and total recurrence (hazard ratio [HR], 1.096; 95% confidence interval [CI], 0.497, 2.416; $p = 0.821$), loco-regional recurrence (HR, 1.204; 95% CI, 0.294, 4.924; $p = 0.796$), contralateral breast recurrence (HR, 0.945; 95% CI, 0.147, 6.061; $p = 0.952$), or distant recurrence (HR, 1.020; 95% CI, 0.339, 3.070; $p = 0.973$). MR imaging was associated with a better OS with 51% reduction, but this was not statistically significant (HR, 0.485; 95% CI, 0.149, 1.585; $p = 0.231$) (Table 3). With inverse probability weighting analysis, MR group slightly tended to show improved OS, but not statistically significant (HR, 0.353; 95% CI, 0.111, 1.122; $p = 0.078$).

The Kaplan-Meier analysis revealed that the MR group showed improved survival outcomes including total recurrence, loco-regional recurrence, distant recurrence, and overall survival in the first 60-month period, but again, this was not significant (Fig. 1). There was also no significant difference in contralateral breast recurrence between the two groups.

Univariable analysis results for the factors associated with RFS and OS in the unbalanced cohort are listed in Supplementary Table 1. Age at the time of ILC diagnosis ($p = 0.047$), menopausal state ($p = 0.023$), lymphovascular invasion ($p < 0.001$), ER positivity ($p = 0.002$), PR positivity ($p = 0.016$), HER2 positivity ($p = 0.048$), and adjuvant endocrine therapy ($p < 0.001$) were found to be significant factors for RFS. For OS, age at the time of diagnosis of ILC ($p = 0.046$), tumor size ($p = 0.034$), lymphovascular invasion ($p < 0.001$), ER positivity ($p = 0.002$), PR positivity ($p = 0.018$), HER2 positivity ($p = 0.020$), mastectomy ($p = 0.017$), adjuvant chemotherapy ($p = 0.022$), and adjuvant endocrine therapy ($p < 0.001$) were statistically significant factors.

The multivariable Cox regression model indicated that lymphovascular invasion (HR, 4.703; 95% CI, 2.136, 10.355; $p < 0.001$) and adjuvant endocrine therapy (HR, 0.175; 95% CI, 0.075, 0.405; $p < 0.001$) were significant independent factors of a poorer and improved RFS, respectively, whereas MR imaging (HR, 0.823; 95% CI, 0.409, 1.658; $p = 0.586$) was not a prognostic factor (Table 4). For OS, lymphovascular invasion (HR, 6.014; 95% CI, 2.273, 15.911; $p < 0.001$) and mastectomy (HR, 2.943; 95% CI, 1.100, 6.875; $p = 0.032$) were significant independent factors for a poorer OS, whereas adjuvant endocrine therapy (HR, 0.089; 95% CI, 0.035, 0.225; $p < 0.001$) was a significant independent factor for an improved OS. MR imaging (HR, 0.478; 95% CI, 0.167, 1.366; $p = 0.168$) was not significantly associated with OS outcomes.

## Discussion

Our findings demonstrate that preoperative MR imaging in ILC patients with no significant effect on improved RFS or OS outcomes. In addition, preoperative MR imaging was not a significant prognostic factor related to either of these survival outcomes. To our knowledge, our study of well-balanced patient groups helps to understand the relationship between preoperative MR imaging and long-term outcomes in ILC patients.

There is a lack of consensus regarding the effect of preoperative MR imaging on long-term outcomes in ILC. Previous meta-analysis [18] insisted that routine preoperative MR imaging does not appear to significantly reduce the risk of breast cancer recurrence. Solin et al [10] found no change in OS, distant metastasis, and any local failure or contralateral breast cancer incidence with or without MR imaging. However, that study was a non-randomized retrospective analysis and did not address whether there was s subset of patients who might have benefitted from MR imaging. In contrast, Fischer et al [19] reported that the rate of local recurrence was lower for patients with MR imaging (1.2% vs 6.8%, $p < 0.001$) although these authors also did not adjust for major differences in tumor and treatment variables, and only 9.7% of the ILC subtype underwent MR imaging. Despite the conflicting evidence from previous studies, the effect of MR imaging on the long-term outcomes in ILC patients had not been investigated. Our current results have revealed that preoperative MR imaging produced a better long-term OS outcome, but without statistical significance (HR, 0.485; 95% CI, 0.149, 1.585; $p = 0.231$), and no significant improvement in total recurrence, loco-regional recurrence, contralateral breast recurrence, or distant metastasis.

