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Research article

Breast magnetic resonance imaging for estimation of the tumour extent in patients with pure ductal carcinoma in situ: Comparison between full diagnostic and abbreviated protocols

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ABSTRACT

Purpose: To evaluate the rate of concordance between pathology and preoperative breast MRI performed with an abbreviated protocol (AP) or a full diagnostic protocol (FDP) for estimation of the tumour extent in patients with pure ductal carcinoma in situ (DCIS).

Methods: This retrospective study included 164 patients with pathologically proven DCIS who underwent preoperative breast MRI. Two radiologists independently evaluated the tumour extent on MRI with (FDP) and without the delayed phase (AP) and compared the readings with the pathological tumour extent. The background parenchymal enhancement (BPE) and morphology were also evaluated. Furthermore, the influence of the degree of BPE, presence or absence of B2 and B3 lesions, and pathological DCIS grade on the accuracy of MRI findings was assessed. Concordance between MRI and pathology was evaluated using correlation analysis.

Results: Spearman's rank correlation coefficients for the concordance between MRI and pathology were 0.63 (reader 1) and 0.69 (reader 2) with AP and 0.65 and 0.73 (readers 1 and 2, respectively) with FDP. For both readers, the difference in the measured value between FDP and pathology was significantly smaller than that between AP and pathology ($p < 0.001$). The inter-reader variation in the measured tumour extent was larger with FDP than with AP. The presence of B3 lesions, low-grade DCIS, and moderate/marked BPE lowered the rate of concordance between MRI and pathology.

Conclusions: Our findings suggest that preoperative MRI with FDP is more accurate than that with AP alone for estimation of the tumour extent in patients with pure DCIS.

1. Introduction

The value of treatment for ductal carcinoma in situ (DCIS) is a controversial topic, because DCIS is a disease that may never progress to invasive breast cancer in a certain percentage of patients [1]. However, a retrospective population-based study reported a negative association between the screen detection of DCIS and subsequent incidence of invasive interval breast cancer, and the authors suggested that the treatment of DCIS after detection is worthwhile for the prevention of future invasive disease [2]. Breast MRI outperforms mammography in terms of the detection and size estimation of DCIS [3–5]. In fact, the detection rate for DCIS is expected to increase with an increase in the use of MRI screening for breast cancer, particularly in high-risk groups.

Theoretically, there is limited potential for recurrence if surgical excision with negative tumour margins is performed in patients with a pathological diagnosis of pure DCIS. Therefore, it is essential to predict the DCIS extent in patients who desire breast-conserving surgery. Preoperative evaluation of the tumour extent, however, is faced with the challenge of discordance between imaging and pathology findings. With regard to the tumour size, the correlation between breast MRI and pathology is better than that between mammography (MMG) or ultrasonography (US) and pathology [6,7]. A prospective study reported that the sensitivities of MRI, MMG, and US for the accurate detection of DCIS components were 89%, 55%, and 47%, respectively [8]. In another study, the re-operation rates for patients with stage 0, I or II breast cancer who received conservative treatment were lower when

Abbreviations: DCIS, ductal carcinoma in situ; AP, abbreviated protocol; FDP, full diagnostic protocol; BPE, background parenchymal enhancement; MMG, mammography; US, ultrasonography

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preoperative breast MRI was performed [9]. Thus, preoperative breast MRI can influence the surgical plan and decrease the rates of tumour-positive resection margins and re-operation [7,9–11]. A recent multicentre, prospective randomized controlled trial evaluating the role of preoperative MRI assessment in cases of limited DCIS did not find sufficient surgical improvement with the use of preoperative MRI for DCIS staging [12]. The authors mentioned that the role of preoperative MRI in cases of DCIS may need to be re-evaluated with the improvement and a better understanding of MRI techniques and parameters [12].

According to previous reports about breast cancer with DCIS components, the correlation between the MRI-measured tumour extent and pathologically measured tumour extent varies between 42% and 89% [11,13–16]. With regard to DCIS, overestimation of the tumour extent on MRI is a common occurrence, probably because of false-positive enhancement caused by the continuum of benign proliferative changes [6,17,18].

Abbreviated breast MRI has been proposed as a supplemental screening method for breast cancer [19]. Breast MRI performed with an abbreviated protocol (AP) can shorten both acquisition times and image interpretation times, while maintaining diagnostic accuracy comparable to that obtained with conventional MRI protocols [19]. Breast MRI is the most sensitive technique for DCIS; it can detect up to 48% of high-grade DCIS cases not detected by mammography [3]. In MRI assessment of DCIS, the most commonly reported morphology was a non-mass lesion (60–80 % of patients); this indicates that morphological signs are more important than kinetics for diagnosis of DCIS [20,21].

