Preoperative Magnetic Resonance Imaging Evaluation Improves Breast Conserving Surgery Rate but Not Local Disease Control in Breast Ductal Carcinoma in Situ Patients: A Propensity Score-matched Analysis with 742 Cases

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Research Article

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Abstract

Purpose: The role of preoperative evaluation by magnetic resonance imaging (MRI) in breast ductal carcinoma in situ (DCIS) management remains controversial. The study aims to evaluate the associations between preoperative MRI examination and breast conserving surgery in DCIS patients.

Methods: Patients with DCIS received surgery between Jan. 2009 and Jan.2021 in two breast centers were retrospectively included. Associations between preoperative MRI examination and clinicopathological characteristics, breast conserving surgery, and prognosis were evaluated after propensity score matching (PSM).

Results: A total of 1351 patients were included. After PSM for age, family history of breast cancer, manifestation at diagnosis, lesion patterns, and nuclear grade, 742 patients were further analyzed. Patients with preoperative MRI examination were more likely to receive breast conserving surgery (BCS) than patients without MRI (28.6% vs. 19.1%; *P*=0.003). For 227 patients planning to receive BCS, initial negative surgical margin was similar between MRI and non-MRI cohorts (73.6% vs. 71.9%; *P*=0.485). In addition, there was no difference in the percentage of patients who received a secondary mastectomy between MRI and non-MRI cohorts (22.0% vs. 23.7%; *P*=0.433). In terms of prognosis, similar locoregional recurrence and breast cancer-related death were observed between MRI and non-MRI cohorts.

Conclusion: Preoperative breast MRI examination was associated with a higher BCS rate in DCIS patients, but had no impact on disease outcome.

Introduction

With the widespread application of breast cancer screening project, the incidence of ductal carcinoma in situ (DCIS) has significantly increased during past years [1]. DCIS was usually considered as an inert lesion, since malignant proliferation of epithelial cells was confined inside the breast ducts with an intact basement membrane [2]. However, a recurrence was inevitable even after radical surgical resection, radiotherapy, and endocrine treatment. Approximately half of ipsilateral recurrences were invasive ductal carcinoma (IDC) for DCIS patients received breast-conserving treatment [3–5]. Therefore, the screening, evaluation and treatment patterns of DCIS were in a similar manner as IDC.

Currently, the common-used preoperative imaging evaluation for DCIS includes mammography and ultrasound, which helps to present the extent and pattern of breast lesions [6, 7]. MRI imaging has been also widely applied in evaluating lesions for breast cancer with superior sensitivity [8]. Compared with mammograph and ultrasound, it shows an advantage of identifying both calcified and noncalcified lesions of DCIS with consistently greater sensitivity [9]. In addition, it was powerful in the assessment of extent of disease. MRI showed a sensitivity of 89% for accurate assessment of DCIS extent compared with 55% for mammography and 47% for ultrasound [10]. However, its role in preoperative evaluation of DCIS was supported by limited studies, remaining controversial. Relatively high false-positive rate of breast MRI was an important problem when discussing its role in evaluating disease, which might

overestimate the extent of lesions and lead to unnecessary biopsies and more extensive surgical resection range [11]. The ability of MRI to accurately predict the scope of DCIS and influence local management has not yet been fully determined [12].

Based on above issues, this study aims to characterize DCIS patients with or without preoperative MRI, thus to evaluate the impact of MRI on local treatment choice and prognosis for DCIS patients.

Patients And Methods

This study retrospectively reviewed all patients with DCIS who received surgery during 2009 to 2021 in two breast centers (Comprehensive Breast Health Center of Ruijin Hospital, Shanghai Jiao Tong University, and Jiaxing Women and Children's Hospital, Zhejiang Province). Patients with a diagnosis of pure DCIS who received surgery with or without preoperative breast MRI examination, and had a minimum follow-up of 1 year were included. Main exclusion criteria included histologically proven invasive disease in biopsy or surgical specimens, metastatic breast cancer, and previous treatment for breast cancer.

