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Review Article

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Breast Magnetic Resonance Imaging for Patients With Newly Diagnosed Breast Cancer: A Review

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ABSTRACT

Despite the high sensitivity and widespread use of preoperative magnetic resonance imaging (MRI), the American Cancer Society and the National Comprehensive Cancer Network guidelines do not recommend the routine use of preoperative MRI owing to the conflicting results and lack of clear benefit to the surgical outcome (reoperation and mastectomy) and long-term clinical outcomes (local recurrence and metachronous contralateral breast cancer). Preoperative MRI detects additional cancers that are occult at mammography and ultrasound but increases the rate of mastectomy. Concerns about overdiagnosis and overtreatment of preoperative MRI might be mitigated by adjusting the confounding factors when conducting studies, using the state-of-the-art image-guided biopsy technique, applying the radiologists' cumulative experiences in interpreting MRI findings, and performing multiple lumpectomies in patients with multicentric cancer. Among the various imaging methods, dynamic contrast-enhanced MRI has the highest accuracy in predicting pathologic complete response after neoadjuvant chemotherapy. Prospective trials aimed at applying the MRI information to the de-escalation of surgical or radiation treatments are underway. In this review, current studies on the clinical outcomes of preoperative breast MRI are updated, and circumstances in which MRI may be useful for surgical planning are discussed.

Keywords: Breast Neoplasms; Magnetic Resonance Imaging; Mastectomy; Recurrence; Reoperation

INTRODUCTION

Contrast-enhanced breast magnetic resonance imaging (MRI) has been used as a guide for surgery in patients with newly diagnosed breast cancer, which is performed to evaluate the disease extent and detect additional cancers in the contralateral and ipsilateral breasts that are not visible on mammography or ultrasound. In addition, MRI has been widely used to monitor the response to chemotherapy and evaluate the extent of residual disease. However, the American Cancer Society and the National Comprehensive Cancer Network do not recommend the routine use of preoperative breast MRI, as it is associated with increased mastectomy rates, and limited evidence exists to support its association with improved clinical outcomes [1,2]. Moreover, additional cancers detected on MRI may have been treated with adjuvant radiation therapy. Furthermore, the use of MRI may delay appropriate

treatment as it generates false-positive findings that require additional biopsies. In this review, current studies on the clinical outcomes of preoperative breast MRI are updated, and the different circumstances in which MRI may be useful for surgical planning are discussed.

EVALUATION OF TUMOR SIZE

In women who are candidates for breast-conserving surgery (BCS), underestimation of the tumor extent could lead to resection margin involvement of the tumor, subsequent reoperation, or occurrence of local recurrence. By contrast, overestimation can lead to unnecessary total mastectomy or surgical deformities. Therefore, preoperative imaging such as mammography, ultrasound, or dynamic contrast-enhanced MRI is used to evaluate the tumor size of the index cancer to help surgeons achieve negative resection margins. In the literature, the correlation coefficients between tumor sizes at imaging and histopathology were 0.26–0.76 for mammography, 0.57–0.68 for ultrasound, and 0.75–0.80 for MRI [3-5]. With regard to the histopathological type, the presence of ductal carcinoma in situ (DCIS) or invasive lobular carcinoma has been considered a factor associated with underestimation on conventional imaging [6-8]. However, in a prospective study including 593 patients with biopsy-proven invasive breast cancer, the sensitivity of preoperative MRI was significantly improved compared with that of mammography and ultrasound for DCIS detection (84.9% vs. 36.7%) [6]. In addition, invasive lobular carcinoma is more accurately depicted on preoperative MRI than on mammography and ultrasound [7,8]. Thus, MRI is the most accurate modality for tumor size evaluation among the imaging techniques for breast tumors [4,5].

DETECTION OF ADDITIONAL CANCERS

Preoperative MRI has consistently detected mammographically occult additional cancers in the contralateral breast as well as the ipsilateral breast, in addition to the index cancer [9,10]. In a meta-analysis of 19 studies, Houssami et al. [11] found that MRI detected additional cancers in the ipsilateral breast in 16% (range: 1%–28%) of 2,610 women with breast cancer. Meta-analysis showed that wide excision was converted to more extensive surgery in 11.3% (95% confidence interval [CI], 6.8–18.3) and to mastectomy in 8.1% (95% CI, 5.9–11.3) of patients, due to the additional foci of cancers identified on MRI [11]. In another analysis of 2,021 patients, 14% (285/2,021) of women had additional cancers detected on MRI and 4% (73/2,021) of them had additional cancers in different quadrants from the index cancer (i.e., multicentric cancers) [12]. Moreover, 76% (56/73) of multicentric cancers were invasive, while 25% (18/73) were larger than 1 cm, which might not be reliably treated with radiation or systemic therapy [12]. In a study including 3,781 patients, multivariable analysis revealed that multifocal cancers detected on preoperative MRI and the human epidermal growth factor receptor type 2 (HER2)-positive subtype were associated with local recurrences [13].

