The Journal of Medical Research

Research Article

JMR 2019; 5(5): 175-179
September- October
ISSN: 2395-7565

www.medicinearticle.com
Received: 13-09-2019
Accepted: 16-10-2019

Comparison of ADC Value and Prognostic Factors in Invasive Ductal Carcinoma

Dr. Ebru Yılmaz*[1], Dr. Ayhan Yılmaz[2], Dr. Sebahat Nacar Dogan[2], Dr. Merve Cin[2], Dr. Rabia Karasu[1]

1 *Şişli Hamidiye Etfal Training and Educational Hospital, Sisli/Istanbul, Turkey*

2 *GOP Taksim Training and Educational Hospital, Taksim, Turkey*

Abstract

Objective: Aim of this study is to investigate whether there is a correlation by comparison of apparent diffusion coefficient (ADC) in invasive ductal carcinoma patients whom magnetic resonance imaging (MRI) was performed before surgery with prognostic factors such as tumour grade, estrogen/progesterone receptors (ER/PR), HER2/neu (c-erbB-2 protooncogene), level of Ki-67. **Methods:** We retrospectively reviewed breast MRI in our radiology department between 2015 and 2017. The patients in whom diagnosed as not otherwise specified invasive ductal carcinoma (NOS-IDC) after tru-cut biopsy and had preoperatively performed MRI were included in this study. **Results:** The retrospective review yielded 27 patients and evaluated ADC value in 30 lesions. Mean ADC value of lesions was 0,911x10^{-3}mm^2/s (0,456-1,30x10^{-3}mm^2/s) and mean ADC value of normal breast parenchyma was 1,613x10^{-3}mm^2/s (1,116-2,453x10^{-3}mm^2/s). Statistically significant difference was not found between grade 1 (1 lesion), grade 2 (19 lesions), grade 3 (10 lesions), ER positive (25 lesions), ER negative (4 lesions), PR positive (1 lesion), PR negative (8 lesions), HER2 negative (21 lesions), HER2 positive (8 lesions) cases (grade; p=0.074, ER; p=0.57, PR; p=0.66, HER2; p=0.58). Mean ADC value was 0,855x10^{-3}mm^2/s (0.660-1.30 x10^{-3}mm^2/s) in lesions of high Ki-67 proliferative index (20 lesions) and was 1,040x10^{-3}mm^2/s (0.985-1.70 x10^{-3}mm^2/s) in lesions of low Ki-67 proliferative index (5 lesions). Statistically significant difference between these two groups was found (p=0.007). **Conclusion:** In our evaluated prognostic factors, correlation with ADC value was found only in Ki-67 proliferative index and statistically significant difference was not found in the others.

Keywords: Breast cancer, Prognostic factors, Diffusion-weighted MR imaging.

INTRODUCTION

The most common cancer type seen in almost all age group of women in the world is breast cancer [1]. Adjuvant hormonotherapy and chemotherapy applied after diagnosis decrease recurrence ratio of disease and reduce death ratio from breast cancer. But this treatment brings with it many risks and it needs to be used in optimal selected patients [2]. Prognostic factors are used in the selection of patients who are at risk of recurrence and who will respond to treatment.

The most important prognostic factors in breast cancer are lymph node metastasis, tumor size, tumor grade, estrogen/progesterone (ER/PR) receptor status, HER2/neu (c-erbB-2 proctooncogene), Ki-67, epidermal growth factor receptor (EGFR) and mitosin, lymphovascular invasion, age and ethnicity [3].

Contrast-enhanced magnetic resonance imaging (MRI) has high sensitivity in breast cancer and is usually used to detect additional lesions and spread of tumor before operation. Diffusion-weighted image (DWI) has been added to routine imaging protocol in recent years to increase the specificity and sensitivity of MRI. Utility of DWI and apparent diffusion coefficient (ADC), which is mathematical statement obtained from DWI, to differentiate benign and malign lesions of breast is shown in many studies [4, 5].

Our purpose in this study was to investigate role of ADC calculation to determine prognosis by comparison of ADC values and important prognostic factors in breast cancer such as tumor grade, ER/PR status, HER2/neu (c-erbB-2 protooncogene), Ki-67.

MATERIALS AND METHODS

Ethics, study design, and patients

We retrospectively reviewed our imaging database for the patients admitted to our radiology department to perform breast MRI between 2015 and 2017. This study included patients in whom diagnosed as not

***Corresponding author:**
Dr. Ebru Yılmaz
Şişli Hamidiye Etfal Training and Educational Hospital, Sisli/Istanbul, Turkey
Email:
ebruyilmaz99[at]yahoo.com

otherwise specified invasive ductal carcinoma (NOS-IDC) after tru-cut biopsy (14-G core biopsy) and had preoperatively performed MRI. If tru-cut biopsy was performed before MRI, there was a special attention being paid to existence of at least 2 weeks between MRI examination and biopsy procedure.