Clinicopathological and treatment information of patients were collected from Shanghai Jiao Tong University Breast Cancer Database. Clinical manifestation at diagnosis were classified in radiographic abnormality including mass, calcification, and other presentation. A multifocal disease is defined as the presence of two or more lesions in the ipsilateral breast based on ultrasound, mammography or MRI examination. Age and tumor size were divided into subgroups according to VNPI index [13]. Nuclear grade was classified into well differentiated (Grade I), intermediate (Grade II) or poorly differentiated disease (Grade III). Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (HER2) status, and Ki-67 were routinely detected by immunohistochemistry in biopsy and surgical specimens, and consistent with the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) guideline recommendations [14, 15]. A positive surgical margin is defined as the distance between the duct or gland involved in DCIS. Patients who planned to receive BCS underwent a secondary mastectomy if definitive negative margin is not achieved.

Patients received every 3 months followed up in the first two years after surgery and every 6 months thereafter. Last follow up was completed by November 1st, 2021. Locoregional recurrence (LRR) was defined as ipsilateral local and/or regional recurrence event of DCIS or invasive breast cancer. Recurrence-free survival (RFS) was defined as time from primary surgery to LRR, distant metastasis, or death from any cause. Cumulative breast cancer incidence was defined as the incidence of recurrence or metastasis, contralateral or secondary primary DCIS or invasive breast cancer. Breast cancer-free interval (BCFI) was defined as time from primary surgery to recurrence or metastasis of breast cancer, or second primary breast cancer, or death from any cause.

All statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL). Statistical analyses including Chi-square ($\chi 2$) test and logistic regression was used to compare the differential factors between patient groups. Propensity score matching (PSM) was performed with 1:1 nearest

neighbor method without replacement, and the caliper value is set to 0.02. Clinical outcome was demonstrated by Kaplan-Meier method and compared between groups using log-rank test. All statistical tests were two-tailed and statistical significance was defined as $P < 0.05$.

Results

Patient characteristics

A total of 1351 patients with a diagnosis of DCIS were included. The demographic and clinicopathological characteristics of the entire cohort were summarized in Table 1. The median age was 52.0 years (ranging from 21.0 to 93.0 years). A total of 122 patients (9.0%) had a family history of breast cancer. Nine hundred and sixty patients(71.1%) were presented with mass, 179 patients (13.2%) with calcification, and 212 patients (15.7%) with nipple discharge or other symptoms. All patients received imaging evaluation including mammography and ultrasound prior to biopsy or surgery. Preoperative MRI examination was performed in 979 patients (72.5%; MRI cohort) while not in 372 patients (27.5%; non-MRI cohort). Multifocal lesions were found in 132 patients (9.8%). Regarding tumor size, 777 patients (57.5%) had tumor ≤ 1.5cm, 497 patients (36.8%) with tumor size between 1.6cm and 4.0cm, and 77 patients (5.7%) with tumor > 4.0cm.

Table 1
Patient and clinicopathological characteristics of entire cohort

Characteristics	Total	MRI	Non-MRI	*P*
	No. (%)	No. (%)	No. (%)	
Age (years)				0.004
< 40	158(11.7%)	132(13.5%)	26(7.0%)	
40–59	793(58.7%)	561(57.3%)	232(62.4%)	
≥ 60	400(29.6%)	286(29.2%)	114(30.6%)	
Family history of breast cancer				0.007
No	1229(91.0%)	878(89.7%)	351(94.4%)	
Yes	122(9.0%)	101(10.3%)	21(5.6%)	
Manifestation at diagnosis				0.001
Mass	960(71.1%)	669(68.3%)	291(78.2%)	
Calcification	179(13.2%)	138(14.1%)	41(11.0%)	
Others	212(15.7%)	172(17.6%)	40(10.8%)	
Tumor size (cm)				0.718
≤ 1.5	777(57.5%)	559(57.1%)	218(58.6%)	
1.6 ~ 4.0	497(36.8%)	366(37.4%)	131(35.2%)	
> 4.0	77(5.7%)	54(5.5%)	23(6.2%)	
Lesion patterns				0.020
Unifocal	1219(90.2%)	872(89.1%)	347(93.3%)	
Multifocal	132(9.8%)	107(10.9%)	25(6.7%)	
Comedo necrosis				0.196
No	1300(96.2%)	938(95.8%)	362(97.3%)	
Yes	51(3.8%)	41(4.2%)	10(2.7%)	
Nuclear grade				0.002
	433(32.1%)	308(31.5%)	125(33.6%)	
	496(36.7%)	339(34.6%)	157(42.2%)	

Abbreviation: MRI, Magnetic Resonance Imaging. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor 2; IHC, immunohistochemistry.

