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# Association among T2 signal intensity, necrosis, ADC and Ki-67 in estrogen receptor-positive and HER2-negative invasive ductal carcinoma

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## Abstract

**Purpose:** To determine whether T2 signal intensity, necrosis, and ADC values are associated with Ki-67 in patients with Estrogen Receptor (ER)-positive and Human epidermal growth factor receptor type 2 (HER2)-negative invasive ductal carcinoma (IDC).

**Materials and methods:** Between March 2012 and February 2013, one hundred eighty seven women with ER-positive and HER2-negative IDC who underwent breast MRI and subsequent surgery were included. Intratumoral signal intensity was evaluated based on a combination of T2-weighted (low or equal, high, or very high) and contrast-enhanced MR images (enhancement or not). Necrosis was defined as very high T2 and no enhancement. Using the analysis of variance and pairwise *t*-test, a model based on intratumoral signal intensity was developed to assess Ki-67 of the surgical specimen. Inter-observer agreement for the developed model was analyzed. Conventional mean and minimum apparent diffusion coefficient (ADC) measurements were performed and correlated with Ki-67.

**Results:** As the grade of the developed model increased (Grade I: low or equal T2, Grade II: high T2, or necrosis < 50%, Grade III: necrosis ≥ 50%), mean Ki-67 significantly increased (Grade I to III: 12.5%, 17.6%, 45.0%, respectively; $P < 0.001$). Good inter-observer agreement was found for the model ($\kappa = 0.846$, $P < 0.001$). ADC did not show significant correlations with Ki-67 (Pearson's correlation coefficient, 0.140 [$P = 0.057$] for mean ADC; −0.079 [$P = 0.284$] for minimum ADC).

**Conclusion:** Intratumoral signal intensity but not ADC was associated with Ki-67 in patients with ER-positive and HER2-negative IDC.

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**Keywords**

Magnetic resonance imaging; T2 signal intensity; Necrosis; Apparent diffusion coefficient; Ki-67

## 1. Introduction

The apparent diffusion coefficient (ADC) values of diffusion-weighted imaging (DWI) generally have negative correlations with cellularity in various organs, including the breast [1]. Many DWI studies have shown that ADC values of breast cancers were lower due to higher cellularity compared with normal or benign breast lesions [2,3]. Breast cancer with high cellularity is generally considered more likely to be a highly proliferative tumor [4].

Assessment of Ki-67 has been proposed as a measure for quantifying cell proliferation in breast cancer [5]. If Ki-67, reflecting proliferation, shows consistently positive correlation with cellularity, it is hypothesized that Ki-67 will have a negative correlation with ADC based on the aforementioned negative correlation between ADC and cellularity [1]. However, debates remain regarding the relationship between the two parameters [4,6–9]. Some studies showed negative correlation between ADC and Ki-67 [4,6], while others showed no correlation between them [7–9]. The reports showing no correlation included various histologic types and molecular subtypes in their study population [7–9]. A study by Mori et al. pointed out that such heterogeneous subjects might be the reason for there being no correlation, and their results showed a negative correlation in estrogen receptor (ER)-positive invasive ductal carcinoma (IDC) not otherwise specified [4]. Another factor in the debates on correlation between the two parameters is that cellularity may decrease due to necrosis in a highly proliferative tumor that rapidly outgrows its vascular supply, leading to areas of prolonged hypoxia and subsequent necrosis [10]. In this situation that necrosis occurs, Ki-67 would not have a negative correlation with ADC because Ki-67 does not positively correlate with cellularity due to necrosis. It is known that necrosis can be demonstrated on magnetic resonance imaging (MRI) with the combined information of T2-weighted (T2W) and contrast-enhanced images [11,12]. In this study, intratumoral necrosis was defined as an area showing very high T2 signal intensity and no enhancement on contrast-enhanced MR images according to the previous publications [11,12]. Although Mori et al. [4] reported a significantly negative correlation between ADC and Ki-67, the study did not consider the effect of necrosis. To re-evaluate the relationship between the two parameters under the consideration of necrosis and to compare the results with those by Mori et al., ER-positive and human epidermal growth factor receptor type 2 (HER2)-negative IDC not otherwise specified was selected for the study population.

As well as a proliferative marker, Ki-67 provides potential prognostic and predictive value in breast cancer patients [13,14]. High Ki-67 is associated with worse disease-free survival and better responsiveness to neoadjuvant chemotherapy in ER-positive and HER2-negative breast cancers [13,14]. The pathologic assessment of Ki-67 using the small and fragmented biopsy specimens may not be representative due to the intratumoral heterogeneity, the inherent characteristics of breast cancer [13]. On the contrary, MRI can evaluate the entire tumor in three dimensions, thus it could assess Ki-67 more comprehensively.

Therefore, the purpose of our study was to determine whether T2 signal intensity, necrosis, and ADC values are associated with Ki-67 in patients with ER-positive and HER2-negative IDC.