With regard to contralateral breast cancers, 2.4% of synchronous contralateral breast cancers were detected by physical examination and mammography in women with newly diagnosed breast cancer [14]. MRI has detected 3.1%–3.6% of additional contralateral breast cancers that are occult on physical examination and mammography [10,15]. In a prospective multicenter study of ACRIN-6667, including 969 women, MRI detected 30 (3.1%) contralateral breast cancers, and the negative predictive value of MRI was 99% [15]. In a single institutional study including 603 women, MRI detected additional contralateral

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cancers that were occult on conventional imaging in 22 women (3.6%) [10]. Therefore, preoperative MRI detects additional cancers, but the rate of detection should be judged based on the clinical outcomes such as reduced reoperation rate, reduced subsequent cancer occurrence rates, and increased mastectomy rate and trade-offs between true-positive findings (**Figure 1**) and false-positive findings (**Figure 2**).

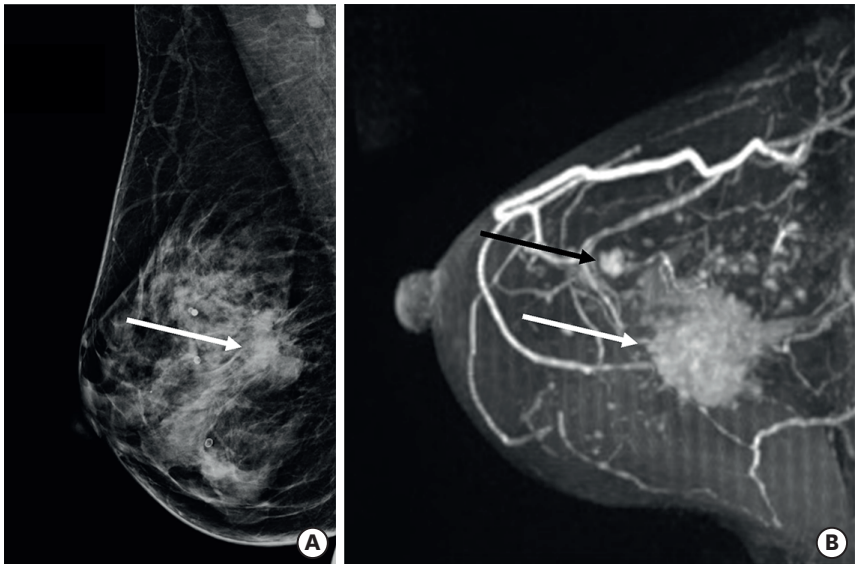

Figure 1. Preoperative images of a 51-year-old woman with biopsy-proven invasive ductal carcinoma (ER-positive, PR-positive, and HER2-negative). (A) Mammogram shows a spiculated mass, which represents the index cancer (white arrow). (B) MRI shows the index cancer (white arrow) and an additional low suspicious mass (black arrow). The additional mass detected on MRI was not visible on the second-look ultrasound. MRI-guided biopsy was performed, and the lesion was diagnosed as invasive ductal carcinoma (ER-positive, PR-positive, and HER2-negative).
ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor type 2; MRI = magnetic resonance imaging.

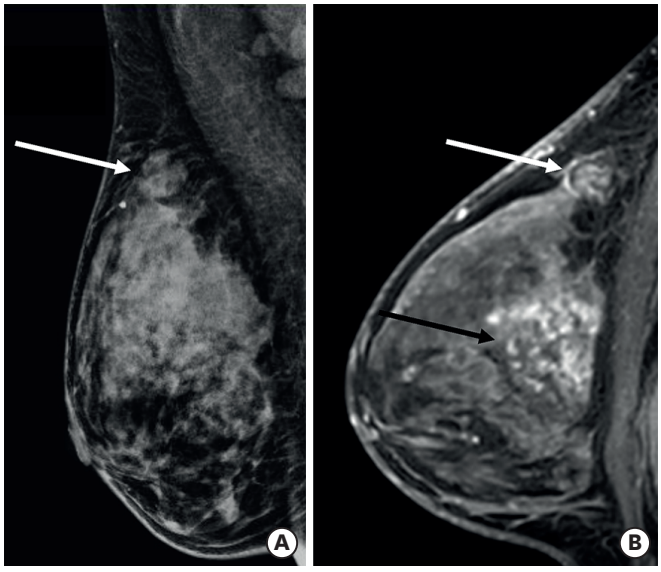

Figure 2. Preoperative images of a 43-year-old woman with biopsy-proven invasive ductal carcinoma of triple-negative subtype. (A) Mammogram shows an oval mass, which represents the index cancer (white arrow). (B) MRI shows an additional 3-cm segmental non-mass enhancement (black arrow) 2-cm lower than the index cancer (white arrow). Second-look ultrasound failed to detect the lesion. MRI-guided biopsy confirmed the fibrocystic changes. The lesion had been stable for more than 2 years.
MRI = magnetic resonance imaging.