Characteristics	Total	MRI	Non-MRI	*P*
	No. (%)	No. (%)	No. (%)	
□	422(31.2%)	332(33.9%)	90(24.2%)	
ER status				0.059
Positive	987(73.1%)	729(74.5%)	258(69.4%)	
Negative	364(26.9%)	250(25.5%)	114(30.6%)	
PR status				0.332
Positive	881(65.2%)	646(66.0%)	235(63.2%)	
Negative	470(34.8%)	333(34.0%)	137(36.8%)	
HER2 status (IHC)				0.287
3+	358(26.5%)	266(27.2%)	92(24.7%)	
2+	472(34.9%)	348(35.5%)	124(33.3%)	
0 ~ 1+	521(38.6%)	365(37.3%)	156(42%)	
Ki-67				0.787
≤ 14%	825(61.1%)	600(61.3%)	225(60.5%)	
> 14%	526(38.9%)	379(38.7%)	147(39.5%)	

Abbreviation: MRI, Magnetic Resonance Imaging. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor 2; IHC, immunohistochemistry.

Factors influencing decision of MRI examination

Patient and clinicopathological characteristics were compared between MRI and non-MRI cohorts. Age was statistically different between two cohorts ($P = 0.004$). Patients under 40 years old accounted for 13.5% in the MRI cohort while 7.0% in the non-MRI cohort. Patients over 60 years old were found in 29.2% and 20.6% of the MRI and non-MRI cohorts. Patients with a family history of breast cancer were associated with more preoperative MRI examination than those without family history (10.3% vs. 5.6%; $P = 0.007$). In terms of clinical manifestation at diagnosis, patients with calcification or other symptoms were more likely to received preoperative MRI examination than patients presenting with mass ($P = 0.001$). More MRI examination were performed in multifocal disease than unifocal disease (10.9% vs. 6.7%; $P = 0.020$). There was no significant difference in tumor size, ER status, PR status, HER2 status, and Ki-67 between two cohorts (all $P > 0.05$).

Impact of MRI on local treatment of DCIS patients

In order to explore the influence of preoperative MRI examination on the decision of local treatment of DCIS patients, PSM were used to reduce bias from data deviation and confounding factors between two

cohorts. After PSM for age, family history of breast cancer, manifestation at diagnosis, lesion patterns, and nuclear grade, a total of 742 patients with balanced clinical and pathological characteristics were included for further analyses (Table 2).

Table 2
Patient and clinicopathological characteristics of MRI and non-MRI cohorts after PSM

Characteristics	Total	MRI	Non-MRI	*P*
	No. (%)	No. (%)	No. (%)	
Age (years)				0.085
< 40	69(9.3%)	43(11.6%)	26(7.0%)	
40–59	444(59.8%)	213(57.4%)	231(62.3%)	
≥ 60	229(30.9%)	115(31.0%)	114(30.7%)	
Family history of breast cancer				0.543
No	696(93.8%)	346(93.3%)	350(94.3%)	
Yes	46(6.2%)	25(6.7%)	21(5.7%)	
Manifestation at diagnosis				0.540
Mass	588(79.3%)	298(80.3%)	290(78.2%)	
Calcification	73(9.8%)	32(8.6%)	41(11.0%)	
Others	81(10.9%)	41(11.1%)	40(10.8%)	
Tumor size (cm)				0.648
≤ 1.5	431(58.1%)	214(57.7%)	217(58.5%)	
1.6 ~ 4.0	270(36.4%)	139(37.5%)	131(35.3%)	
> 4.0	41(5.5%)	18(4.9%)	23(6.2%)	
Lesion patterns				0.774
Unifocal	690(93.0%)	344(92.7%)	346(93.3%)	
Multifocal	52(7.0%)	27(7.3%)	25(6.7%)	
Comedo necrosis				0.665
No	720(97.0%)	359(96.8%)	361(97.3%)	
Yes	22(3.0%)	12(3.2%)	10(2.7%)	
Nuclear grade				0.361
□	260(35.0%)	136(36.7%)	124(33.4%)	
□	295(39.8%)	138(37.2%)	157(42.3%)	