## 2. Materials and methods

### 2.1. Study population

The Institutional Review Board of our institution approved this retrospective study, and the informed consent requirement was waived. Between March 2012 and February 2013, we identified 612 consecutive breast cancer patients who underwent breast MRI and subsequent surgery in our institution. As above mentioned in introduction, we focused on the ER-positive and HER2-negative IDC not otherwise specified. Accordingly, patients with breast cancers other than the ER-positive and HER2-negative IDC not otherwise specified ($n$ = 198) were excluded. Patients who underwent neoadjuvant chemotherapy ($n$ = 153) were also excluded, because neoadjuvant chemotherapy can cause reduction of Ki-67 [4]. In addition, patients who underwent excisional biopsy ($n$ = 69) and those with non-visualized tumors on ADC map ($n$ = 5) were excluded. Finally, a total of 187 women (mean age, 53.4 ± 10.9 years; median, 53 years [range, 25–86]) with the ER-positive and HER2-negative IDC not otherwise specified were included. In this study, T2W signal intensity was used as a surrogate marker for necrosis, but T2W signal intensity might be considerably determined by the background matrix in invasive cancers of special histologic type (e.g. mucinous carcinoma with very high T2 signal intensity due to abundant mucinous background matrix). Our study only included IDC not otherwise specified, thus such potential bias would be minimal.

### 2.2. MRI protocol

Breast MRI was performed with patients in the prone position using a 3.0-T scanner (MR750, GE Medical Systems, Waukesha, WI) with a dedicated eight-channel breast coil. The routine protocol sequentially consisted of T2W fast spin echo axial images (TR/TE, 9100/100 ms; flip angle, 110°; field of view (FOV), 320 mm; matrix, 416 × 256 pixels; section thickness, 3 mm), T2W short time inversion recovery (STIR) axial images (TR/TE, 5000/70 ms; inversion time, 200 ms; flip angle, 110°; FOV, 320 mm; matrix, 320 × 256 pixels; section thickness, 3 mm), axial DWI using single-shot echo planar imaging (application of diffusion-sensitizing gradients along the x-, y-, and z-directions, with $b$ values of 0 and 600 s/mm$^2$; TR/TE, 6000/70 ms; FOV, 320 mm; matrix, 128 × 128; section thickness, 3 mm), and T1-weighted fat-suppressed pre-contrast and 3D dynamic post-contrast enhanced (DCE) axial images (TR/TE, 5.6/1.7 ms; flip angle, 12°; FOV, 320 mm; matrix, 280 × 512 pixels; section thickness, 3 mm) with one pre-contrast and six post-contrast dynamic series obtained before and after a bolus injection of 0.1 mmol/kg body weight of gadolinium-based contrast agent (Dotarem, Guerbet, Paris, France; Magnevist, Berlex Laboratories, Wayne, NJ, or Gadovist, Bayer Schering Pharma, AG, Berlin, Germany) at a rate of 2 mL/s, followed by 20 mL saline flush. Post-processing, image subtraction was performed by subtracting the pre-contrast images from post-contrast images.

### 2.3. Image analysis

Intratumoral signal intensity of the whole tumor (multiple slices occupying the whole tumor) was visually assessed using the T2W STIR and contrast-enhanced MR images. Intratumoral necrosis was defined as an area showing very high T2 signal intensity stronger than or almost identical to that of water or vessels and no enhancement on post-contrast subtracted images of all dynamic series [11,12,15]. When reviewing MR images, the images were first scanned whether necrosis corresponding to the aforementioned definition was present. If necrosis was present, the proportion of necrosis within the entire tumor volume was evaluated. Intratumoral signal intensity was finally categorized as one of the following four categories. Category 1: Whole tumor shows low or equal T2 signal intensity compared to the normal breast parenchyma without necrosis [defined as very high T2 signal intensity and no enhancement]. This type was considered to have low cellularity and/or fibrosis [11,12,15]. Category 2: Tumor shows high T2 signal intensity compared to the normal breast parenchyma without necrosis. This type was considered to have high cellularity [11,12,15]. Category 3: necrosis < 50% of the entire tumor volume. Category 4: necrosis ≥ 50% of the entire tumor volume.

Conventional measurement of mean and minimum ADC were obtained by placing a region of interest (ROI) on the ADC map using the same method described by Mori et al. [4] because this study aimed to re-test a negative correlation between ADC and Ki-67 suggested by Mori et al. To measure mean ADC, the largest tumor cross-section was selected on the ADC map, and the largest circular ROI was placed inside the tumor [4]. To measure minimum ADC, three ROIs were placed on the ADC map where the ADCs visually appeared to be most decreased within the tumor contour to measure the mean ADC values of the individual ROIs; the minimum of these was recorded as the minimum ADC [4]. When measuring minimum ADC, cystic or necrotic areas based on T2W and contrast-enhanced MR images were carefully excluded from the ROI [7,8,16]. ADC value was calculated according to the following equation: $ADC = [1 / (b_2 - b_1)] \times \ln [S_1 / S_2]$, where S1 and S2 are signal intensities in the ROI obtained by two gradient factors, $b_1$ and $b_2$ ($b_1 = 0$ s/mm$^2$, $b_2 = 600$ s/mm$^2$).