We hypothesized that AP may be also sufficient for preoperative assessment of the tumour extent in patients with DCIS, as the MRI morphology of non-mass lesions could be indistinct due to strengthening of background parenchymal enhancement (BPE) in the delayed phase. Few studies have focused on the dynamic phase of contrast-enhanced MRI for preoperative evaluation of the tumour extent in patients with pure DCIS; moreover, major guidelines do not refer to the optimal method for tumour extent assessments [22,23]. Therefore, the primary aim of the present study was to determine the rate of concordance between pathology and preoperative breast MRI performed with an AP or a full diagnostic protocol (FDP) for estimation of the tumour extent in patients with pure DCIS. The secondary aim was to evaluate factors that influenced this concordance rate.

2. Materials and methods

This study was approved by our institutional review board, which waived the need for informed consent because of the retrospective nature of the study.

2.1. Patients

We retrospectively reviewed the pathological records of 258 patients who were pathologically diagnosed with pure DCIS between May 2009 and May 2018. From these, 40 patients who did not undergo breast MRI within 6 months before surgery and 40 with a previous history of breast surgery and/or neoadjuvant chemotherapy were excluded. In the final pathological analysis, four of the remaining 178 women showed lateral margin positivity without re-operation, while one showed lateral margin positivity after re-operation. These five patients were excluded because accurate estimation of the pathological tumour extent would not be possible. Subsequently, another nine women were excluded because DCIS lesions were not detected on breast MRI. Finally, 164 pure DCIS lesions in 164 patients were included in the study. The menstrual cycle phase was not considered because of the retrospective design; therefore, we did not analyse this parameter during MRI interpretation.

2.2. Imaging

All breast MRI studies were performed using a 1.5 T device (Symphony®, Siemens Medical Solutions) with a maximum gradient field strength of 30 m T/m and a 4-ch CP breast array coil. Both breasts were examined with the patient in a prone position. The standard imaging protocol included coronal T2-weighted spectral-attenuated inversion recovery imaging (T2-FS) with the following parameters: repetition time (TR)/echo time (TE), 4000 ms/73 ms; flip angle, 150°; field of view, 35 × 35 cm; matrix size, 806 × 896; slice thickness, 4 mm; gap, 0; and number of excitations (NEX), 1. Coronal diffusion-weighted images (DWI) were also obtained at b-values of 0, 1000, and 1500s/mm^2, with the following parameters: TR/TE, 5600 ms/87 ms; field of view, 5 × 35 cm; matrix size, 234 × 320; slice thickness, 3.5 mm; slice gap, 0; and NEX, 5. Apparent diffusion coefficient (ADC) maps were automatically generated on the operating console by using the least squares method with all three images and b-values of 0, 1000, and 1500s/mm^2. Dynamic contrast-enhanced images were acquired using a three-dimensional fat-suppressed volumetric interpolated breath-hold examination sequence with the following parameters: TR/TE, 5 ms/2.41 ms; flip angle, 15°; field of view, 340 mm; matrix, 768 × 768; receiver bandwidth, 340 kHz/pixel; mean partition thickness, 0.9 mm; time of acquisition, 60 s; and NEX, 1. The section thickness varied depending on the size of the breast. Sections were acquired without a gap. After pre-contrast fat-supressed T1-weighted images were obtained, three contrast-enhanced images were taken at 60, 120, and 240 s after the start of intravenous administration of gadopentetate dimeglumine (0.1 mmol/kg; Gadovist, Bayer Health Care) at a rate of 1 mL/s; this was followed by a 15-mL saline flush with an automatic injector.

2.3. Interpretation of MRI findings

Two radiologists (T.I. and M.S.; 17 and 4 years of experience in breast MRI interpretation; readers 1 and 2, respectively) independently evaluated all breast MRI in retrospect. These radiologists were only aware about the diagnosis of pure DCIS; they were otherwise blinded to

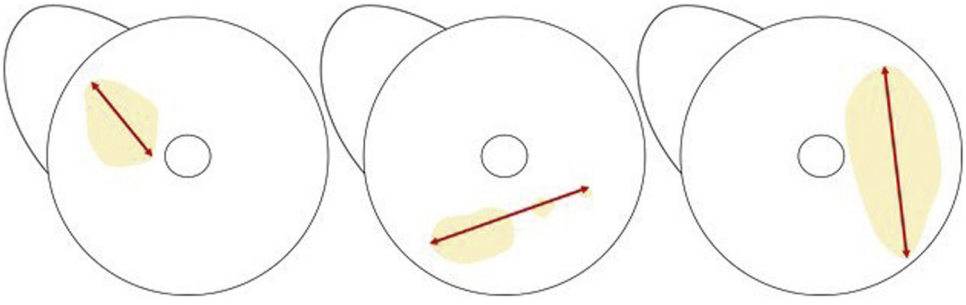

Fig. 1. Assessment of the tumour extent using MRI in patients with DCIS. The tumour extent is measured as the maximum diameter in the transverse or craniocaudal direction on coronal images. DCIS: ductal carcinoma in situ.

