

# Correlation of the apparent diffusion coefficient values on diffusion-weighted imaging with prognostic factors for breast cancer

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**Objective:** The aim of this study was to correlate the apparent diffusion coefficient (ADC) value of breast cancer with prognostic factors.

**Methods:** 335 patients with invasive ductal carcinoma not otherwise specified (IDC NOS) and ductal carcinoma *in situ* (DCIS) who underwent breast MRI with diffusion-weighted imaging were included in this study. ADC of breast cancer was calculated using two *b* factors (0 and 1000 s mm<sup>-2</sup>). Mean ADCs of IDC NOS and DCIS were compared and evaluated. Among cases of IDC NOS, mean ADCs were compared with lymph node status, size and immunochemical prognostic factors using Student's *t*-test. ADC was also correlated with histological grade using the Kruskal–Wallis test.

**Results:** Mean ADC of IDC NOS was significantly lower than that of DCIS ( $p < 0.001$ ). However, the mean ADC of histological grade of IDC NOS was not significantly different ( $p = 0.564$ ). Mean ADC of oestrogen receptor (ER)-positive or progesterone receptor (PR)-positive cancer was significantly lower than that of ER-negative or PR-negative cancer ( $p = 0.003$  vs  $p = 0.032$ ). Mean ADC of Ki-67 index-positive cancer was significantly lower than that of Ki-67 index-negative cancer ( $p = 0.028$ ). Mean ADC values of cancers with increased microvascular density (MVD) were significantly lower than those of cancer with no MVD increase ( $p = 0.009$ ). No correlations were observed between mean ADC value and human growth factor receptor 2 expression, tumour size and lymph node metastasis.

**Conclusion:** Low ADC value was correlated with positive expression of ER, PR, increased Ki-67 index, and increased MVD of breast cancer.

Breast MRI is an established supplemental technique to mammography and ultrasonography for evaluation of suspicious breast lesions. Diffusion-weighted MRI (DWI) has recently been integrated into the standard breast MRI for discrimination of benign and malignant breast lesions obtained with dynamic contrast-enhanced MRI [1–13]. DWI is a non-invasive technique that represents the biological character of the mainly Brownian movement of protons in bulk water molecules *in vivo*. Apparent diffusion coefficient (ADC) values are quantified by measurement of mean diffusivity along three orthogonal directions, which are affected by cellularity of the tissue, fluid viscosity, membrane permeability and blood flow [7, 9–11]. Microstructural characteristics, including water diffusion and blood microcirculations in capillary networks, were associated with ADC value. Decreased movement of molecules in highly cellular tissue showed correlation with a low ADC value [3, 4]. Several studies of DWI of the breast have reported significantly lower ADC values in malignant tumours, compared with benign breast lesions and normal tissue [1–3, 5–11, 14]. Classic prognostic markers, including tumour size and grade, and lymph node status in patients with breast cancer, and molecular markers, including oestrogen receptor (ER), progesterone receptor (PR), Ki-67

index, human growth factor receptor 2 (HER2) protein and angiogenic molecular markers, have been reported [1, 15, 16]. Few studies have examined the correlation between ADC values and prognostic factors [1, 8]. The purpose of this study is to compare ADC values of DWI of breast cancer with prognostic factors.

## Methods and material

### Patients

Our institutional review board approved the study and waived patient informed consent because of the retrospective design. Between December 2005 and November 2010, 731 consecutive patients underwent MRI with diffusion in our institution. Cases involving previous excisional biopsy ( $n = 84$ ), neoadjuvant chemotherapy ( $n = 82$ ), evaluation for screening owing to mammoplasty ( $n = 75$ ), no pathological confirmation ( $n = 27$ ), benign lesion ( $n = 31$ ) and male patient ( $n = 1$ ) were excluded. 64 lesions were excluded because the ADC value was not evaluated or because of technical issues with DWI acquisition resulting in failure of lesion detection. 34 lesions were excluded because they were confirmed to be a special type of invasive ductal carcinoma (IDC), including mucinous, medullary, papillary and infiltrative lobular carcinoma. Finally, 335 breast lesions in 333 consecutive patients (2 patients with bilateral breast cancer) with pathology-proven lesions, with IDC not

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otherwise specified (NOS;  $n=231$ ), IDC NOS with ductal carcinoma *in situ* (DCIS;  $n=59$ ) and pure DCIS ( $n=45$ ), were evaluated retrospectively. Patients ranged in age from 24 to 85 years, with a mean age of 50.6 years.