The image analysis consisted of the two sessions. In the first review session, the two radiologists (S.-Y.K. and M.J.K. with 4 and 13 years of experience in breast MRI, respectively) reviewed the intratumoral signal intensity in consensus. They also reviewed the lesion type (mass vs. non-mass enhancement) [17] and lesion size on MRI in consensus, because non-mass enhancement (compared to mass) or smaller lesion size may increase the intra- and/or inter-observer variability of ADC measurement [18,19]. In addition, one radiologist (S.-Y.K.) measured ADC values. The second review session was performed six months after the first review session by the same two radiologists. They independently re-analyzed the intratumoral signal intensity to evaluate the inter-observer agreement and the diagnostic performance of the developed model. In addition, they independently measured ADC values to evaluate intra- and inter-observer agreement for ADC measurement. For intra-observer agreement, the data obtained by a radiologist (S.-Y.K.) in the first and second review session were used. For inter-observer agreement, the data obtained by the two radiologists in the second review session were used. For patients with multiple tumors, only

the index tumor with a largest diameter was evaluated, which was the same method described in the study by Mori et al. [4] During the image analysis, the radiologists were blinded to pathologic characteristics including Ki-67.

### 2.4. Pathologic diagnosis

All patients underwent therapeutic surgery, and surgical specimens were fixed in 10% buffered formalin, and 5-μm-thick sections were obtained. One dedicated breast pathologist (J.S.K.) with 10 years of experience evaluated the specimens. ER positivity was defined as ≥1% nuclear staining [20]. HER2 positivity was defined as having immunohistochemistry (IHC) score of 3+ or using gene amplification by fluorescence in situ hybridization in tumors with IHC HER2 score of 2+ [21]. IHC staining for Ki-67 was scored by counting the number of cells with positively stained nuclei, and this value was expressed as a percentage of the total tumor cells [22]. Low-proliferation group was defined as Ki-67 < 14% and high-proliferation group was defined as Ki-67 ≥ 14% [13].

### 2.5. Statistical analysis

The relationships between intratumoral signal intensity and Ki-67 were assessed using the analysis of variance (ANOVA) and the pairwise *t*-test. The correlation between ADC and Ki-67 was evaluated using Pearson's correlation coefficient. Inter-observer agreement for the suggested model was analyzed using Cohen's kappa statistics. A kappa value (κ) of 0.81–0.99 was considered almost perfect, 0.61–0.80 substantial, 0.41–0.60 moderate, 0.21–0.40 fair, and ≤0.20 slight agreement [23]. Intra- and inter-observer agreement for the ADC measurement was assessed using intraclass correlation coefficient (ICC). Landis criteria were used to interpret ICC agreement level: slight (r = 0.0–0.19), fair (r = 0.20–0.39), moderate (r = 0.40–0.59), substantial (r = 0.60–0.79), and almost perfect (r = 0.80–1.0) [23]. Chi-square test was used to evaluate the difference in the proportion of high proliferation group according to the grades of the suggested model. Accuracy of the model as a surrogate for Ki-67 was calculated with grade 1 indicative of low proliferation group and grades 2–3 indicative of high proliferation group. All analyses were performed with SPSS software (PASW Statistics, version 20; SPSS, Chicago, Ill.). Probability values of < 0.05 were considered statistically significant.

## 3. Results

### 3.1. Pathological and MRI characteristics of study population

Pathological and MRI findings of study population are shown in Table 1. All were ER-positive and HER2-negative IDC not otherwise specified. Median Ki-67 was 10 (range, 1–80). One hundred twelve (59.9%) lesions were categorized as low proliferation group (Ki-67 < 14%) and 75 (40.1%) lesions were categorized as high proliferation group (Ki-67 ≥ 14%). One hundred and forty seven (78.6%) women had single cancer, 29 (15.5%) had multifocal cancers, and 11 (5.9%) had multicentric cancers. The mean size of the index tumors in the high proliferation group was significantly larger than that in the low proliferation group (size on pathology, 2.4 ± 1.0 vs. 1.9 ± 1.0, $P = 0.003$; size on MRI, 2.2 ± 1.1 vs. 1.9 ± 0.9, $P = 0.017$). Twenty one (11.2%) tumors were < 1 cm, and 166 (88.8%) tumors were 1 cm or larger on MRI. Ninety seven (51.9%) tumors showed low or equal T2 signal intensity, 34

(18.2%) showed high T2 signal intensity, and 56 (29.9%) showed necrosis on MRI. The median time between biopsy and MRI was 7 days (range, 4–47 days). Ninety nine (52.9%) women had interval time ≤ 7 days and 88 (47.1%) women had interval time > 7 days between biopsy and MRI.

### 3.2. Association between intratumoral signal intensity and Ki-67

There were significant differences in mean Ki-67 values according to the four categories of intratumoral signal intensity (Table 2, $P < 0.001$). However, there was no significant difference in the mean Ki-67 between category 2 and 3 (20.0 ± 17.0 vs. 16.0 ± 14.1, $P = 0.232$). Thus, we suggested a model to predict Ki-67 by combining the two categories into the same grade (Grade II, Fig. 1). In the suggested model, as grade increased, the mean values of Ki-67 significantly increased as follows: Grade I: 12.5 ± 14.3, Grade II: 17.6 ± 15.4, Grade III: 45.0 ± 23.8, $P < 0.001$ (Table 2, Figs. 2–4). As grade increased, the proportion of high proliferation group (Ki-67 ≥ 14%) significantly increased (Table 2, $P = 0.003$). All tumors with ≥50% necrosis had ≥14% of Ki-67. The accuracy for grades 1 and 2 was 59% ([67 + 41]/183), and accuracy for grade 3 was 100% (4/4).