Preoperative MR imaging is known to change the therapeutic plan in approximately one third of patients with ILC [20]; in 15–20% of these cases, the plan changes from breast conservation surgery to mastectomy. In our previous study [15], MR imaging was found to be associated with lower frequency of reoperation (odds ratio, 0.140; $p < 0.001$), but a similar likelihood of initial mastectomy (odds ratio, 0.876; $p = 0.528$) and final mastectomy (odds ratio, 0.744; $p = 0.151$) compared with patients without MR imaging. Thus, our previous study [15] supports the conclusion of other studies [6, 9–11, 18] that suggest preoperative MR imaging may be beneficial for short-term outcomes. Preoperative MR imaging enables the detection of additional occult lesions in the contralateral breast [21] making it a worthwhile part of a preoperative workup in ILC patients as it can detect approximately 7–10% of contralateral lesions [20]. With regard to contralateral breast recurrence, Wang et al [13] have reported that preoperative MR imaging increases the detection rate of synchronous contralateral breast cancer but is not associated with a decrease in contralateral breast cancer occurrence. That study had few ILC patients in its population (6.1%), and two thirds of these ILC cases did not undergo preoperative MR imaging. Another study of metachronous contralateral breast cancer reported that an interval to a second cancer of less than

**Table 2** Survival outcomes before propensity score matching

| | No MR group ($N = 167$) | MR group ($N = 120$) | $p$ value |
|---|---|---|---|
| No recurrence | 143/167 (85.6%) | 107/120 (89.2%) | 0.818 |
| Total recurrence[a] | 24/167 (14.4%) | 13/120 (10.8%) | 0.482 |
| Loco-regional | 7/167 (4.2%) | 4/120 (3.3%) | |
| Contralateral breast | 5/167 (3.0%) | 2/120 (1.7%) | |
| Distant | 12/167 (7.2%) | 7/120 (5.8%) | |
| Death | 16/167 (9.6%) | 5/120 (4.2%) | 0.132 |

All numbers shown are numbers of patients, total number of patients in both groups including matched patients

Data in parentheses indicate the percentages

The statistical method uses chi-square test for categorical variables

[a] Total recurrences were divided into three subgroups according to the first breast cancer recurrence in each patient

3 years is a strong prognostic factor in distant disease-specific survival (DFS) [22]. In our study, MR group showed a tendency toward better survival outcomes including total recurrence, loco-regional and distant recurrence, and overall survival within the first 2 years, but was insignificant. In our previous study of preoperative MR imaging in ILC patients [15], the synchronous contralateral malignancy rate was 3.8% in the MR cases. In the present study, the contralateral breast recurrence was 1.9% in the MR group after matching. However, this did not reach statistical significance compared to the no MR cohort which had a 2.9% contralateral breast recurrence rate. The equivalent incidence of contralateral breast recurrence at follow-up in both groups may be a consequence of adjuvant therapy, which reduces the subsequent occurrence of metachronous contralateral cancer [23] or may be limited interpretation due to the relatively small sample size. Nevertheless, the clinicians should take account of the fact that MR imaging may detect contralateral breast cancer at an earlier stage, although it does not reduce the incidence of contralateral breast recurrence.

**Table 3** Hazard models of the association between preoperative MR imaging and loco-regional, contralateral breast, and distant recurrence and death rates after propensity score matching