### Breast MRI

All MRI was performed with a 1.5T scanner (Sonata; Siemens, Erlangen, Germany). All patients were examined in the prone position using a breast array coil. An axial, fat-suppressed,  $T_2$  weighted fast spin-echo sequence [repetition time (TR)/echo time (TE)=6640/101, 30 slices with a field of view (FOV) of 320 mm, a matrix of 512×256, number of excitations (NEX)=2, a 3.5-mm section thickness with a 0.7-mm intersection gap, an acquisition time of 3 min 54 s] and a  $T_1$  weighted spin-echo sequence were obtained. Axial DW-MRI with single-shot echo-planar imaging (EPI;  $b=0$  and  $1000 \text{ s mm}^{-2}$ , TR/TE=5000/110, an FOV of 320 mm, a matrix of 128×128, NEX=3, a 3.5-mm slice thickness with a 0.7-mm slice gap and an acquisition time of 1 min 7 s) was performed. A contrast-enhanced axial  $T_1$  weighted three-dimensional fast low-angle shot (FLASH) sequence with fat suppression (TR/TE=4.36/1.5, a flip angle of  $12^\circ$ , a 1.5-mm section thickness with no gap, an acquisition time of 1 min 20 s, an FOV of 320 mm and a matrix of 330×512) was obtained prior to injection of contrast medium, and then every 80 s, repeated five times, after a bolus injection of  $0.1 \text{ mmol kg}^{-1}$  gadodiamide (Omniscan, GE Healthcare, Carrigtwohill, Ireland). Standard subtraction images were created from the non-enhanced and early and late contrast-enhanced FLASH sequences. The largest malignancies were measured by dynamic enhanced subtraction MRI. Sizes of the IDC NOS ranged from 0.7 to 9.8 cm (mean size 2.09 cm).

### Diffusion image acquisition and ADC analysis

DWI was obtained along each of the  $x$ -,  $y$ - and  $z$ -axes. ADC value was calculated according to the formula  $\text{ADC}=[1/(b_2-b_1)] \ln(S_2/S_1)$ , where  $S_1$  and  $S_2$  are the signal intensities in the regions of interest (ROIs) obtained by two gradient factors,  $b_2$  and  $b_1$  ( $b_1=0$  and  $b_2=1000 \text{ s mm}^{-2}$ ). For measurement of the ADC value, one radiologist with 10 years of experience in breast imaging manually placed a ROI with a diameter of 5–10 mm<sup>2</sup>. Care was taken to avoid areas of  $T_2$  shine-through, such as cystic or necrotic portions of the tumour shown as high-signal intensity on  $T_2$  weighted images and ADC maps. When comparing with dynamic contrast enhanced MR images, the enhancing solid portion was used to site ADC measurements. A ROI at the corresponding location was manually defined on averaged DW images to include the area of hyperintensity. The ADC value was automatically calculated when the ROI was drawn. Three measurements where the ADC value was shown to be lower were selected on the ADC map, and were averaged and used as the ADC value.

### Histological analysis

The method described by Elston and Ellis [17] was used for assessment of histological grades of IDC NOS

using a numerical scoring system for tubule formation, pleomorphism and mitotic count. The total score could range from 3 to 9, with a total score of 3–5 representative of grade 1, a total score of 6 or 7 representative of grade 2 and a total score of 8 or 9 representative of grade 3. Lymph node specimens were obtained by sentinel lymph node (SLN) resection followed by immediate lymph node dissection if one or more SLNs were positive and were histologically assessed on routinely stained sections. The presence of a metastasis was regarded as a positive finding.