### 3.3. Correlation between ADC and Ki-67

There were non-significant positive correlations between mean ADC and Ki-67 (Pearson's correlation coefficients, 0.140 [$P = 0.057$] for all 187 tumors, 0.064 [$P = 0.465$] for 131 tumors without necrosis, 0.245 [$P = 0.078$] for 56 tumors with necrosis). There were non-significant negative correlations between minimum ADC and Ki-67 (Pearson's correlation coefficients, −0.079 [$P = 0.284$] for all 187 tumors, −0.056 [$P = 0.528$] for 131 tumors without necrosis, −0.047 [$P = 0.732$] for 56 tumors with necrosis).

### 3.4. Inter-observer agreement and reassessment of the model

For the suggested model to predict Ki-67, almost perfect agreement was found between the two reviewers (Table 3, $\kappa = 0.846$, $P < 0.001$). Both reviewers agreed for necrosis > 50% ($n = 4$). They did not agree in 15 (8.0%) cases. When the performance of the suggested model was re-evaluated in the second image review session, it was again demonstrated that mean Ki-67 significantly increased according to the grades of the model (Grade I: 12.1 ± 1.3, Grade II: 18.1 ± 16.8, and Grade III: 45.0 ± 23.8 in reader 1; Grade I: 11.5 ± 1.2, Grade II: 18.3 ± 17.4, and Grade III: 45.0 ± 23.8 in reader 2; all $P < 0.001$ using ANOVA).

### 3.5. Intra- and inter-observer agreement for ADC measurement

Regarding intra-observer agreement (Table 4), the ICC value for the mean ADC was 0.724 (95% confidence interval [CI]: 0.597–0.815), and the ICC value for the minimum ADC was 0.615 (95% CI: 0.455–0.737). Regarding inter-observer agreement, the ICC value for the mean ADC was 0.697 (95% CI: 0.561–0.796), and the ICC value for the minimum ADC was 0.543 (95% CI: 0.364–0.684).

## 4. Discussion

Breast cancers with high proliferative activity (i.e. with high Ki-67 expression) are generally regarded to have higher cellularity than those with low proliferative activity. However,

highly proliferative cancers may outgrow the oxygen supply of their vascular system, resulting in necrosis and decreased cellularity [14]. Our results were concordant with this hypothesis: tumors with high cellularity (Category 2) had higher mean Ki-67 than those with low cellularity (Category 1), and tumors with necrosis ≥ 50% (Category 4) had higher mean Ki-67 than those with necrosis < 50% (Category 3). However, contrary to the hypothesis, tumors with necrosis < 50% (Category 3) did not have higher mean Ki-67 than non-necrotic tumors but with high cellularity (Category 2). One possible reason is that the actual difference in necrosis may not be as significant as demonstrated on MRI between the two category groups: In fact, most tumors with necrosis < 50% were considered to have a mild degree of necrosis < 25% (Table 1, 82.7%, 43 of 52). Tumors with high cellularity might have a minimal degree of necrosis, although not discernible to the human eye. Based on these results, we developed a model to predict Ki-67 by combining Category 2 and 3 into the same grade. In this model, Ki-67 significantly increased as the grade increased. The model was re-analyzed 6 months after the first review session. In the second review session, Ki-67 again significantly increased according to the grades of the model in both reviewers, and the model showed high inter-observer agreement ($\kappa = 0.846$), which reflects high reproducibility of the model. Although the accuracy for grade 3 was 100%, that for grades 1 and 2 was just 59%, which may be low for the radiological grade to be used as a surrogate for high/low Ki-67. Our results suggest that ADC may not be an appropriate indicator to assess Ki-67. Both mean and minimum ADC did not show significant correlations with Ki-67, consistent with prior studies [7–9]. On the contrary, in a recent study by Mori et al., both mean and minimum ADC showed significantly negative correlations with Ki-67 [4]. The presence of necrosis and its possible effect on ADC were not mentioned or analyzed in the study [4]. In addition, our study analyzed more than double number of breast cancers (187 tumors in our study vs. 85 tumors in the study [4]). In our study, moderate to substantial inter-observer agreement was found for the ADC measurements, which was the lower agreement compared to that in the study by Mori et al. (ICC: 0.543–0.697 in our study vs. 0.722–0.919 in the study [4]), despite the same measurement method and comparable lesion type (the proportion of non-mass enhancement: 16.6% (31 of 187) vs. 17.4% (15 of 86) in the study [4], $P = 0.870$). Presence of small tumors < 1 cm on MRI in our study (11.2%, 21 of 187) but absence in the study [4] might affect the lower agreement level in our study. Inter-observer agreement was lower than the intra-observer agreement (ICC: 0.543–0.697 vs. 0.615–0.724), and the minimum ADC showed a lower intra- and inter-observer agreement than the mean ADC (ICC: 0.543–0.615 vs. 0.697–0.724), consistently with the prior studies [4,18,19]. Until now, the role of ADC in predicting Ki-67 has been investigated by a number of studies, but the role of T2W or the combination of T2W and contrast-enhanced MR images has not been fully evaluated. To our knowledge, this was the first study exclusively focusing on the relationship between intratumoral signal intensity on MRI and Ki-67. Considering the limitations of ADC application, such as standardization of DWI parameters and inter- and intra-observer variability [24], our model might be advantageous as it can be visually and simply analyzed with high reproducibility and good performance in predicting Ki-67.