all other clinical and pathological information. The tumour extent was defined as the maximum extent of the lesion on a coronal image without considering the spread in the sagittal direction (Fig. 1). The main reasons for use of this measurement technique were as follows. First, the maximum tumour extent on a coronal image is considered to affect the decision to perform breast-conserving surgery. Second, the same measurement method was used for pathological assessment of the tumour extent in this study. The radiologists initially measured the tumour extent using AP, which involved pre-contrast and 60-s contrast-enhanced T1-weighted images with maximum intensity projection (MIP). Subsequently, they measured the tumour extent again using FDP; this involved assessments on T2-FS, DWI, ADC maps, and 120-s and 240-s contrast-enhanced T1-weighted images, in addition to the images used in AP. Then, the following parameters were also assessed: relative amount of fibroglandular tissue (FGT), BPE, and morphology. The relative amount of FGT, degree of BPE, and tumour morphology (hereafter defined as "morphology") were assessed on the basis of the Breast Imaging Reporting and Data System (BI-RADS) criteria [22]. Specifically, the relative amount of FGT was classified as fat, scattered, heterogenous, and extreme, while the degree of BPE was classified as minimal, mild, moderate, and marked. Based on morphology, the lesions were categorised as non-mass and mass lesions. When both non-mass and mass lesions were observed, they were categorized as non-mass lesions.

2.4. Histopathological analysis

Data regarding the pathological tumour extent, DCIS grade, presence of benign lesions (B2) and lesions with uncertain malignant potential (B3) [24], and margin status of the tumour were obtained from pathology reports. All breast specimens were sectioned at 5-mm intervals at an angle perpendicular to the connecting line between the nipple and the tumour. The pathological tumour extent was determined as the maximum extent of the lesion in the horizontal direction, without considering the extent of the depth from the skin to the fascia, corresponding to the tumour extent in the sagittal direction on MRI. When the location of the tumour was difficult to identify in the pathological specimen, it was similarly sectioned along the long axis of the area presumed to have lesions. Then, the long diameter of the plotted lesion was recorded as the maximum extent of the lesion.

B2 lesions included benign breast lesions such as fibroadenoma, fibrocystic change and cysts, some papillary lesions, and inflammatory conditions, while B3 lesions included atypical epithelial proliferations, such as atypical ductal hyperplasia and atypical lobular hyperplasia [25].

2.5. Statistical analysis

All statistical analyses were performed using SPSS (ver. 25; IBM). Continuous variables were analysed using the Mann–Whitney *U* test. Spearman's rank correlation coefficients were calculated to assess the rate of concordance between MRI and pathology and factors considered to influence the concordance rate. Scatter diagrams were also generated to determine the influence of these factors on the concordance rate. Inter-reader differences in tumour extent measurements were analysed using Bland–Altman plots. A p-value of < 0.05 was considered to be statistically significant.

3. Results

In total, 71 (43%) patients underwent total mastectomy and 93 (57%) underwent partial mastectomy. The mean age of patients was 54 (range, 19–81) years. The mean tumour size measured by pathology was 3.8 (range, 0.1–11.0) cm. The patient and tumour characteristics are shown in Table 1. In total, pathologically proven DCIS with B3 lesions and DCIS with B2 + B3 lesions were observed in 38 (23%) and 63 (38%) patients, respectively. The inter-reader agreement for the degree of BPE was substantial and that for the morphology was almost perfect (Table 2). Spearman's rank correlation coefficients for the concordance between MRI and pathology findings were as follows: 0.63 and 0.69 for readers 1 and 2, respectively, with AP, and 0.65 and 0.73 for readers 1 and 2, respectively, with FDP (all $p < 0.05$). For both readers, differences in the measured value between FDP and pathology (reader 1: -0.45 ± 1.95 cm, reader 2: -0.65 ± 2.51 cm) were significantly smaller than those between AP and pathology (reader 1: -1.00 ± 2.00 cm, reader 2: -0.83 ± 1.87 cm; $p < 0.001$). When correct estimation was defined by a difference of < 10 mm between the MRI-measured tumour extent and pathologically measured tumour extent, underestimation was more frequent than overestimation (Table 3). There was no significant difference in the correlation coefficient between AP and FDP for both readers ($p = 0.76$ and $p = 0.47$ for readers 1 and 2, respectively; Table 3). Bland–Altman plots showed that the variation in tumour extent measurements between readers was slightly larger when FDP was used than when AP was used (difference between readers: -1.68 ± 19.36 cm with AP and 2.19 ± 21.36 cm with FDP; Fig. 2).

The concordance rate between MRI and pathology was lower for patients with mass lesions (correlation coefficients with AP: 0.44 and 0.61 for readers 1 and 2, respectively; FDP: 0.50 and 0.62 for readers 1 and 2, respectively, all $p < 0.05$) than for those with non-mass lesions (AP: 0.59 and 0.67, respectively; FDP: 0.65 and 0.69, respectively, all $p < 0.05$). The concordance rate between MRI and pathology was lower for patients with moderate/marked BPE (correlation coefficients with AP: 0.48 and 0.58 for readers 1 and 2, respectively; FDP: 0.49 and 0.63 for readers 1 and 2, respectively, all $p < 0.05$) than for those with minimal/mild BPE (correlation coefficients with AP: 0.68 and 0.73, respectively; FDP: 0.70 and 0.75, respectively, all $p < 0.05$; Fig. 3). Furthermore, the concordance rate was lower for patients with B3

Table 1
Patient and tumour characteristics in a cohort of patients with DCIS.

	n,(%)
Age	
< 50	66(40)
50≦	98(60)
Tumour size (mm)	
< 10	18(11)
10≦, < 50	101(62)
50≦	45(27)
Amount of fibroglandular tissue	
fat	4(2)
scattered	57(35)
heterogeneous	94(57)
extreme	9(5)
DCIS grade	
low	106(65)
high/intermediate	58(35)
B3 lesion	
positive	38(23)
negative	126(77)

DCIS: ductal carcinoma in situ.