In addition, immunohistochemical analysis was performed for ER, PR, HER2, Ki-67 and microvascular density (MVD). The status of ER and PR was considered to be negative if expression was <10% and positive if expression was  $\geq 10\%$ . Results for HER2 expression were scored as negative, 1+, 2+ or 3+, according to the manufacturer's recommendations. Tumours with 0 or 1+ were classified as HER2 negative and 2+ or 3+ were HER2 positive. Ki-67 staining of  $\geq 20\%$  was considered positive expression and <20% was considered negative expression. Microvascular density (MVD) was assessed by counting structures stained with CD 31 in three microscopic fields at  $\times 200$  magnification by determination of the average number of structures in the most vascularised areas at the periphery of the tumour [18]. Staining of CD 31 was scored as 0, 1+, 2+ or 3+ and considered positive when vascularity was scored as 1+, 2+ or 3+.

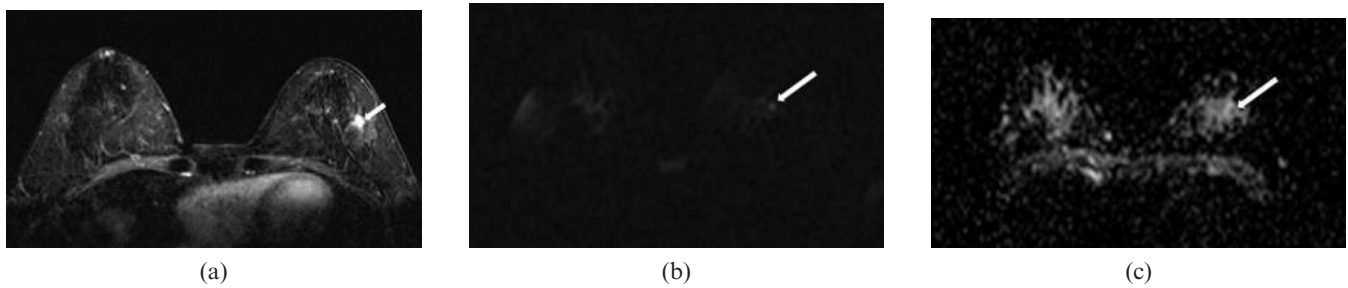
### Statistical analysis

For evaluation of differentiation between DCIS and IDC NOS, the  $t$ -test was used for analysis of mean ADC values between pure DCIS and IDC NOS. Mean ADC for histological grade of IDC NOS was also analysed using the Kruskal–Wallis test.

Among cases of IDC NOS, tumour sizes measured by dynamic enhanced subtraction MRI were divided using the cut-off value of 2 cm and analysed with mean ADC values by  $t$ -test. Mean ADCs were compared with lymph node metastasis, ER status, PR status, extent of HER2 expression, Ki-67 index and MVD, respectively, by  $t$ -test. SPSS v. 14.0 software (SPSS, Chicago, IL) was used for statistical analyses of data.

### Results

Mean ADC value of IDC NOS ( $0.907 \times 10^{-3} \pm 0.160 \text{ mm}^2 \text{ s}^{-1}$ ) was significantly lower than that of DCIS ( $1.113 \times 10^{-3} \pm 0.231 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ,  $p < 0.001$ ; Figure 1). However, mean ADC value of histological grade of IDC NOS was not significantly different ( $p=0.564$ ; Table 1). Mean ADC of ER-positive cancers ( $0.885 \times 10^{-3} \pm 0.152 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ) was significantly lower than that of ER-negative cancers ( $0.941 \times 10^{-3} \pm 0.168 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ,  $p=0.003$ ). Mean ADC of PR-positive cancers ( $0.888 \times 10^{-3} \pm 0.148 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ) was significantly lower than that of PR-negative cancers ( $0.928 \times 10^{-3} \pm 0.171 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ,  $p=0.032$ ). Mean ADC of Ki-67 index-positive cancers ( $0.890 \times 10^{-3} \pm 0.164 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ) was significantly lower than that of Ki-67 index-negative cancers ( $0.933 \times 10^{-3} \pm 0.152 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ,  $p=0.028$ ). Mean ADC



**Figure 1.** MR images of a 46-year-old woman with ductal carcinoma *in situ* (arrow) on (a) contrast-enhanced FLASH early subtraction image, (b) diffusion-weighted image ( $b=1000 \text{ s mm}^{-2}$ ) and (c) ADC map ( $1.324 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ).

value of cancers with increased MVD ( $0.894 \times 10^{-3} \pm 0.147 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ) was significantly lower than that of cancer with no MVD increased ( $0.954 \times 10^{-3} \pm 0.154 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ,  $p=0.009$ ). lymph node (LN) statuses between metastasis negative ( $0.919 \times 10^{-3} \pm 0.166 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ) and positive ( $0.885 \times 10^{-3} \pm 0.147 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ) showed borderline significance ( $p=0.090$ ; Figures 2–3). However, HER2 expression status and tumour size showed no statistically significant correlation with mean ADC (Table 2).