The clinical significance of necrosis on MRI has not been fully established. In several studies, necrosis was a relatively uncommon finding in ER-positive and HER2-negative

breast cancers [11,25]. In our study, 29.9% (56 of 187) had some degree of necrosis on MRI, and only 2.1% (4 of 187) had necrosis ≥ 50%. According to Uematsu et al., necrosis was more frequently observed in triple-negative cancers compared to ER-positive and HER2-negative cancers (34% [19 of 56] vs. 12% [9 of 78], $P = 0.002$) [11]. The utility of our model in predicting Ki-67 could be further evaluated for other breast cancer subtypes, in which the incidence of necrosis is reportedly higher than in ER-positive and HER2-negative cancer [11,25]. Furthermore, few studies have reported necrosis as a prognostic factor in breast cancer [25–27]. The presence of marked necrosis, expressed as rim enhancement in several studies, was associated with early systemic metastases and worse survival outcome compared with absent to slight necrosis [25,26]. Prognosis might be different according to the degree of necrosis on MRI, and further studies are needed regarding this issue.

We acknowledge several limitations. First, this was a retrospective study from a tertiary academic institution. Further prospective and multicenter study is required to validate our results. Second, we did not analyze cellularity and necrosis using the histopathology of surgical specimens, which is currently known as the gold standard. Instead, intratumoral MR signal intensity was used as a surrogate marker for cellularity and necrosis based on previous studies [11,12,15]. Third, DWI can be affected by microperfusion as well as Brownian incoherent motion (diffusion) [24]. At low b values, microperfusion effects are visible and the ADC values tend to be larger [24]. Use of a higher b value reduces the contribution of the microperfusion effect in ADC measurements [24]. Several papers showed that a b value of 1000 s/mm$^2$ was considered optimal [28], but a b value of 600 s/mm$^2$ was used in this study. Fourth, intratumoral signal intensity was visually evaluated, and quantitative analysis was not performed. Visual assessment by radiologists has been traditionally and widely performed in the field of radiologic analysis, and our suggested model showed high inter-observer agreement between two radiologists with different experience levels. An objective and quantitative computer-aided analysis could be considered in future studies. Fifth, post-biopsy hematoma of late sub-acute or chronic stage (> 7 days after biopsy) might have a similar appearance to necrosis on MRI theoretically [29]. However, we only used a 14-gauge needle with 4–6 biopsy times, thus massive bleeding usually did not occur by biopsy. We also tried to differentiate post-biopsy hematoma from necrosis using the pre-contrast T1 signal intensity (usually high signal intensity for hematoma), the location (hematoma usually being located at the edge or peripheral area, while necrosis usually being observed in the internal and central area) and the biopsy tract (if associated).

In conclusion, Intratumoral signal intensity based on T2W and contrast-enhanced MR images was associated with Ki-67 in patients with ER-positive and HER2-negative IDC, whereas ADC was not correlated with Ki-67. The intratumoral signal intensity could be used in predicting Ki-67 as an imaging biomarker and in selecting the candidates who may benefit from neoadjuvant chemotherapy in women with ER-positive and HER2-negative IDC. It could be used to assess Ki-67 supplementary to the conventional pathologic assessment, or as an independent method for patients without available Ki-67 information. This approach could ultimately lead to a more tailored therapy for each patient.