Table 2
MRI findings for BPE and morphology in patients with DCIS.

	BPE		Morphology	
	Minimal/Mild	Moderate/Marked	Mass lesion	Non-mass lesion
Reader1	130	34	36	128
Reader2	121	43	30	134
		κ = 0.779		κ = 0.848

BPE: background parenchymal enhancement, DCIS: ductal carcinoma in situ.

Table 3
Correct estimation, overestimation, and underestimation rates for assessment of the tumour extent using MRI in patients with DCIS.

		Correlation Coefficient*	Tumour extent differences between MRI and pathology (cm)**	Underestimation, n(%)	Correct estimation n (%)	Overestimation, n(%)
Reader1	AP	0.63	−1.00 ± 2.00	53(32)	101(62)	10(6)
	FDP	0.65	−0.45 ± 1.95	42(26)	98(60)	24(15)
Reader2	AP	0.69	−0.83 ± 1.87	50(30)	103(63)	11(7)
	FDP	0.73	−0.65 ± 2.51	45(27)	104(63)	15(9)

Correct estimation is defined by a difference of < 10 mm between the MRI-measured tumour extent and pathologically measured tumour extent.
AP: abbreviated protocol, FDP: full diagnostic protocol, DCIS: ductal carcinoma in situ.
* No significant difference in the correlation coefficient between AP and FDP for both readers (Reader 1: p = 0.76, Reader 2: p = 0.47).
** Means ± standard deviations, calculated as follows: tumour size by MRI − tumour size by pathology (Reader 1: p < 0.001; Reader 2: p < 0.001; Wilcoxon test).

lesions (correlation coefficients with AP: 0.48 and 0.62 for readers 1 and 2, respectively; FDP: 0.52 and 0.66 for readers 1 and 2, respectively, all $p < 0.05$) than for those without B3 lesions (AP: 0.68 and 0.74, respectively; FDP: 0.73 and 0.78, respectively, all $p < 0.05$; Fig. 4). When patients with B2 + B3 lesions were considered, the correlation coefficients were 0.62 and 0.63, respectively, with AP and 0.68 and 0.60, respectively, with FDP (all $p < 0.05$). With regard to the DCIS grade, the concordance rates were lower for patients with low-grade DCIS (correlation coefficients with AP: 0.60 and 0.66, respectively; FDP: 0.66 and 0.71, respectively, all $p < 0.05$) than for those with intermediate/high-grade DCIS (correlation coefficients with AP: 0.74 and 0.76, respectively; FDP: 0.75 and 0.76, respectively, all $p < 0.05$; Fig. 5). There was no difference in the pathological tumour extent between low-grade DCIS and intermediate/high-grade DCIS (median tumour size: 3.5 cm for low-grade DCIS and 3.6 cm for intermediate/high-grade DCIS).

4. Discussion

This retrospective study assessed the rate of concordance between preoperative MRI using AP and FDP and pathology for estimation of the tumour extent in patients with pure DCIS.

Contrary to our hypothesis, the rate of concordance between MRI and pathology was higher with FDP than with AP. Variation in measurements between the two readers, however, tended to be slightly higher when FDP was used than when AP was used. We speculate that the MRI morphology of non-mass lesions could be indistinct due to strengthening of BPE, such that interpretation of the delayed phase could be affected by the degree of BPE. However, our results suggest that preoperative MRI assessment with FDP could aid in reduction of the rate of positive tumour margins in patients with pure DCIS (Fig. 6). In particular, among patients with low-grade DCIS, the concordance rate was higher when FDP was used than AP was used.

Baltzer et al. evaluated non-mass lesions and reported difficulty in distinguishing benign and malignant lesions on the basis of kinetic information provided by breast MRI [26]. Similarly, specific kinetic parameters that are predominant in DCIS have not been identified [12]. Given those reports, high-visibility morphological information is regarded as being more important than kinetic information for the purposes of using preoperative breast MRI with FDP to determine tumour extents in patients with DCIS, which frequently presents as non-mass lesions. Our study showed that the concordance rate between MRI and pathology was lower for patients with mass lesions than for patients with non-mass lesions. This may be attributed to the presence of only pathologically proven DCIS around mass lesions on MRI, which could not be identified as an entity other than a mass lesion on MRI by both readers. Thus, the tumour extent was underestimated on MRI in these cases. The prevalence of non-visible DCIS around mass lesions on MRI were 32% for reader 1 and 29% for reader 2.