Abbreviation: PSM, propensity score matching. MRI, Magnetic Resonance Imaging. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor 2; IHC, immunohistochemistry.

Characteristics	Total	MRI	Non-MRI	*P*
	No. (%)	No. (%)	No. (%)	
□	187(25.2%)	97(26.1%)	90(24.3%)	
ER status				0.810
Positive	519(69.9%)	261(70.4%)	258(69.5%)	
Negative	223(30.1%)	110(29.6%)	113(30.5%)	
PR status				0.647
Positive	474(63.9%)	240(64.7%)	234(63.1%)	
Negative	268(36.1%)	131(35.3%)	137(36.9%)	
HER2 status (IHC)				0.781
3+	190(25.6%)	98(26.4%)	92(24.8%)	
2+	251(33.8%)	127(34.2%)	124(33.4%)	
0 ~ 1+	301(40.6%)	146(39.4%)	155(41.8%)	
Ki-67				0.128
≤ 14%	468(63.1%)	244(65.8%)	224(60.4%)	
> 14%	274(36.9%)	127(34.2%)	147(39.6%)	

Abbreviation: PSM, propensity score matching. MRI, Magnetic Resonance Imaging. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor 2; IHC, immunohistochemistry.

Local treatment patterns in DCIS patients between two groups were listed in Table 3. A total of 227 patients (30.6%) were planned to receive BCS as primary surgery based on preoperative evaluation. BCS was ultimately performed in 177 of 742 patients (23.9%). Positive surgical margin was observed in 60 cases (26.4%) of primary BCS. Among these patients, a secondary BCS with more extensive resection range to obtain extra negative surgical margin was performed in 10 patients, and a secondary mastectomy was performed in 50 patients.

Table 3
Local treatment between MRI and non-MRI cohorts

Characteristics	Total No. (%)	MRI No. (%)	Non-MRI No. (%)	*P*
Breast surgery				0.003
Mastectomy	565(76.1%)	265(71.4%)	300(80.9%)	
BCS	177(23.9%)	106(28.6%)	71(19.1%)	
Initial surgical margin (in patients planning to receive BCS)				0.485
Positive	60(26.4%)	39(28.1%)	21(23.9%)	
negative	167(73.6%)	100(71.9%)	67(76.1%)	
Final breast surgery type (in patients planning to receive BCS)				0.433
Mastectomy	50(22.0%)	33(23.7%)	17(19.3%)	
BCS	177(78.0%)	106(76.3%)	71(80.7%)	
Radiotherapy (in patients received BCS)				0.215
No	46(26.0%)	24(22.6%)	22(31.0%)	
Yes	131(74.0%)	82(77.4%)	49(69.0%)	
Abbreviation: MRI, magnetic resonance imaging. BCS, breast conserving surgery.				

Figure 1 shows the differences in breast surgery between MRI and non-MRI cohorts. Patients in MRI cohort received a higher rate of BCS than patients in non-MRI cohort (28.6% vs. 19.1%; $P = 0.003$). Moreover, among 227 patients planned to receive BCS, initial negative surgical margin was similar regardless of preoperative MRI examination (73.6% vs. 71.9%; $P = 0.485$). There was also no difference in secondary mastectomy rate between MRI and non-MRI cohorts (22.0% vs. 23.7%; $P = 0.433$). Regarding postoperative radiotherapy, 131 of 177 patients (74.0%) received radiation following BCS. No association was observed between preoperative MRI and adjuvant radiotherapy decision (77.4% vs. 69.0%; $P = 0.215$).