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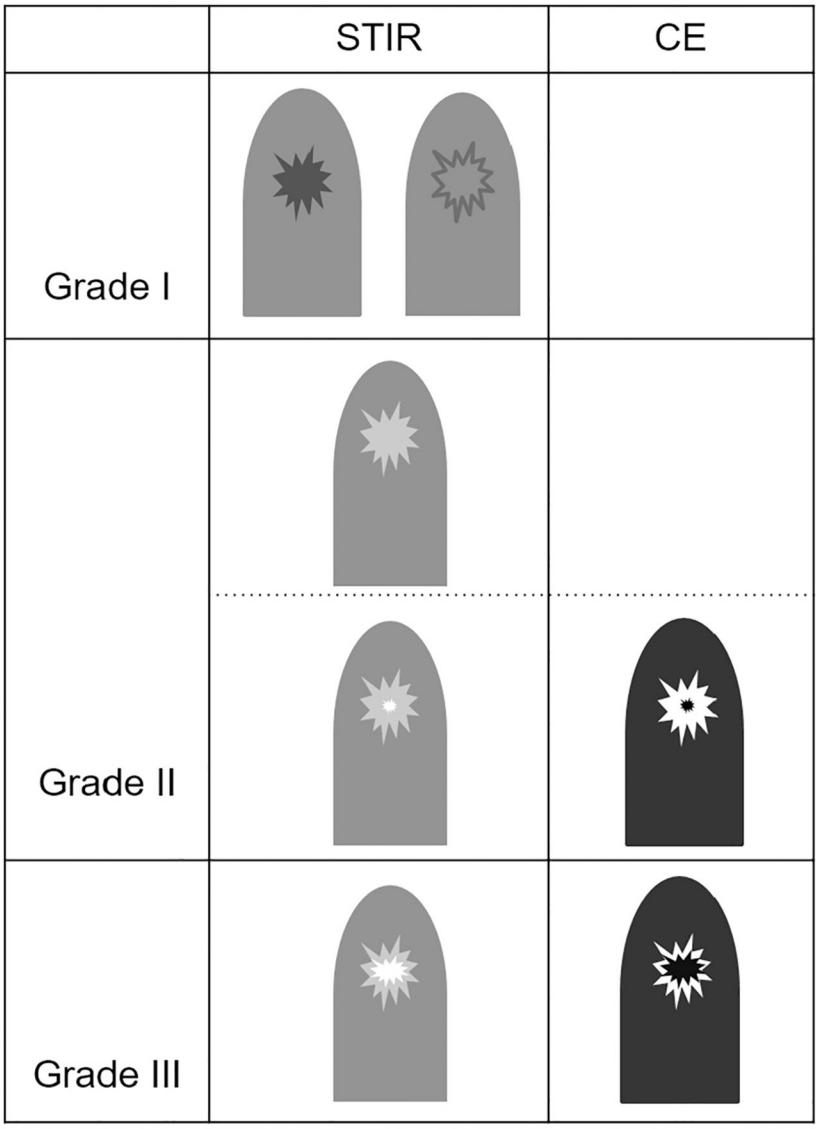


**Fig. 1.**
Schematic drawing for the suggested model to predict Ki-67.

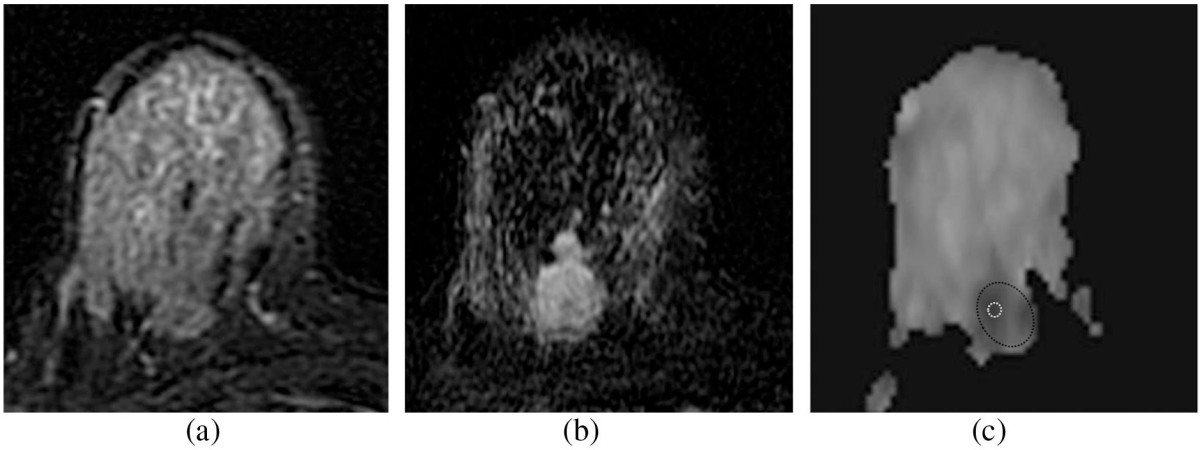


**Fig. 2.**

A ER-positive and HER2-negative breast cancer (Ki-67: 5%) in a 47-year old woman showed a low to equal T2 signal intensity without necrosis (Grade I of the suggested model). Mean ADC (black region of interest (ROI)) was $1.077 \times 10^{-3}$ $mm^2/s$ and minimum ADC (white ROI) was $0.998 \times 10^{-3}$ $mm^2/s$ (a: fat-suppressed T2-weighted short-time inversion recovery (STIR) axial image, b: fat-suppressed second post-contrast image, c: ADC map).