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Table 1. Summary of preoperative MRI study results on reoperation and mastectomy rates

Study	Design	Population	MRI	No-MRI	Reoperation rate			Mastectomy rate		
					MRI (%)	No-MRI (%)	*p*-value	MRI (%)	No-MRI (%)	*p*-value
Turnbull et al. (2010) (COMICE) [16]	RCT	Cancer patients scheduled for wide excision	816	807	19	19	0.770	7	1	NR
Peters et al. (2011) (MONET) [17]	RCT	Nonpalpable tumors with BCS	53	50	34	12	0.008	32	34	0.776
Gonzalez et al. (2014) (POMB) [18]	RCT	Cancer patients < 56 years old	220	220	5	15	< 0.001	43	41	NR
Houssami et al. (2017) [19]	Meta-analysis	Cancer patients from 3 RCT and 16 comparative studies	15,274* 2,342†	70,701* 4,415†	Pooled OR for reoperation after BCS: 1.19 (95% CI, 0.85–1.66; p = 0.316)			Pooled OR for mastectomy: 1.39 (95% CI, 1.23–1.57; p < 0.001)		
Balleyguier et al. (2019) (IRCIS) [20]	RCT	Patients with DCIS	173	172	20	27	0.130	18	17	0.930
Sardanelli et al. (2022) (MIPA) [21]	Prospective observational study	Cancer patients	3,133	2,763	8.5	11.7	< 0.001	36.3	18.0	< 0.001

Values are presented as number of subjects included in the analysis.
BCS = breast-conserving surgery; CI = confidence interval; COMICE = Comparative Effectiveness of MRI in Breast Cancer; DCIS = ductal carcinoma in situ; IRCIS = Evaluation of the Diagnostic Performance of MRI ± Biopsy to Optimize Resection of Ductal Carcinoma In Situ Breast Cancer; MIPA = multicenter international prospective analysis; MONET = MR Mammography of Nonpalpable Breast Tumors; MRI = magnetic resonance imaging; NR = not reported; POMB = Preoperative MRI of the Breast; RCT = randomized controlled trial; BI-RADS = Breast Imaging Reporting and Data System; OR = odds ratio.
*Number of patients included in the analysis of reoperation rates; †Number of patients included in the analysis of mastectomy.

EFFECT ON SURGICAL OUTCOMES

Reoperation rate and mastectomy rate

Table 1 summarizes the results of preoperative MRI studies evaluating the reoperation rate and mastectomy rates. The first randomized controlled trial (RCT) that compared the reoperation rates between the MRI and no-MRI groups was the Comparative Effectiveness of MRI in Breast Cancer (COMICE) trial that included 1,623 patients who were lumpectomy candidates in the United Kingdom [16]. The reoperation rate was 19% both in the MRI (n = 816) and no-MRI groups (n = 807) (p = 0.77). The mastectomy rates were higher in the MRI group than in the no-MRI group (7% vs. 1%). Moreover, one-third of the mastectomy procedures performed in the MRI group might have been avoidable, based on the surgical histopathology. However, the COMICE trial only included patients from small centers with radiologists who had varying degrees of imaging experience, which could have affected the MRI results [16].

The second RCT, the Netherlands MR Mammography of Nonpalpable Breast Tumors (MONET) study, assessed the effect of preoperative MRI on nonpalpable tumors [17]. In this study, the reoperation rate of the MRI group was higher than that of the no-MRI group (34% [18/53] vs. 12% [6/50], p = 0.008). The increased reoperation rate in the MRI group might have been attributed to the higher proportion of DCIS and poor MRI quality in this study [17]. Furthermore, as only one-third of the included patients had breast cancer, the sample size of the study was too small to draw solid conclusions.

The third RCT was the Preoperative MRI of the Breast (POMB) trial in Sweden. Contrary to the COMICE and MONET trials, this trial reported significantly reduced reoperation rates in the MRI group (5% [11/220] in the MRI group vs. 15% [33/220] in the no-MRI group, p < 0.001) [18]. Although 18% (40/220) of the patients in the MRI group changed their treatment plan, the final number of mastectomy procedures did not differ between the 2 groups. This study included women younger than 56 years old, and a negative margin of at least 10 mm was the requirement for excision, which might have affected the study results. Furthermore, for the additional findings on preoperative MRI, a second-look ultrasound-guided biopsy or

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MRI-guided biopsy was performed in this study, which are important technical factors that are necessary for translating the high accuracy of MRI to better outcomes.