Compared to previous studies which assessed invasive cancer with DCIS components, the present study showed a relatively higher rate of underestimation and lower rate of concordance between MRI and pathology [11,14–16]. This discrepancy may have occurred because DCIS exhibits no enhancement or less vascularity on MRI due to the lack of actively recruiting periductal blood vessels and invasive growth [27,28]. Our results also showed that low-grade DCIS was associated with greater discordance between MRI and pathology than intermediate/high-grade DCIS, which was associated with a strong positive correlation between pathology and MRI. Some authors have reported that the detectability of high-grade DCIS is higher than that of low-grade DCIS because the former shows greater enhancement than the latter on contrast-enhanced MRI [3,29]. Moreover, high-grade DCIS generally presents as a larger lesion on MRI than does low-grade DCIS [30]. In addition, the detectability of high-grade DCIS on MRI could be higher because the lesions exhibit greater vessel density [3]. In the present study, the number of low-grade DCIS components was greater

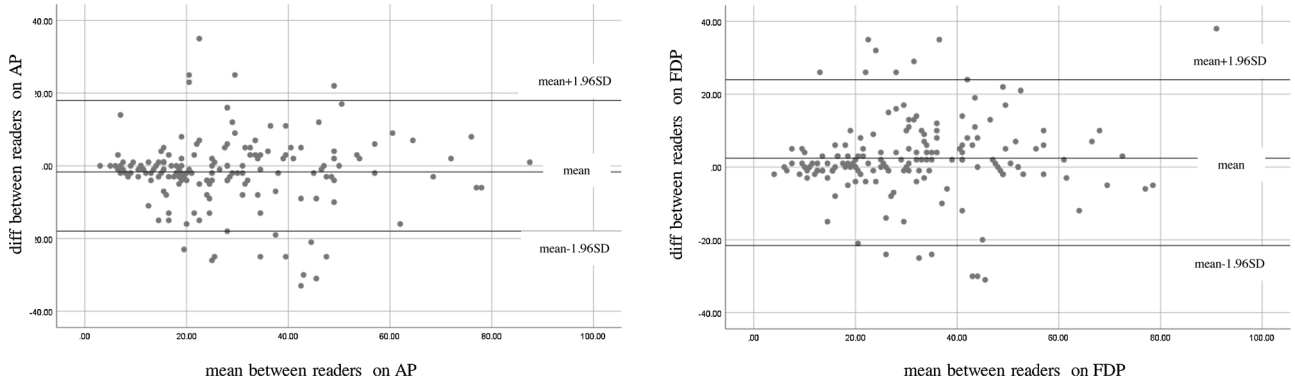

Fig. 2. Bland–Altman plots showing differences between two readers with regard to tumour extent measurements recorded using full diagnostic and abbreviated MRI protocols for patients with DCIS. Abbreviated protocol: Bias = −1.68, SD = 9.88, limits of agreement = −21.04, 17.68. Full diagnostic protocol: Bias = 2.19, SD = 10.9, limits of agreement = −19.17, 23.55. SD: standard deviation, DCIS: ductal carcinoma in situ.