| Outcomes | No. of events | Hazard ratio | 95% confidence interval | $p$ value | Hazard ratio[b] | 95% confidence interval[b] | $p$ value[b] |
|---|---|---|---|---|---|---|---|
| Total recurrence[a] | | | | | | | |
| MR (−) | 14 (13.5%) | 1.096 | 0.497, 2.416 | 0.821 | 0.973 | 0.484, 1.958 | 0.939 |
| MR (+) | 12 (11.5%) | | | | | | |
| The first recurrence | | | | | | | |
| Loco-regional | | 1.204 | 0.294, 4.924 | 0.796 | 1.061 | 0.332, 3.389 | 0.920 |
| MR (−) | 4 (3.8%) | | | | | | |
| MR (+) | 4 (3.8%) | | | | | | |
| Contralateral breast | | 0.945 | 0.147, 6.061 | 0.952 | 1.006 | 0.191, 5.300 | 0.994 |
| MR (−) | 3 (2.9%) | | | | | | |
| MR (+) | 2 (1.9%) | | | | | | |
| Distant | | 1.020 | 0.339, 3.070 | 0.973 | 0.899 | 0.320, 2.523 | 0.839 |
| MR (−) | 7 (6.7%) | | | | | | |
| MR (+) | 6 (5.8%) | | | | | | |
| Death | | | | | | | |
| MR (−) | 9 (8.7%) | 0.485 | 0.149, 1.585 | 0.231 | 0.353 | 0.111, 1.122 | 0.078 |
| MR (+) | 4 (3.8%) | | | | | | |

All numbers shown are numbers of patients

Data in parentheses indicate the percentages

Cox proportional hazards model was used and $z$-test for coefficient of Cox regression analysis

[a] Total recurrences were divided into three subgroups according to the first breast cancer recurrence in each patient