A meta-analysis by Houssami et al. [19] evaluated the aforementioned 3 RCTs and 16 comparative studies including 15,274 patients who underwent preoperative MRI. Consistent evidence showed that MRI was associated with increased odds of undergoing mastectomy (odds ratio [OR], 1.39; 95% CI, 1.23–1.57; $p < 0.001$). However, they did not find any statistical evidence revealing the effect of MRI on the rates of re-excision, reoperation, or positive margins [19]. They insisted that the increased mastectomy rate persisted in the analyses stratified by study timeframe, indicating that the trend is independent of the availability of MRI-guided biopsy [19].

Another randomized multicenter study, the Evaluation of the Diagnostic Performance of MRI ± Biopsy to Optimize Resection of Ductal Carcinoma In Situ Breast Cancer (IRCIS) trial that evaluated the efficacy of combined MRI and mammography for 360 women with DCIS in France, reported reoperation rates of 20% (35/173) in the MRI group and 27% (47/172) in the no-MRI group ($p = 0.13$) [20]. When we considered the per-protocol population with an assessable endpoint alone, the difference was 9% (stratified OR, 0.59; 95% CI, 0.35–1.0; $p = 0.05$) [20]. The total mastectomy rates were not different between the MRI and no-MRI groups (18% [31/173] vs. 17% [30/172], $p = 0.93$). Therefore, this study did not show sufficient surgical improvement; however, the addition of MRI did not lead to a high number of unnecessary mastectomy procedures.

More recently, an observational multicenter international prospective analysis (MIPA) including 5,896 patients from 27 centers found that the MRI group had a higher overall mastectomy rate (36.3% vs. 18.0%, $p < 0.001$) compared with that of the no-MRI group (mammography with ultrasound) [21]. They reported that the planned mastectomy rates were 22.4% and 14.4% ($p < 0.001$) in the MRI and no-MRI groups, respectively. After MRI, the first-line mastectomy rate was 33.7% vs. 15.6%, and the overall mastectomy rate including second-line mastectomy was 36.3% vs. 18.0% ($p < 0.001$). The reoperation rates in the MRI and no-MRI groups were 8.5% and 11.7%, respectively ($p < 0.001$). Therefore, results of conventional imaging suggested the necessity of mastectomy in 67% of women who finally underwent mastectomy, indicating that MRI was used to confirm a surgeon's decision to perform mastectomy based on conventional imaging. The additional first-line mastectomy rate after MRI was 11.3%, and the MRI group had a reoperation rate of only 3.2% (8.5% and 11.7%, $p < 0.001$) [21]. The results from the MIPA study are in line with those of POMB and IRCIS trials in terms of the reoperation rates, which reduced from 15% to 5% and from 27% to 20%, respectively. The MIPA study found that a reduction in reoperation rate could be attributed to the protective role of first-line mastectomy against reoperation.

In addition to the selection bias that the MRI is used as a confirmation tool, the association between MRI and increased mastectomy rate could be attributed to the guidelines that recommend mastectomy for multicentric cancer [22]. Kuhl et al. [22] suggested that overtreatment caused by MRI can be avoided when the multicentric cancer recommended for mastectomy is diagnosed by mammography alone, which was the criterion for Veronesi's [23] and Fisher's [24] randomized trials of BCS. Additional breast cancers detected on ultrasound or MRI can be treated by additional lumpectomy, not by mastectomy. The German guidelines [25] and the ACOSOG Z11102 trial [26] support that BCS is feasible for 2 or 3 cancer sites.

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Table 2. Summary of preoperative MRI study results on local recurrence and contralateral breast cancer rates

Study	Design	Population	MRI	No-MRI	Local recurrence rate			Contralateral breast cancer rate		
					MRI (%)	No-MRI (%)	*p*-value	MRI (%)	No-MRI (%)	*p*-value
Fischer et al. (2004) [27]	Retrospective	Cancer patients	121	225	1.2	6.8	< 0.001	1.7	4	< 0.001
Solin et al. (2008) [29]	Retrospective	Early-stage invasive or DCIS scheduled for BCT	215	541	3	4	0.320	6	6	0.390
Vapiwala et al. (2017) [30]	Retrospective	Early-stage invasive or DCIS scheduled for BCT	215	541	8	8	0.590	10	8	0.100
Houssami et al. (2014) [31]	Meta-analysis	Cancer patients from 1 RCT and 3 non-RCTs	1,347	1,833	97*	95*	0.870		NR	
Yi et al. (2015) [34]	Retrospective/Propensity score matching	Cancer patients	97†	97†	3.1	4.1	0.180	1.0	21.7	< 0.001
Wang et al. (2016) [35]	Retrospective/Propensity score matching	Stages I and II breast cancer	6,377	32,594		NR		126.4‡ 3.3¶	42.9‡ 4.5¶	< 0.001‡ < 0.002¶
Freitas et al. (2022) [36]	Retrospective/Propensity score matching	Cancer patients	470	235		NR		5.7‡ 4.5¶	2.1‡ 4.3¶	0.047‡ > 0.990¶