Prognostic value of MRI in DCIS patients

A total of 1351 patients received complete follow-up, among which 742 cases after PSM were included in prognosis analysis. After a median follow-up of 45.0 months (ranging from 3.0 to 144.0 months), 3 cases of ipsilateral breast tumor recurrence (0.4%), 2 cases of regional lymph node recurrence (0.3%), 10 cases of contralateral breast cancer (1.3%), and 4 cases of distant metastases (0.5%) were observed (Table 4). Among the 8 death events (1.1%), 3 cases were breast cancer-related deaths (0.4%), and 5 cases were resulted from other causes (0.7%).

Table 4
Summary of recurrence and death events in MRI and non-MRI cohorts

Characteristics	MRI	Non-MRI
Ipsilateral breast tumor recurrence	2	1
Contralateral breast cancer	5	5
Regional lymph node recurrence	1	1
Distant metastasis	2	2
Death		
Breast cancer-related	2	1
Others causes	0	5
Second primary tumor	2	6

Abbreviation: MRI, magnetic resonance imaging.

The 5-year and 10-year RFS for all patient after PSM was 99.16% and 98.54%, respectively. There was no significant difference in LRR between MRI and non-MRI cohorts at 5 year (0.50% vs. 0.30%) and at 10 year (1.5% vs. 0.3%; $P = 0.641$; Fig. 2A). The cumulative breast cancer incidence at 5-year (3.17% vs. 2.82%) and at 10-year (5.39% vs. 4.80%; $P = 0.875$) were also similar between MRI and non-MRI cohorts (Fig. 2B). No difference in breast cancer-related death was observed between MRI and non-MRI cohorts (0.54% vs. 0.27%; $P = 0.668$; Fig. 2C).

Discussion

MRI has been increasingly used for preoperative evaluation of lesions in breast cancer patients. Although MRI could provide a clear imaging with high sensitivity especially for non-mass lesions in breast, its value in surgery decision-making and prognosis remains controversial [16–18]. In addition, there has been limited evidence on the application of MRI in DCIS. In this study, we demonstrated that younger age, family history of breast cancer, manifestation at diagnosis, and lesion patterns were associated with the choice of preoperative MRI evaluation of DCIS. MRI examination was related with a higher rate of BCS, but had limited impact on disease outcome.

Mammography played a pivotal role in breast disease screening. However, it is less sensitive to non-calcified lesions, which is commonly seen in DCIS patients [19, 20]. With the MRI technical development, it shows a higher sensitivity in detecting DCIS lesions than mammography and ultrasound [8, 10], especially for high-level DCIS [21]. Bae et al. found that preoperative MRI in DCIS patients could detect additional lesions in both ipsilateral and contralateral breast [22]. This advantage was more distinct in patients over 50 years old or with lesions larger than 2.5cm. Bijker et al. and Tunonde Lara et al. found that DCIS patients under 40 years old were more likely to be presented with non-mass symptoms

including nipple discharge or breast pain [23, 24]. According to our results, MRI was more likely to be applied in patients younger than 40 years, with a family history of breast cancer, presenting with non-mass clinical manifestation, multifocal lesions, and high-grade disease, which was consistent with previous studies. The size of tumor and other pathological factors including hormone-receptor status or Ki-67 showed no significant impact on the decision of preoperative MRI examination.

Patients with DCIS are eligible for BCS with equivalent safety and survival benefit compared with mastectomy [25]. Preoperative breast MRI has been used in breast cancer patients to help decision-making on surgical management, thus to reduce the rate of BCS positive margin and the possibility of BCS failure [26]. Lehman et al. demonstrated that MRI showed superior ability in detecting the extent of DCIS lesions compared with mammography or ultrasound, with acceptable specificity [21]. Renata Faermann et al. found that the volume ratio measurement of MRI could assist patients in choosing the best type of surgery and can convert a proportion of patients from mastectomy to BCS [27]. Our study used PSM to balance clinicopathological factors between groups and found that DCIS patients received preoperative MRI examination had a higher BCS rate compared with patients received no MRI. The possible explanations included providing a more accurate assessment of lesions and excluding the existence of multifocal lesions by MRI, thereby increasing surgeon's willing and confidence to make a reasonable surgical plan of BCS.