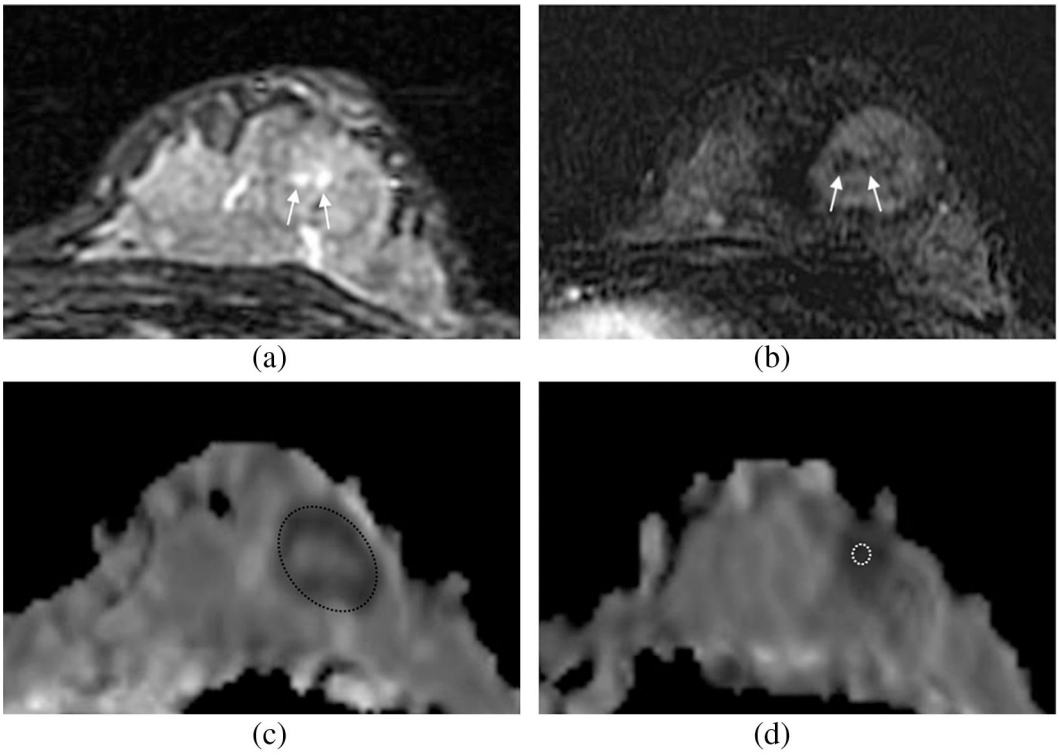


**Fig. 3.**

A ER-positive and HER2-negative breast cancer (Ki-67: 20%) in a 31-year-old woman showed focal very high T2 signal intensity (arrows) and a corresponding area (arrows) without enhancement < 50% of the total tumor volume (Grade II). Mean ADC (black ROI) was $1.142 \times 10^{-3}$ $mm^2/s$ and minimum ADC (white ROI) was $0.757 \times 10^{-3}$ $mm^2/s$ (a: fat-suppressed T2-weighted short-time inversion recovery (STIR) axial image, b: fat-suppressed second post-contrast image, c and d: ADC map).

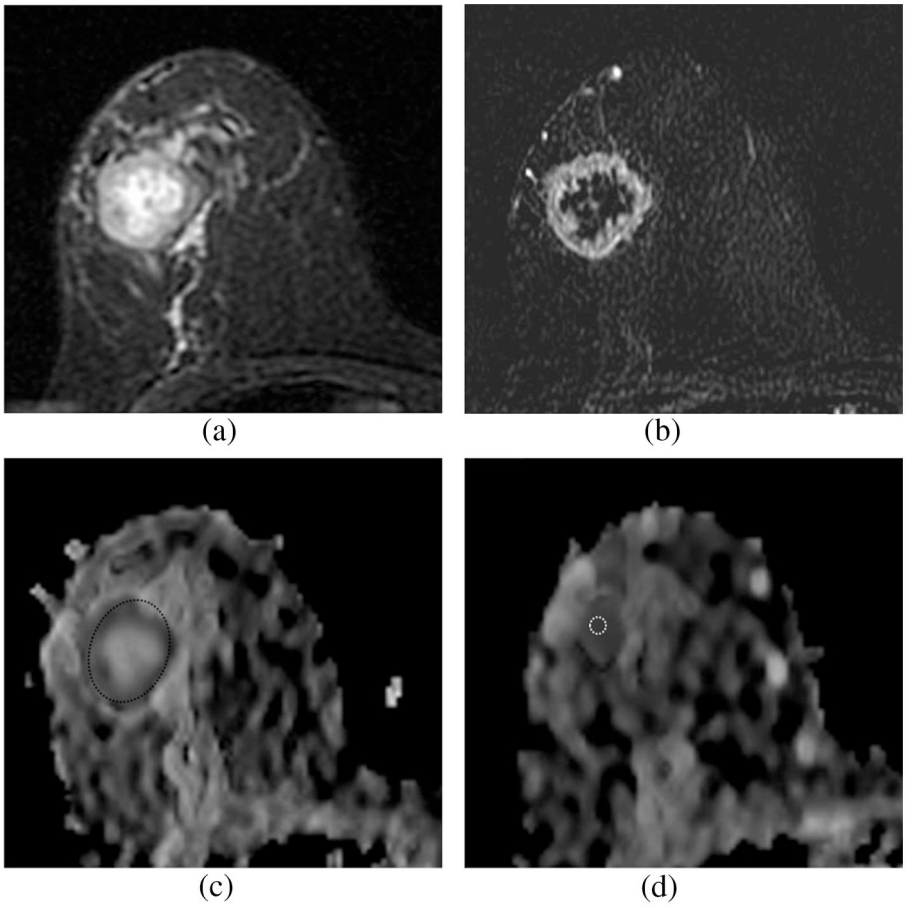


**Fig. 4.**

A ER-positive and HER2-negative breast cancer (Ki-67: 60%) in a 66-year-old woman showed a focal very high T2 signal intensity and a corresponding area without enhancement > 50% of the total tumor volume (Grade III). Mean ADC (black ROI) was $1.799 \times 10^{-3}$ $mm^2/s$ and minimum ADC (white ROI) was $0.899 \times 10^{-3}$ $mm^2/s$ (a: fat-suppressed T2-weighted short-time inversion recovery (STIR) axial image, b: fat-suppressed second post-contrast image, c and d: ADC map).