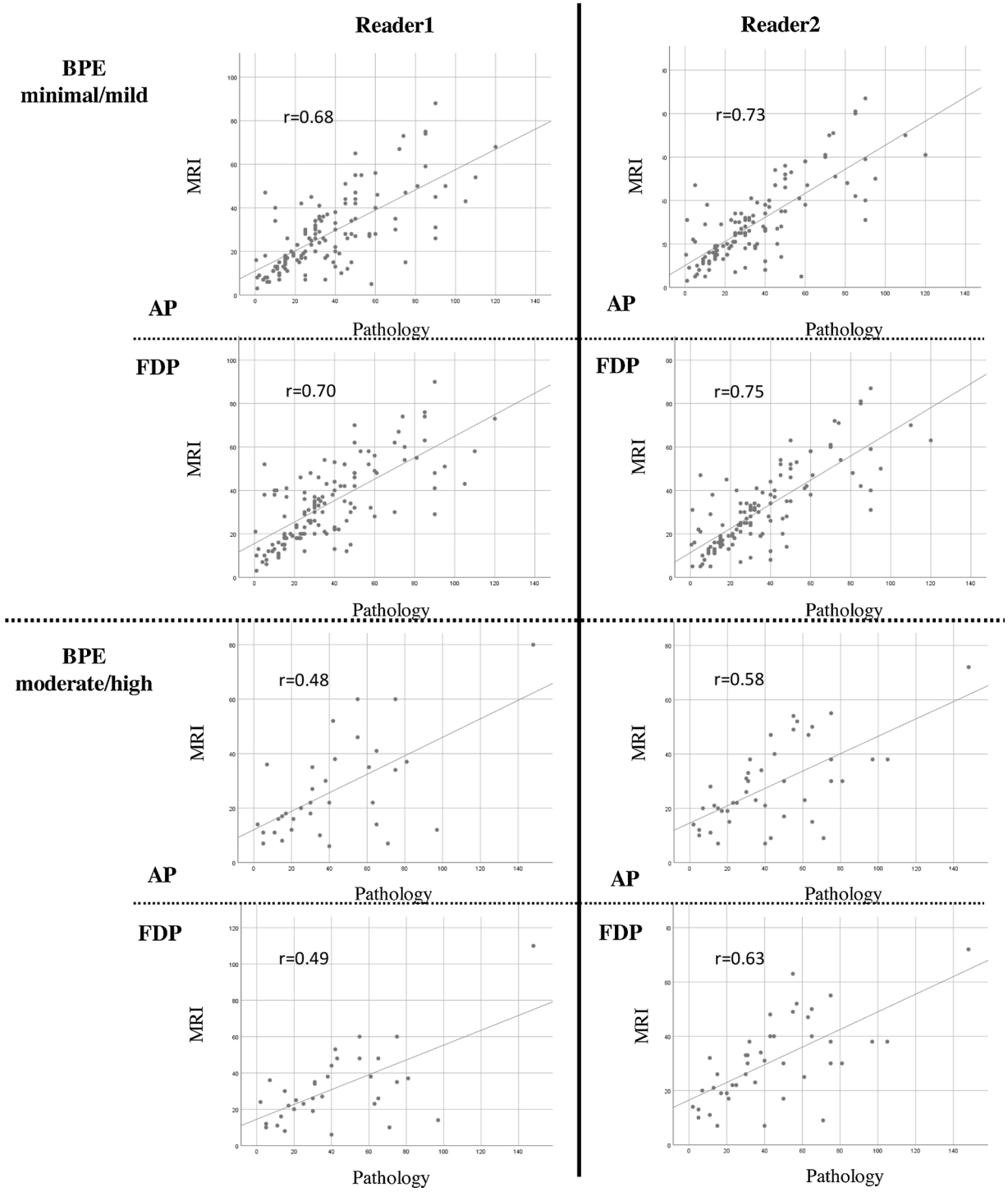

Fig. 3. Scatter diagrams with correlation coefficients (r) showing the concordance between MRI (FDP and AP) and pathology for estimation of the tumour extent in patients with DCIS showing minimal/mild BPE or moderate/marked BPE. AP: abbreviated protocol, FDP: full diagnostic protocol, BPE: background parenchymal enhancement, DCIS: ductal carcinoma in situ.

than that of intermediate/high-grade DCIS components. Consequently, the underestimation rate was relatively higher than the overestimation rate.

In the present study, moderate/marked BPE and B3 lesions weakened the concordance between MRI and pathology for both readers. Moderate/marked BPE is reported as a reason for discordance between MRI and pathology [13]. Our results suggest that appropriate timing for contrast-enhanced breast MRI examination, with consideration of the menstruation cycle, is necessary to minimise BPE and accurately estimate the tumour extent. Kuhl et al. reported that the most major reason for false-positive MRI diagnoses is atypical proliferation, because such tissue changes show contrast enhancement [31]. Our results showed that B3 lesions, which were equivalent to atypical proliferation, could be associated with not only false-positive diagnoses but also overestimation of the tumour extent. Our results also revealed that B2 lesions have little effect on the estimation rate.

The role of preoperative MRI remains controversial, particularly in cases of DCIS. The first and latest prospective study assessing this