Among well-established risk factors for recurrence in DCIS patients, surgical margin status was described as the most important one [28, 29]. Sufficient evidence had shown that complete resection of tumor with negative surgical margins followed by radiotherapy could reduce the risk of ipsilateral recurrence for DCIS patients [30]. Therefore, a secondary mastectomy should be performed in patients who planned BCS if negative surgical margins were not available. Although preoperative MRI is important for determining BCS, its role in achieving negative surgical margin remain unanswered. Previous study by Lehman et al. found that MRI showed an advantage in tumor detection, size measurement, and to reduce the chance of positive surgical margin in DCIS patients [21]. However, a large meta-analysis demonstrated no statistical difference in positive surgical margins for DCIS patients regardless of receiving preoperative MRI [31]. In our study, we found that MRI examination was not associated with a lower rate of positive surgical margin among planned BCS patients. The rate of a secondary mastectomy was also similar between MRI and non-MRI cohorts, which was consistent with previous studies. One possible explanation could be the choice of candidates to received planned BCS. For patients in the non-MRI cohort, surgeon may choose patients with conservative strategy to receive BCS. Patients with uncertainty of achieving negative surgical margin would receive mastectomy directly.

Currently, the treatment pattern for DCIS includes surgery, postoperative radiotherapy, and endocrine therapy. An excellent clinical outcome could be achieved following standard therapy, with over 80% DCIS patients would not experience local recurrence or distant metastasis during 15-year follow-up [32]. In our cohort, all patients receiving standard treatment and regular follow-up showed superior RFS and BCFI. No significant difference in prognosis between MRI and non-MRI cohorts was observed in our study.

Our study still has several limitations. Firstly, this is a retrospective study. There was no consensus across breast centers on preoperative evaluation standard. The decision of receiving preoperative MRI examination or not largely depends on surgeon's experience. Moreover, the follow-up period in our study is limited, considering the long natural history of DCIS. More large-scaled prospective studies are needed to further explore the role of preoperative MRI in DCIS patients' management.

In summary, our study evaluated the role of preoperative MRI in determining local management of DCIS patients and found that preoperative MRI evaluation were associated with a higher rate of BCS, but had no impact on disease outcome.

Declarations

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COMPETING INTERESTS

The authors declare that they have no known competing interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHORS' CONTRIBUTIONS

YY analyzed and interpreted the patient data; X Zhang was a major contributor in writing the manuscript; X Zhu contributed to the data collection and acquisition; KS and JZ substantively revised the manuscript; XC made substantial contributions to the conception of the work, and substantively revised the manuscript.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are not publicly available due to privacy policy of patients, but are available from the corresponding author on reasonable request.