Values are presented as number of patients included in the analysis.
BCT = breast-conserving therapy; DCIS = ductal carcinoma in situ; MRI = magnetic resonance imaging; NR = not reported; RCT = randomized controlled trial.
*The 8-year local recurrence-free survival; †Patients in the bilateral MRI period; ‡Synchronous contralateral breast cancer per 1,000 person-years in a study by Wang et al. [35]; ¶Metachronous contralateral breast cancer per 1,000 person-years in a study by Wang et al. [35].

EFFECT ON LONG-TERM CLINICAL OUTCOME

Local recurrence rate and contralateral breast cancer rate

Table 2 summarizes the results of preoperative MRI studies on the local recurrence and contralateral breast cancer rates. In the first retrospective study, Fischer et al. [27] reported that preoperative MRI was associated with lower local recurrence (1.2% [1/86] vs. 6.8% [9/133], $p < 0.001$) and contralateral breast cancer occurrence rates (1.7% [2/121] vs. 4% [9/225], $p < 0.001$) in 346 patients who had undergone breast-conserving therapy in Germany. This earlier study was noteworthy because of the promising results; however, 15% (7/47) of the node-positive patients in the MRI group and 31% (31/103) of node-positive patients in the no-MRI group did not receive chemotherapy. Imbalances in tumor size and treatment in both groups were the main limitations of this study [28].

Contrary to this earlier study, no association was found between preoperative MRI and the risk of breast cancer occurrence in subsequent studies. In 756 patients with early-stage invasive breast cancer or DCIS who underwent breast-conserving therapy, the University of Pennsylvania reported comparable outcomes of ipsilateral breast tumor recurrence and contralateral breast cancer rates between the MRI and no-MRI groups at the 8-year follow-up (3% vs. 4%, $p = 0.32$; 6% vs. 6%, $p = 0.39$) and 15-year follow-up (8% vs. 8%, $p = 0.59$; 10% vs. 8%, $p = 0.10$) [29,30]. Multivariate analysis demonstrated no significant impact of breast MRI on local failure ($p = 0.96$).

In terms of the local recurrence rate, a meta-analysis by Houssami et al. [31] pooled the individual data from 3,169 patients including 4 studies (Hwang et al. [32], Solin et al. [29], Miller et al. [33], and COMICE trial [16]). They found that the 8-year local recurrence-free survival did not significantly differ between the MRI and no-MRI groups (97% vs. 95%, $p = 0.87$), and the use of MRI had no effect on the local recurrence-free survival: the hazard ratio (HR) for MRI (vs. no-MRI) was 0.88 ($p = 0.65$) [31].

As regards the contralateral breast cancer events, contrary to the reports from the University of Pennsylvania, a matched cohort study from Seoul National University Hospital demonstrated

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that preoperative MRI was associated with an 85% reduction in the risk of recurrence (HR, 0.15; 95% CI, 0.07–0.32; $p < 0.001$), mainly with the reduction of contralateral breast recurrence risk (HR, 0.03; 95% CI, 0.04–0.21; $p < 0.001$) [34]. They selected cohorts (371 pairs in the unilateral imaging group and 97 pairs in the bilateral imaging group) from 4,400 consecutive breast cancer patients after matching 11 clinicopathologic variables to reduce the selection of high-risk women who underwent MRI in retrospective studies. Contrary to the fact that only one (5%, 1/22) metachronous contralateral cancer was found in the MRI group, the majority (95%, 21/22) of metachronous contralateral breast cancers were found in the no-MRI group, of which 57% were stage II or III.

In another propensity score matching study using Surveillance, Epidemiology, and End Results (SEER) data, Wang et al. [35] reported that the use of preoperative breast MRI was associated with a higher rate of synchronous (< 6 months after primary cancer diagnosis) contralateral breast cancer detection (126.4 vs. 42.9 per 1,000 person-years; HR, 2.85; $p < 0.001$) and a lower rate of subsequent (i.e., metachronous) contralateral breast cancer detection (3.3 vs. 4.5 per 1,000 person-years; HR, 0.68; $p < 0.002$) in women aged 66 years and older.