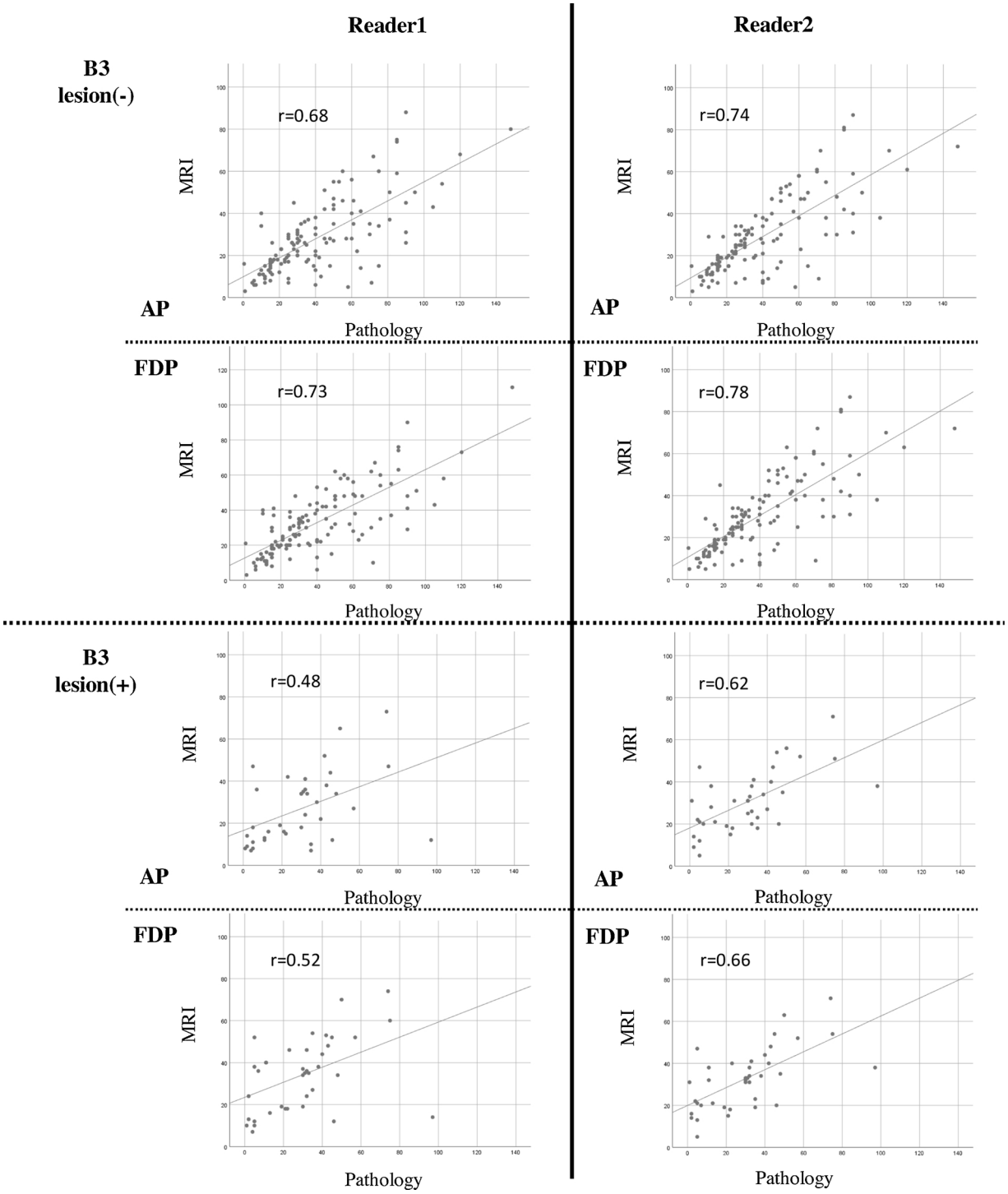

Fig. 4. Scatter diagrams with correlation coefficients (r) showing the concordance between MRI (FDP and AP) and pathology for estimation of the tumour extent according to the presence [B3 lesion(+)] or absence [B3 lesion(−)] of B3 lesions in patients with DCIS. AP: abbreviated protocol; FDP: full diagnostic protocol, DCIS: ductal carcinoma in situ.

problem showed a re-intervention rate of 20% in the MRI arm and 27% in the control arm. The absolute difference of 7% corresponded to a relative reduction of 26%, which was not clinically relevant [12]. We are sceptical concerning whether MR images could facilitate estimation of lesion extent for surgeons during surgery. Our research results suggest that preoperative assessment of the extent of DCIS on coronal images acquired in the delayed phase (based on FDP) can assist in accurate diagnosis of the extent of DCIS.

This study has several limitations. First, it used a retrospective design and therefore exhibited a possibility of selection bias. Additional prospective studies are necessary to confirm our results. Second, we did not consider that the pathological breast tissue specimens could shrink after histological fixation in formalin [32]. Any amount of shrinkage may have affected the concordance rates. Third, the delayed phase of FDP was only implemented for 4 min after injection in the present study, because later scans were considered to provide little diagnostic information [33]. However, there is a possibility that further studies beyond delayed phases contribute to better diagnosis of the tumour