## Discussion

The ADC is a quantifiable value that provides a measurement of signal attenuation and is affected by microscopic motion, including molecular diffusion of water and blood microcirculation in the capillary network [1–3, 19–21]. Water diffusion is greatly influenced by factors such as cellularity, fluid viscosity, intra- and extracellular membrane permeability, active transport, flow and structural directionality [1, 9, 22]. Several studies have reported that malignant tumours usually show higher signal intensity on DWI, compared with benign lesions and normal fibroglandular tissue, resulting in lower ADC values [2, 3, 5, 7, 9–12, 21]. It has been suggested that the decreased ADC value in malignant tumours may be due to their increased cellularity, larger nuclei with more abundant macromolecular proteins, and less extracellular space [5, 20]. Several studies have reported that ADC values appear to be lower in invasive tumours than in carcinoma *in situ* [2, 3, 5, 7, 9–11, 13, 21]. In our study, the ADC value was significantly lower in IDC NOS than in DCIS. IDC features densely packed

tumour cells, which inhibit the effective motion of water molecules and restrict diffusion, compared with DCIS, showing lower ADC values [4, 21]. Few studies have analysed the relationship between tumour grading and ADC values; high-grade tumours are likely to have more limited water diffusion than low-grade tumours, based on cancer cell morphology and arrangements of the extracellular matrix, leading to non-conclusive results [1, 21]. However, some authors have not demonstrated a direct relationship between cellularity and ADC values or between cellularity and tumour grade [4, 22]. In our results, tumour grading among IDC NOS was not statistically significant compared with ADC values.

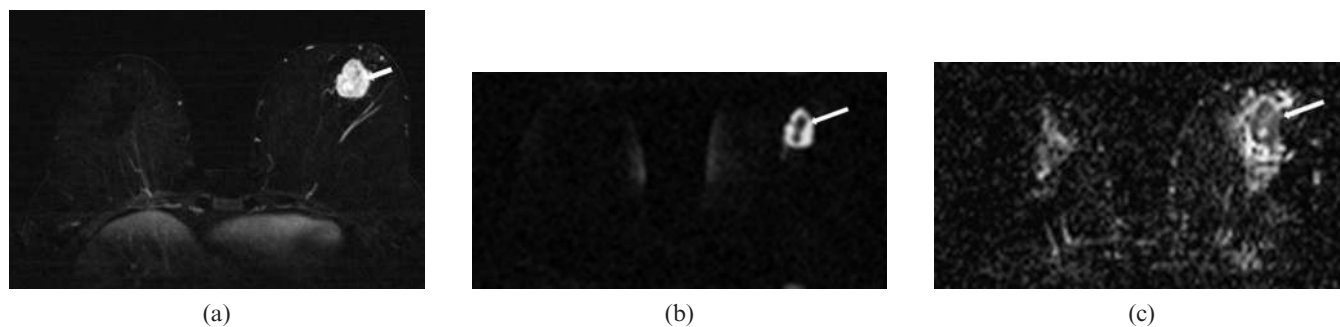
Few studies have analysed the relationship between prognostic factors and ADC values [1, 8, 23]. Razek et al [23] reported an association of lower ADC values with pathological prognostic factors, including higher histological grade, larger tumour size and presence of axillary lymph nodes. Jeh et al [8] reported an association of low ADC value with positive expression of ER and negative expression of HER2 in 107 women with IDC. Their study showed no significant correlation of ADC values with other prognostic factors (*i.e.* PR expression, Ki-67 expression, epidermal growth factor receptor, tumour size, LN metastasis and histological grade). However, they obtained ADC values from 1.5 and 3T MRI machines with different  $b$ -values. Different magnetic fields of MR and different  $b$ -values may influence different ADC values [1]. In our study, several prognostic factors of biological markers, including ER status, PR status, Ki-67 index and MVD, show a statistically significant difference in ADC values; however, pathological prognostic factors, including tumour size, grade and lymph node status were not significant. Oestrogen receptors and progesterone receptors are intracellular steroid hormone receptor proteins, which have been used as indicators of prognosis and as a guide to hormone and endocrine therapy [16, 24]. ER was the confounding factor that influenced PR. Overexpression of the PR status is an indication of the ER pathway, even in cases in which overexpression of ER was reported to be negative [1, 24]. Some studies have reported that the ER affected the ADC value because of inhibition of the angiogenic pathway and induced a decrease in perfusion [1, 25]. Another study reported that ER-positive tumours showed high cellularity [26]. This finding corresponds with our results showing that ER-positive cancer and PR-positive cancer showed lower mean ADC values, compared with negative ones. Ki-67 index is a nuclear antigen