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Figures

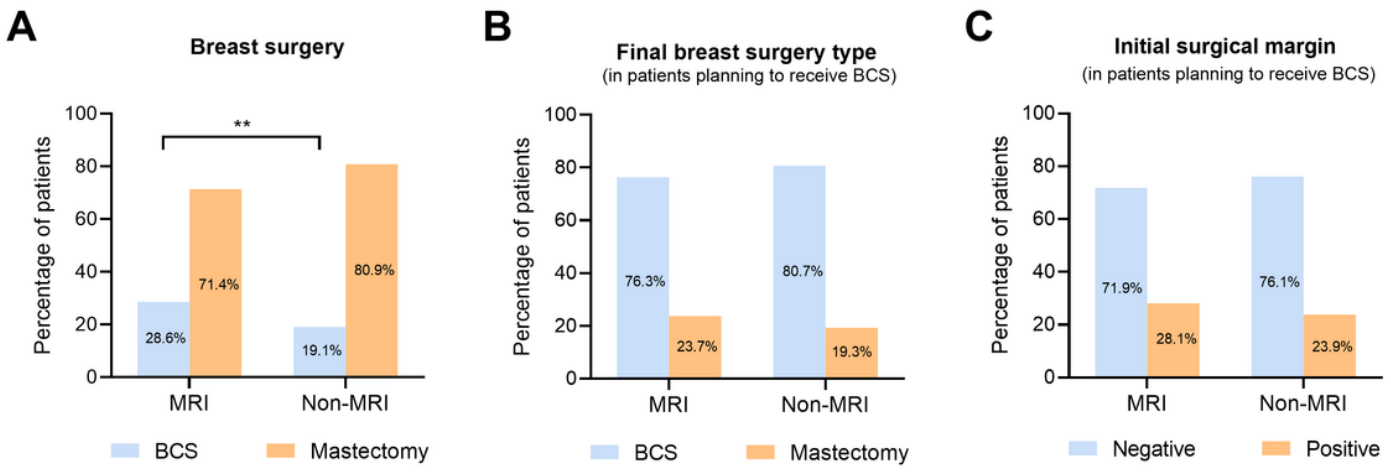

Figure 1

Local treatment between MRI and non-MRI cohorts A) Distribution of breast surgery type; B) Final breast surgery type in patients planning to receive BCS; C) Initial surgical margin in patients planning to receive BCS. (Abbreviation: MRI, magnetic resonance imaging; BCS, breast conserving surgery)

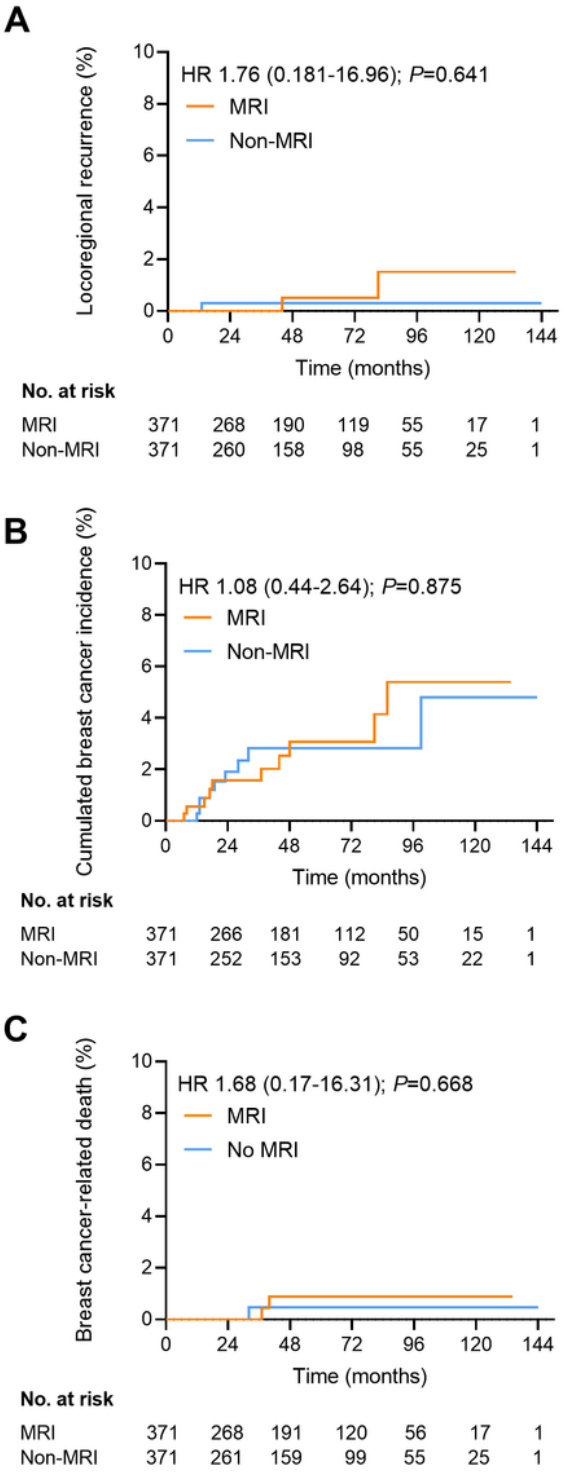

Figure 2

Kaplan-Meier estimates of A) Locoregional recurrence, B) Cumulative breast cancer incidence, and C) Breast cancer-related death of MRI and non-MRI cohorts. (Abbreviation: MRI, magnetic resonance imaging)