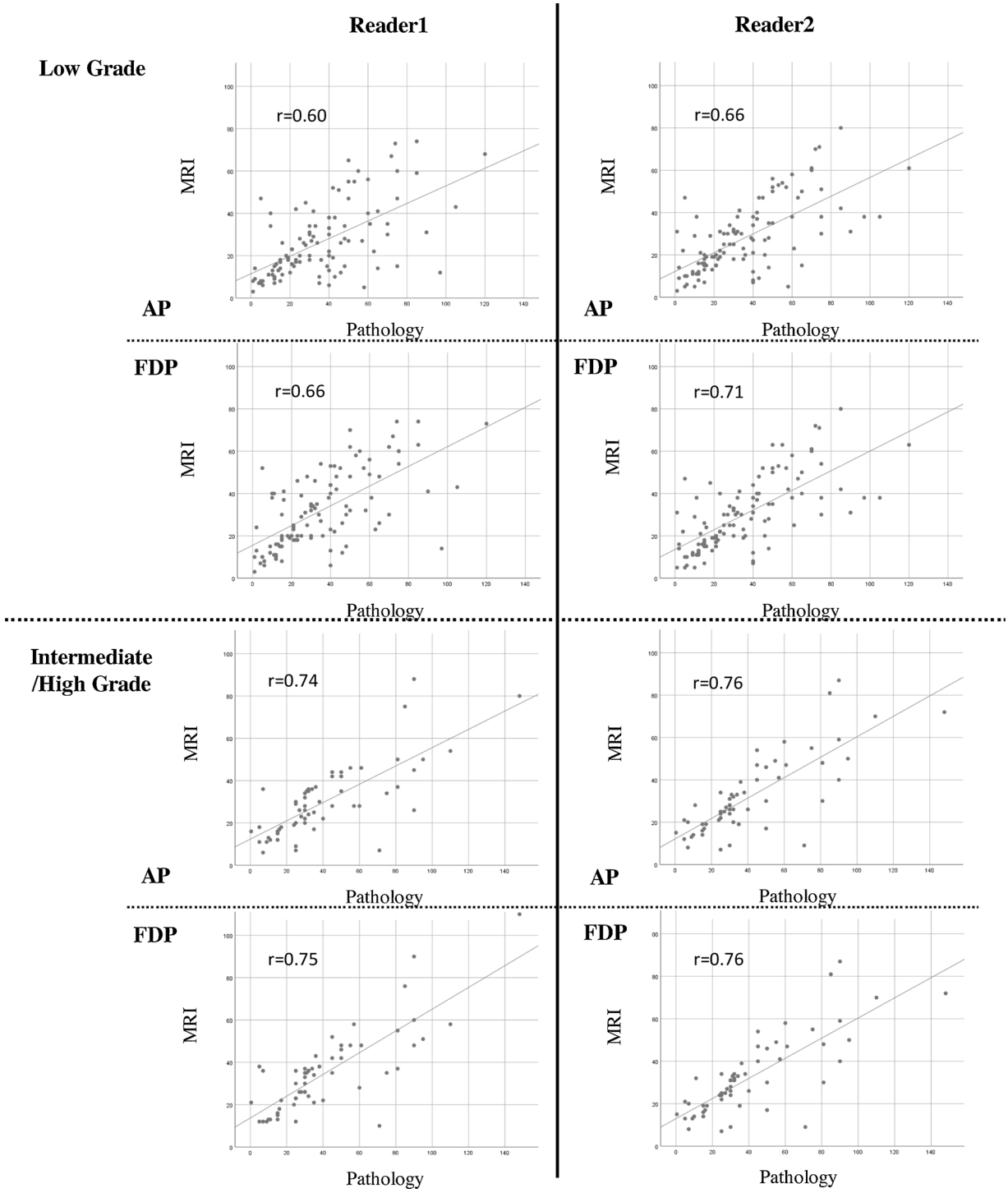

Fig. 5. Scatter diagrams with correlation coefficients (r) showing the concordance between MRI (FDP and AP) and pathology for estimation of the tumour extent according to the grade of DCIS (low grade and intermediate/high grade). AP: abbreviated protocol; FDP: full diagnostic protocol, DCIS: ductal carcinoma in situ.

extent in patients with pure DCIS.

In conclusion, our findings suggest that preoperative breast MRI with FDP is more accurate than that with AP alone for estimation of the tumour extent in patients with pure DCIS. Moreover, moderate/marked BPE, B3 lesions, and low-grade DCIS may increase the discordance between the MRI-measured tumour extent and pathologically measured tumour extent.

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Declarations of Competing Interest

None.

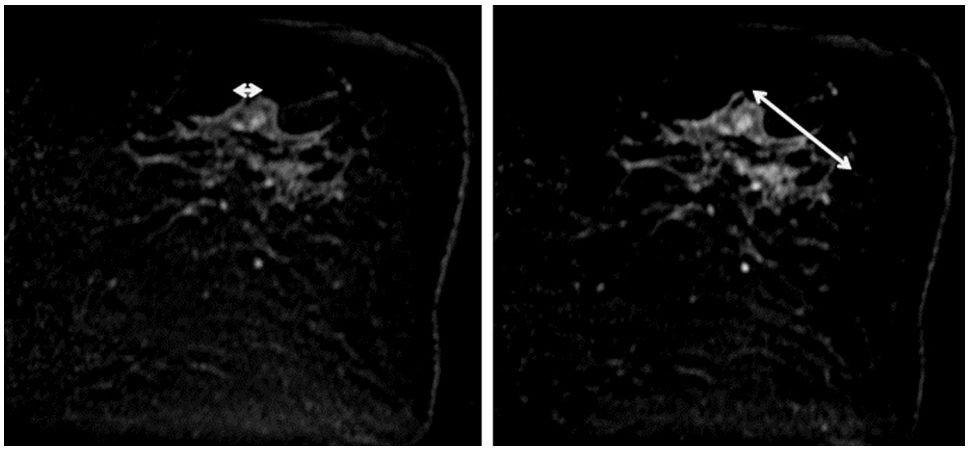

Fig. 6. MRI findings for a representative case involving a 61-year-old patient with low-grade DCIS without B3 lesions. The tumour extent as measured by pathology was 4.3 cm. Amount of FGT is scattered and BPE is minimal/mild. The tumour extent (double-headed arrow) on 60-s contrast-enhanced T1-weighted images is 1.1 cm (A), while that on 240-s contrast-enhanced T1-weighted images is 4.3 cm (B). Reader assessments: Reader 1, 1.0 cm with AP and 4.2 cm with FDP; Reader 2, 0.9 cm with AP and 4.0 cm with FDP. DCIS: ductal carcinoma in situ, BPE: background parenchymal enhancement, FGT: fibroglandular tissue.

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