[b] Adjusted using inverse probability weighting analysis

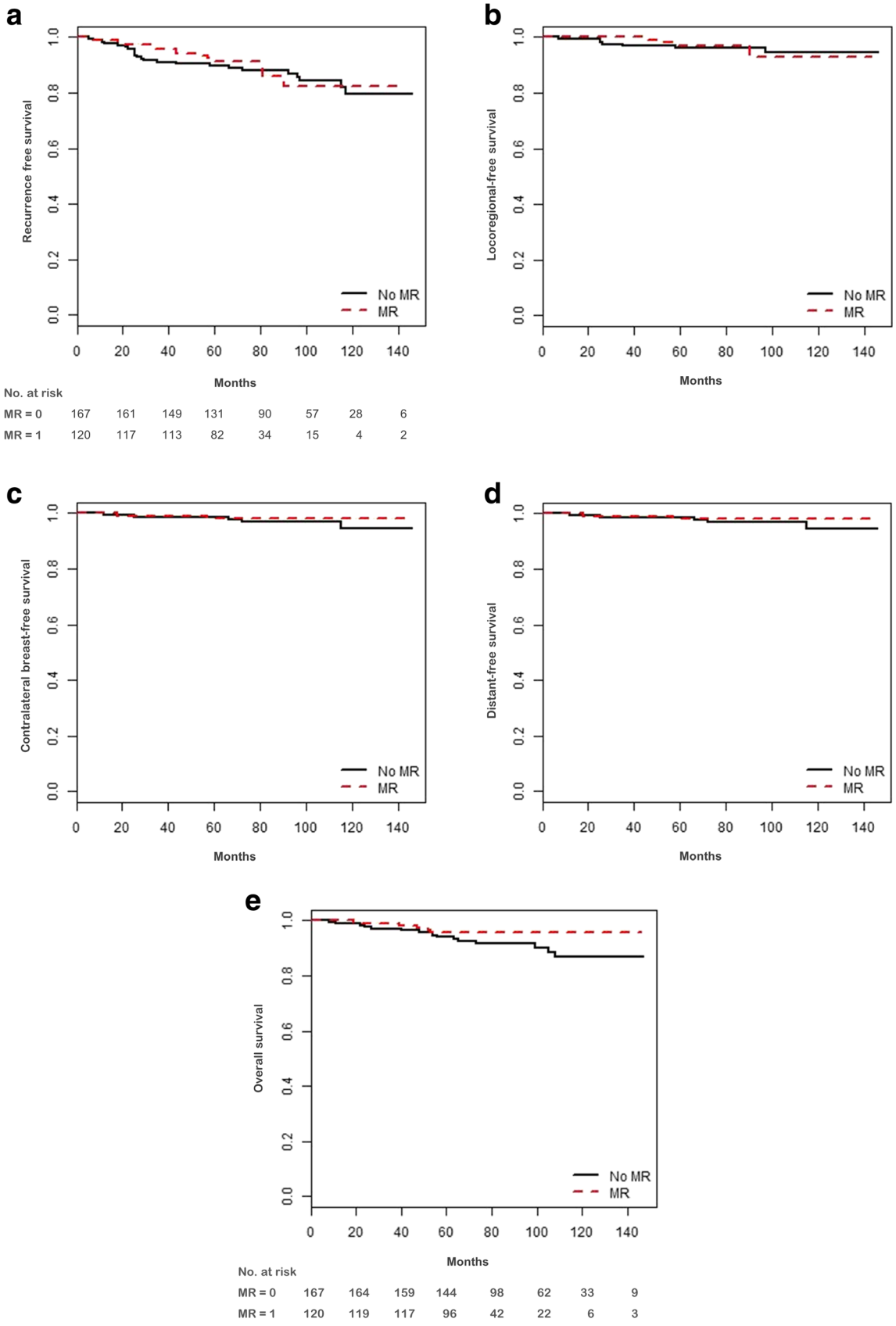


**Fig. 1** Kaplan-Meier survival curves for overall survival and recurrence-free survival in patients with invasive lobular carcinoma with and without preoperative magnetic resonance imaging. **a** Total recurrences. **b** Local-regional recurrences. **c** Contralateral breast cancer. **d** Distant recurrences. **e** Overall survival

**Table 4** Multivariable Cox proportional hazard analysis of variables associated with recurrence-free survival and overall survival in the unmatched cohort

| Variable | Recurrence-free survival | | | Overall survival | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% confidence interval | *p* value | Hazard ratio | 95% confidence interval | *p* value |
| Receipt of MRI | 0.823 | 0.409, 1.658 | 0.586 | 0.478 | 0.167, 1.366 | 0.168 |
| LVI | 4.703 | 2.136, 10.355 | < 0.001[a] | 6.014 | 2.273, 15.911 | < 0.001[a] |
| Adjuvant endocrine therapy | 0.175 | 0.075, 0.405 | < 0.001[a] | 0.089 | 0.035, 0.225 | < 0.001[a] |
| Mastectomy | | | | 2.943 | 1.100, 7.875 | 0.032[a] |

The statistical method uses *z*-test for coefficient of Cox regression analysis

*LVI* lymphovascular invasion

[a] *p* values less than 0.05 were considered to indicate a statistically significant difference

One of the largest prior studies of ILC by Wasif et al [24] using the Surveillance, Epidemiology, and End Results (SEER) registry observed that even though ILC presents at a more advanced stage than invasive ductal carcinoma, it is associated with a better 5-year DFS among patients matched for T and N stage due to ER positivity. A large tumor size, triple-negative breast cancer, and the presence of lymphovascular invasion are known as poor prognostic factors for recurrence and survival in ILC [25–27]. ER and PR positivity have been reported as protective factors against death [3, 24, 28]. In our present study, ER and PR positivity and adjuvant endocrine therapy were associated with better RFS and OS outcomes. Regarding poor OS outcome, mastectomy was related with higher hazard of death (HR, 2.943; 95% CI, 1.100, 6.875; $p = 0.032$). Similarly, Hwang et al [29] also showed a lower hazard of death associated with breast conservation than mastectomy. In this study [29], lobular cancers were associated with higher mastectomy rate when compared to ductal carcinoma (53% to 44% respectively). Further studies would be required to verify this and to determine which factors may be contributing to this effect.

Our study had several limitations. First, it was from a single tertiary institution and was retrospective in design with a relatively small sample size and short follow-up period. We cannot exclude the possibility that a longer follow-up could reveal an MR imaging-related benefit. A prospective randomized clinical trial with a longer follow-up period will thus be needed. Second, we recognize that there were very few ipsilateral and contralateral breast recurrence events throughout the follow-up period. It is thus reasonable to predict that the power of our analysis to detect small differences in the recurrence rates would have been limited. Finally, breast MR protocols were non-uniform during the study period which has evolved, and therefore was difficult to compare as a confounder in the analysis.

Our analysis of ILC patients demonstrates that preoperative MR imaging does not show prognostic value in ILC as there is no apparent benefit of in terms of recurrence or survival outcomes.

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## Compliance with ethical standards

**Guarantor** The scientific guarantor of this publication is Eun Young Chae.

**Conflict of interest** The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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**Informed consent** Written informed consent was waived by the Institutional Review Board.

**Ethical approval** Institutional Review Board approval was obtained.

**Study subjects or cohorts overlap** Some study subjects or cohorts have been previously reported in Radiology 2018 Jun; 287(3): 771–777 by Ha et al.

**Methodology**
- retrospective
- case-control study
- performed at one institution

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