**Table 1.** Correlation of ADC with IDC NOS and DCIS

Pathology	ADC value ( $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ )	$p$ -value
DCIS ( $n=45$ )	$1.113 \pm 0.231$	
IDC NOS ( $n=290$ )	$0.907 \pm 0.160$	$<0.001$
Grade 1 ( $n=14$ )	$0.914 \pm 0.222$	
Grade 2 ( $n=214$ )	$0.911 \pm 0.161$	
Grade 3 ( $n=62$ )	$0.891 \pm 0.142$	$0.564$

ADC, apparent diffusion coefficient; DCIS, ductal carcinoma *in situ*. IDC NOS, invasive ductal carcinoma not otherwise specified.

ADC value is expressed as mean  $\pm$  standard deviation.

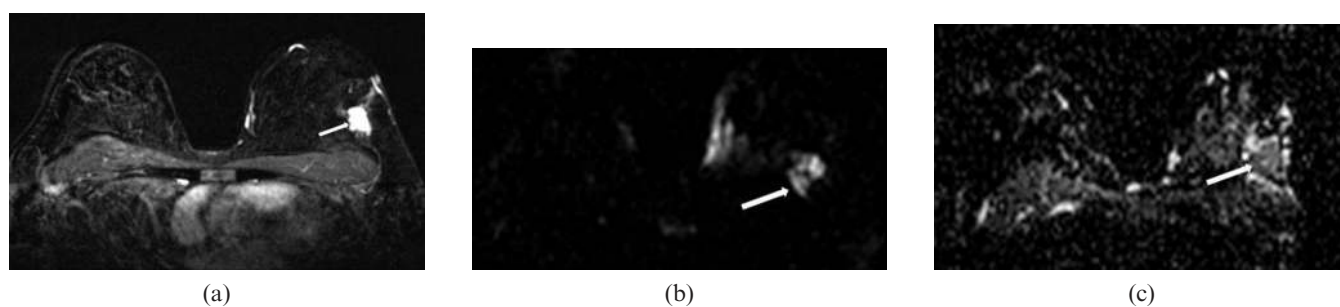


**Figure 2.** A 53-year-old woman with invasive ductal carcinoma, histological grade 1 (arrow). Immunohistochemical staining for oestrogen receptors and progesterone receptors showed positivity. HER2 gene expression showed positivity. Ki-67 index showed a positive increase of over 20%. Microvascular density showed mild increase. Lymph node metastasis revealed negativity. (a) Contrast-enhanced FLASH early subtraction image. (b) Diffusion-weighted image ( $b=1000 \text{ s mm}^{-2}$ ), and (c) ADC map ( $0.754 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ).

appearing during the proliferative phase, which represents tumour proliferation and significant correlation with high mitotic counts, usually using 20% as the cut-off for defining high and low proliferation indices [1, 27]. High Ki-67 index is associated with poor prognostic differentiation and with lymph node metastasis [24]. In our study, mean ADC value was significantly lower in cases of Ki-67 index positive IDC NOS, compared with negative cases. The result could be an indication that increased Ki-67 index is a marker of increased cellularity and correlated with lower ADC values. *In vivo*, the ADC value is affected not only by microscopic motion from diffusion but also by perfusion. The perfusion effect would cause significantly greater artificially increased ADC in malignant lesions owing to increasing microvessel count of tumour angiogenesis [1, 2, 22, 28]. According to several studies, the ADC value was significantly lower in malignant than in benign lesions, indicating that this effect might be mainly owing to the effect of high cell density overcoming the opposite effects of perfusion [1, 5, 14]. In our study, mean ADC value was significantly lower in increasing MVD, compared with cancer with no MVD increase. A decrease in the ADC is expected with increased intracellular tissue caused either by cell swelling or increased cellular density rather than vascular perfusion. HER2-positive expression had a more malignant phenotype accompanied by cell proliferation, invasion and metastasis [1, 2, 8]. However, in our study, no statistically significant difference was observed between the negative and positive group of IDC