In addition, a recent study using propensity score matching to evaluate the effect of MRI screening of the contralateral breast on the overall survival found that the MRI group had a higher rate of contralateral synchronous breast cancer detection (5.7% vs. 2.1%, $p = 0.047$) and better overall survival (HR, 2.51; 95% CI, 1.25–5.06, $p = 0.01$) [36]. However, no differences were found in the contralateral metachronous breast cancer occurrence rate between the MRI and no-MRI groups (4.5% vs. 4.3%, $p > 0.99$) [36]. Notably, the benefit was greater in patients with a larger primary tumor size (> 2 cm) and histological grade III [36]. The improved survival rates through earlier detection of contralateral breast cancers on preoperative MRI were attributed to the prevention of more aggressive, chemotherapy-resistant tumors treated with adjuvant chemotherapy.

FUTURE DIRECTION FOR PREOPERATIVE BREAST MRI

Earlier randomized prospective studies had smaller sample size, obtained a lower image quality, included radiologists with varying levels of imaging experience, and had limitations in translating MRI interpretations into surgical planning. Subsequent retrospective studies have shown conflicting results in terms of surgical outcomes, although a recent MIPA study reported an increased mastectomy rate and reduced reoperation rate in the MRI group, suggesting the protective role of first-line mastectomy against reoperation. The conflicting results on surgical outcomes might be due to the different confounding factors related to the patients, radiologists, surgeons, and treatment guidelines. Women who underwent preoperative MRI tended to be young, had genetic mutations, had more aggressive tumor subtypes, and were more frequently examined at tertiary academic institutions where immediate reconstructive surgeries were performed [37,38]. Therefore, women who undergo preoperative MRI tend to undergo mastectomy followed by immediate reconstructive surgery. The definition of resection margin negativity may have affected the reoperation rates [28]. In addition, to evaluate the effects of additional MRI-detected lesions on the surgical outcomes, the availability of MRI-guided biopsy or second-look ultrasound-guided localization and excision is crucial. Indeed, the reduced contralateral breast recurrence rate, reported in a retrospective study, could have been attributed to the image-guided histology confirmation of all additional lesions detected on MRI in the institution over the last decade [34].

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Similar to the fact that high-quality mammography has enabled the transition from mastectomy to breast-conserving therapy in women with unifocal cancer, the MRI information could serve as a basis for developing a more targeted and individualized surgical treatment for patients [37]. Multiple lumpectomies instead of mastectomy for patients with multicentric disease or lumpectomy without radiation therapy for low-risk unifocal cancer can be offered based on the MRI results [22].

Currently, 2 prospective preoperative MRI trials, the ECOG-ACRIN E4112 trial for DCIS and the Alliance trial A011104/ACRIN 6694 for early-stage invasive breast cancer, are underway [22]. The ECOG-ACRIN E4112 trial (ClinicalTrials.gov identifier: NCT02352883) investigate whether performing a preoperative MRI with a 12-gene assay in women with wide local excision of DCIS will help identify the candidates who can safely omit radiation treatment. In the Alliance trial A011104/ACRIN 6694 (ClinicalTrials.gov identifier: NCT01805076), the reoperation rate and locoregional recurrence rate will be compared between the MRI group (experimental arm) and the mammography with ultrasound group (control arm) to determine the impact of preoperative MRI on surgery and long-term local control.

EVALUATION OF NEOADJUVANT CHEMOTHERAPY (NAC)

NAC reduces the extent of breast cancer surgery and axillary lymph node dissection without increasing the risk of locoregional recurrence [39]. Achieving a pathologic complete response (pCR) is a useful surrogate for improving the survival, although the overall survival outcomes of women who underwent NAC are similar to those of women who have undergone adjuvant chemotherapy [40]. Imaging after NAC is aimed at assessing the response to chemotherapy and determining the extent of residual tumor in order to achieve a negative margin during BCS [41]. MRI is the most accurate modality among the conventional methods, including clinical examination, mammography, and ultrasound [42-46], because contrast-enhanced MRI can distinguish post-chemotherapy fibrosis from viable tumors (**Figure 3**). A previous meta-analysis reported that the median sensitivity of MRI was 92%, while the median specificity was 90% across studies [43]. The accuracy of MRI after NAC varies depending on the tumor characteristics [47-49]. Residual DCIS component without invasive component can be considered as pCR in the breast; however, the residual DCIS component should be included within the tumor extent to achieve negative margins during surgery. Therefore, a refined interpretation strategy is necessary, considering the purpose of MRI, the histopathologic or molecular tumor subtype, and the phase and degree of enhancement on dynamic contrast-enhanced MRI.