**Table 1**

Pathological and MRI characteristics of study population.

| Characteristics | No. of patients (%) |
|---|---|
| Ki-67 (%) on surgical pathology | |
| Median (range) | 10 (1–80) |
| Mean ± SD | 15.5 ± 15.7 |
| Low proliferation group | 112 (59.9) |
| High proliferation group | 75 (40.1) |
| Tumor size on surgical pathology (cm) | |
| Median (range) | 2.0 (0.4–7.0) |
| Mean ± SD in total group | 2.1 ± 1.1 |
| Mean ± SD in low proliferation group (median) | 1.9 ± 1.0 (1.8) |
| Mean ± SD in high proliferation group (median) | 2.4 ± 1.0 (2.2) |
| Tumor size on MRI (cm) | |
| Median (range) | 1.8 (0.4–6.0) |
| Mean ± SD in total group | 2.0 ± 1.0 |
| Mean ± SD in low proliferation group (median) | 1.9 ± 0.9 (1.8) |
| Mean ± SD in high proliferation group (median) | 2.2 ± 1.1 (1.9) |
| Lesion type on MRI | |
| Mass | 156 (83.4) |
| Non-mass enhancement | 31 (16.6) |
| Intratumoral signal intensity on MRI | |
| Low or equal T2 | 97 (51.9) |
| High T2 | 34 (18.2) |
| 0% < necrosis < 25% | 43 (23.0) |
| 25% ≤ necrosis < 50% | 9 (4.8) |
| 50% ≤ necrosis < 75% | 3 (1.6) |
| 75% ≤ necrosis < 100% | 1 (0.5) |
| Mean ADC ($\times 10^{-3}$ $mm^2/s$) | |
| Mean ± SD | 1.132 ± 0.216 |
| Minimum ADC ($\times 10^{-3}$ $mm^2/s$) | |
| Mean ± SD | 0.947 ± 0.214 |

Note. Number of patients (%) unless otherwise indicated. SD = standard deviation.

Definition of necrosis = very high T2 and no enhancement.

Low proliferation group = Ki-67 < 14%. High proliferation group = Ki-67 ≥ 14%.

**Table 2**

Association between Intratumoral Signal Intensity and Ki-67.

| Intratumoral signal intensity | Ki-67 (%) | Suggested model | Ki-67 (%) | Low proliferation group | High proliferation group |
|---|---|---|---|---|---|
| Category 1: Low or equal T2 | 12.5 ± 14.3 (1–80) | Grade I: Low or equal T2 | 12.5 ± 14.3 (1–80) | 67 (69.1) | 30 (30.9) |
| Category 2: High T2 | 20.0 ± 17.0 (1–80) | Grade II: High T2 or necrosis < 50% | 17.6 ± 15.4 (1–80) | 45 (52.3) | 41 (47.7) |
| Category 3: Necrosis < 50% | 16.0 ± 14.1 (1–70) | | | | |
| Category 4: Necrosis ≥ 50% | 45.0 ± 23.8 (20–70) | Grade III: Necrosis ≥ 50% | 45.0 ± 23.8 (20–70) | 0 (0.0) | 4 (100.0) |

Note. Values are mean ± standard deviation (ranges) or number of patients (%).

Definition of necrosis = very high T2 signal intensity and no enhancement.

Grade II = combination of Category 2 and 3.

Low proliferation group = Ki-67 < 14%. High proliferation group = Ki-67 ≥ 14%.

## Table 3

Inter-observer agreement for the suggested model.

| | R2 G1 (*n* = 92) | R2 G2 (*n* = 91) | R2 G3 (*n* = 4) | Kappa | *P* value |
|---|---|---|---|---|---|
| R1 G1 (*n* = 97) | 87 | 10 | 0 | 0.846 | < 0.001 |
| R1 G2 (*n* = 86) | 5 | 81 | 0 | | |
| R1 G3 (*n* = 4) | 0 | 0 | 4 | | |

Note. Values are number (*n*) of patients.

G = grade of the model.

R1 = Reviewer 1 with 4 years of experience.

R2 = Reviewer 2 with 13 years of experience.

**Table 4**

Intra- and inter- observer agreement for ADC measurement.

| | Intra-observer agreement | Inter-observer agreement |
|---|---|---|
| Mean ADC | 0.724 (0.597–0.815) | 0.697 (0.561–0.796) |
| Minimum ADC | 0.615 (0.455–0.737) | 0.543 (0.364–0.684) |

Note. Values are interclass correlation coefficient (95% confidence intervals).