NOS. Partridge et al [7] reported that malignant tumours had significantly lower ADC values, compared with benign lesions, for both masses and lesions with non-mass-like enhancement, and that the diagnostic performance of DWI based on ADC thresholds was comparable for both lesion types. They also reported that no association was identified between lesion size and ADC values. In our study, no significant difference in ADC values with size of mass was noted among IDC NOS. Using a lower  $b$ -value, the image would be more affected by a perfusion-induced slightly increased ADC value in malignant lesions due to tumour angiogenesis. By contrast, using higher  $b$ -values, the image may be distorted because it has a long TE [1–3]. Our study used  $b=1000 \text{ s mm}^{-2}$  for calculating ADC. At present there is no consensus regarding optimal  $b$ -values in the diagnosis of breast cancer, and further study will be needed in the future [29]. A single 1.5 T machine was used in performance of our study, using  $b$ -values of  $1000 \text{ s mm}^{-2}$  in a relatively large number of IDC NOS. However, our study had several limitations. Our study was a retrospective review and imaging was performed at 1.5 T for evaluation of ADC values. Therefore, there is a possibility that small malignancies may have been missed. In 3 T MRI, signal-to-noise ratio and the contrast-to-noise ratio of ADC images was higher with 3 T than with 1.5 T and may better show small or diffuse lesions.

In conclusion, we found ADC values correlated with several biological markers of disease. Low ADC was



**Figure 3.** A 53-year-old woman with invasive ductal carcinoma, histological grade 3 (arrow). Immunohistochemical staining for oestrogen receptors and progesterone receptors showed negativity. HER2 gene expression showed negativity. Ki-67 index showed a negative increase of over 20%. Microvascular density showed a mild increase. Lymph node metastasis revealed positive metastasis. (a) Contrast-enhanced FLASH early subtraction image, (b) diffusion-weighted image ( $b=1000 \text{ s mm}^{-2}$ ) and (c) ADC map ( $0.796 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ ).

**Table 2.** Correlation of ADC with prognostic factors in IDC NOS

Prognostic factors	No. of cases (n=290)	ADC value ( $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ )	p-value
Oestrogen receptor	Negative (n=113)	0.941 $\pm$ 0.168	0.003
	Positive (n=177)	0.885 $\pm$ 0.152	
Progesterone receptor	Negative (n=135)	0.928 $\pm$ 0.171	0.032
	Positive (n=155)	0.888 $\pm$ 0.148	
HER2	Negative (n=149)	0.911 $\pm$ 0.158	0.677
	Positive (n=141)	0.903 $\pm$ 0.164	
Ki-67	<20% (n=112)	0.933 $\pm$ 0.152	0.028
	>20% (n=178)	0.890 $\pm$ 0.164	
MVD	Not increased (n=63)	0.954 $\pm$ 0.167	0.009
	Increased (n=227)	0.894 $\pm$ 0.156	
Size	<2 cm (n=133)	0.918 $\pm$ 0.162	0.294
	>2 cm (n=157)	0.898 $\pm$ 0.159	
LN metastasis	Negative (n=188)	0.919 $\pm$ 0.166	0.090
	Positive (n=102)	0.885 $\pm$ 0.147	

ADC, apparent diffusion coefficient; HER2, human growth factor receptor 2; IDC NOS, invasive ductal carcinoma not otherwise specified; LN, lymph node; MVD, microvascular density.

associated with positive ER and PR expression, increased Ki-67 and increased MVD. ADC values may be of use in differentiating between DCIS and invasive breast carcinoma, and in providing prognostic information about disease.

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