Monitoring response to chemotherapy

The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 are used in evaluating the tumor response to chemotherapy in clinical practice as well as in clinical trials [50]. Four response categories are classified based on the longest tumor diameter changes: complete response, partial response, stable disease, and progressive disease. Tumor size measured on contrast-enhanced MRI outperforms clinical examination, mammography, and ultrasound [51]. In the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and molecular Analysis (I-SPY) trial (ClinicalTrials.gov identifier: NCT00043017), functional tumor volume, defined as the volume of enhancing tissue which enhances greater than a predefined threshold on contrast-enhanced MRI images, outperformed the longest diameter in predicting the response to pathologic outcomes and recurrence-free survival [52].

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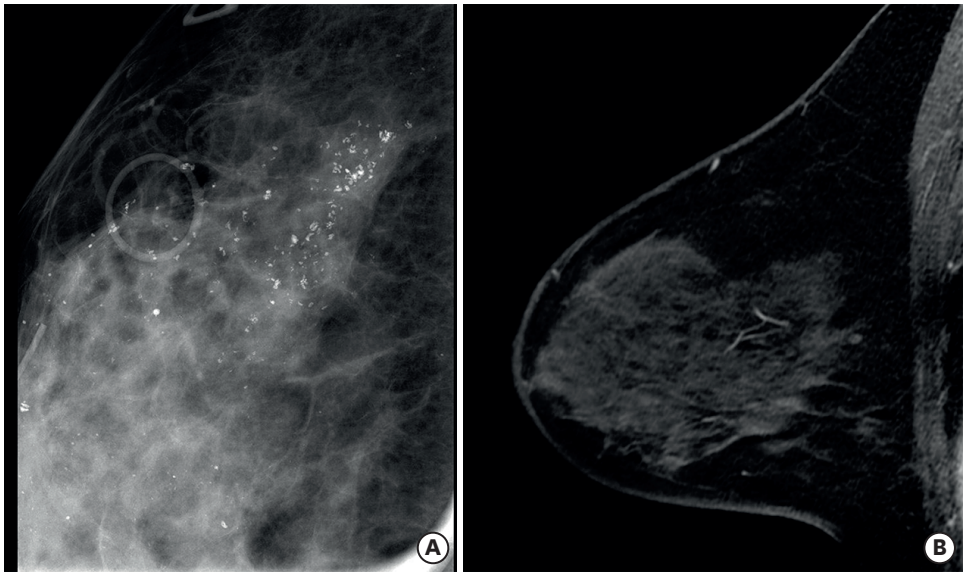

Figure 3. Images after completion of NAC in a 45-year-old woman with human epidermal growth factor receptor type 2-enriched (estrogen receptor-negative, progesterone receptor-negative, and human epidermal growth factor receptor type 2-positive) breast cancer. (A) Post-NAC mammogram shows residual 8-cm extent segmental fine pleomorphic microcalcifications in the right upper outer breast (false-positive). (B) Post-NAC magnetic resonance imaging shows no residual enhancement in the tumor bed (true-negative). Breast-conserving surgery was performed, and no residual cancer was found on histopathological examination.
NAC = neoadjuvant chemotherapy.

With regard to the appropriate time points during chemotherapy cycles, the early prediction of non-responders allows the modification of treatment into a more effective regimen or conversion to surgery to avoid toxicity. However, the prediction of response after the earlier cycles of chemotherapy was less accurate than that during the mid-cycles of treatment or post-treatment [52].

Evaluation of residual tumor extent

In the prediction of residual tumor or pCR, MRI is a more accurate modality for evaluating triple-negative tumors or HER2-positive tumors than for evaluating hormone receptor (HR)-positive/HER2-negative tumors [46,53,54]. In HR-negative/HER2-positive tumors, 100% sensitivity and 100% negative predictive values were achieved by assessing the early enhancement alone. Subtle enhancement in the original tumor area during the late phase could be an important finding in patients with HR-positive/HER2-negative tumors [55]. The size of lobular cancers or HR-positive/HER2-negative tumors tends to be underestimated on MRI, compared with that of ductal cancers or other subtypes [56]. The total tumor size, including invasive tumor and DCIS detected on histopathological examination, showed higher agreement of the tumor size measurements on delayed-phase MRI than on early-phase MRI (intra-class correlation coefficient (ICC), 0.76 vs. 0.56; $p < 0.001$) [56]. However, the invasive tumor size alone showed comparable agreement with the sizes on early- and delayed-phase MRI (ICC, 0.76 vs. 0.74; $p = 0.55$) [56]. Therefore, delayed-phase MRI is more accurate in guiding BCS, while early-phase MRI is more accurate in assessing the response to chemotherapy. Quantification of the degree of enhancement after chemotherapy may help distinguish the viable tumors from chemotherapy-induced changes without cancer cells [57]. A lesion-to-background parenchymal signal enhancement ratio of ≤ 1.6 has been shown to improve the identification of pCR compared with the tumor size alone [57].

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FUTURE DIRECTION FOR NAC

Omission of breast surgery

With the advent of targeted therapies and newest chemotherapy regimens, the rates of pCR have increased, and omission of breast surgery in women with a high possibility of pCR has been investigated [58-61]. At present, the accuracy of MRI is not sufficiently high to predict the pCR in order to consider de-escalation of breast surgery [22]. According to an initial multicenter pooled analysis of 164 patients who achieved complete clinical response (according to the definitions at the unit level) after NAC, the false-negative rate of image-guided biopsy was 71% [59]. Sampling of the tumor bed at least 5 cores and use of stringent MRI criteria for enrollment have shown increased negative predictive values [62,63]. The Minimally Invasive Complete Response Assessment of the Breast After Neoadjuvant Systemic Therapy for Early Breast Cancer (MICRA) trial in the Netherlands found that 14-gauge ultrasound-guided core biopsy with a false-negative rate of 37% (29 of 78) is not accurate to identify the breast pCR [64]. The NRG BR005 study has prospectively assessed the accuracy of trimodality imaging (mammography, ultrasound, and MRI) and image-guided biopsy to determine pCR, and the primary results on 98 patients found that the negative predictive value was only 77.5% [65], which was below the targeted negative predictive value of ≥ 90%. The OPTIMIST trial, a Korean prospective multicenter trial initiated in the second half of 2022, uses stringent MRI criteria for enrollment and 7–10-gauge ultrasound- or mammography-guided vacuum-assisted biopsy for tumor bed sampling.

Radiomics and deep learning

The application of radiomics and deep learning in breast imaging is an expanding research field that can be potentially used as an imaging biomarker in precision medicine [66]. These techniques are applied in various fields of breast imaging, such as for the differentiation between benign and malignant breast lesions, prediction of prognostic factors or molecular subtypes, and prediction of response to NAC [67]. As mentioned earlier, current imaging techniques, including MRI, are limited in their ability to accurately predict the response to NAC. Radiologists use these rapidly developing techniques to overcome the limitations of current imaging techniques.

Radiomics analyzes a large amount of quantitative data extracted from the imaging data [67]. Radiomics assumes that quantitative data that are invisible to the human eye reflect the genetic and molecular characteristics of the tissues [67]. The process of radiomics research includes image acquisition, region of interest (ROI) segmentation, feature extraction, feature selection, and model building [66]. For example, if we aim to develop a radiomics model to predict pCR using MRI, we draw the ROIs for the tumors on MRI images using automated or semi-automated software, extract hundreds or thousands of quantitative features using dedicated software, select several features associated with pCR, and then develop a prediction model using the selected features.

Computer-aided deep learning techniques can investigate the relationship between input data (e.g., pre-NAC MRI data) and the corresponding outcome (e.g., pCR or non-pCR) from the input data themselves [68]. Therefore, deep learning does not require an intermediate feature extraction or engineering process, which is its most notable difference from radiomics techniques [68].

To date, a few retrospective studies have evaluated the performance of radiomics [69,70] and deep learning [71,72] in predicting pCR. In these studies, the accuracy was variable, with AUCs ranging from 0.69 to 0.96 [69-72]. The challenges of radiomics and deep learning techniques

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are the lack of reproducibility and requirement of large input data, respectively. Hence, more multicenter validation studies are needed to examine its reliability and clinical applicability.

CONCLUSION

Although MRI is the most sensitive modality for breast cancer, preoperative breast MRI had no substantial benefits in terms of the chances of reoperation and local recurrence. Preoperative MRI has been associated with a higher mastectomy rate as per a recent MIPA study and previous meta-analyses. Regarding the occurrence of contralateral breast cancer, detecting synchronous contralateral breast cancer on preoperative MRI is associated with less occurrence of metachronous contralateral breast cancer and improved survival outcomes. Translating the high accuracy of MRI to better surgical outcomes or survival outcomes requires the performance of image-guided biopsy for all suspicious findings using multidisciplinary approaches.

With regard to the NAC setting, MRI is the most accurate modality for monitoring the response to chemotherapy and evaluating the residual tumor extent. Based on the MRI findings, prospective randomized trials are underway to identify women who can safely omit radiotherapy and those who have a high possibility of achieving pCR in order to omit an unnecessary definitive surgery.

Breast MRI can be a powerful tool for personalized surgical management in patients with newly diagnosed breast cancer. Deep learning or radiomics is expected to improve the accuracy of MRI.

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