Specific types of invasive ductal carcinoma such as mucinous, medullary, papillary and invasive lobular carcinoma were excluded from the study. Also, patients who had excisional biopsy and neoadjuvant chemotherapy before MRI examination were not included in study.

Mean age was 47±10.7 (range, 31-73).

The study protocol was reviewed and approved by our institutional ethics committee. However, informed consent was not obtained from patients because of retrospective study.

Imaging protocols

MR imaging was performed using a 1.5T SignaHDx (GE Medical System, Milwaukee, WI, USA) with eight-channel phased array breast coil. MRI examinations was performed on premenopausal women between 5-15th days of menstrual cycle. Conventional contrast-enhanced MR images composed of axial fat-saturated T2-weighted turbo spin-echo (TR/TE, 4500/97; field of view [FOV],330 mm;NEX, 1; matrix, 384 × 512; slice thickness, 3 mm; gap, 1 mm), axial T1-weighted (TR/TE, 720/20; FOV, 330 mm; NEX:2; matrix, 320 × 320; slice thikness, 3 mm) and pre- and post-contrast fat saturated 3D T1-weighted (4.3 ms/1.4 ms; flip angle, 12°; FOV, 320 mm; matrix, 307 × 512; slice thickness, 1,5; gap, 1 mm fast low angle shot [FLASH]). Meglumin Gadoterat (Dotarem; LaboratoireGuerbet, Roissy, France) was administered intravenously using power injector by accounting dose of 0.01 mmol/kg and 15-20 cc saline was injected after contrast administration to supply homogeneous spread of contrast material.After saline injection, contrast-enhanced images were obtained by 5 times repetition. Each sequence continued approximately 1 minute.

DWI that is an echo-planar imaging (TR/TE, 8500/70; FOV, 330 mm; matrix, 192x192; NEX, 1; slice thickness, 4.5 mm; gap, 1 mm) was obtained in axial plane before contrast-enhanced sequences. ADC maps were generated from diffusion gradients by using b values of 0 and 1000 s/mm^2.

ADC Analysis

ADC map is a negative logarithm of signal ratio of imaging obtained from b values of 0 and 1000 s/mm^2 and is formed automatically via workstation. Mean ADC values in all lesions were calculated automatically from these maps by formula of ADC= (lnS0-lnS)/b (S0: signal intensity value in b=0 s/mm^2, S: signal intensity value in b=1000 s/mm^2). Measurements were made by mean 0.5 mm diameter circular region of interest (ROI) placed on lesions. ADC measurements of heterogeneous lesion were applied on contrast-enhanced solid parts that were evaluated on conventional sequences.

ROI did not include normal parenchyma and hemorrhagic or necrotic parts of lesions. At least 3 ADC value calculated and the lowest ADC value was concerned. After ADC calculation of lesion, ADC value of normal parenchyma at the same level of lesion was measured. During calculation, same dimension of ROI was used.

Histologic Analysis

Appropriate treatment plan for all breast cancer patients in our hospital was planned by breast council that consisted of radiologist, pathologist, oncologist and radiation oncologist. The patients who had operation after neoadjuvant chemotherapy were excluded from study. The exact diagnosis of tumor and molecular prognostic factors were histopathologic diagnosis after operation.

Size of tumor was determined by measuring maximum diameter of tumor in specimen.

Modified Scarff-Bloom-Richardson (SBR) classification was used to grade [6]. Pleomorphism, differentiation and mitotic index were scored between 1 and 3 and all scores were added to find grade. Lesions were classified as well-differentiated (grade 1) if score was between 3 and 5, moderate differentiated (grade 2) if score was between 6 and 7, undifferentiated (grade 3) if score was between 8 and 9. Risk of recurrence increases as tumor grade increases [7].

Ki-67, another molecular prognostic factor, is a nuclear antigen that occurs during proliferative phase of cell cycles. Ki-67 proliferative index is used to evaluate tumor proliferation [8]. Threshold value is 14% and is defined as high-low proliferative index. Both Ki-67 proliferative index and tumor grade are parameters that indicate tumor mitosis and so cellularity.

ER/PR are intracellular steroid hormone receptor proteins. 10% in 10 big magnification area and more nuclear dying are accepted as positive.

HER2 (c-erbB-2 protooncogene) is an oncogene that encodes tyrosine kinase receptors in cell membrane and resembles epidermal growth factor. Dying of HER2 is scored as 0, 1+, 2+, and 3+. 3+ scores are accepted as HER2-positive, 0 and 1+ scores as negative. İn situ hybridization was made for 2+ scores.

Statistical Analysis

Normality audit was assessed using Shapiro Wilk test by drawing histogram, Q-Q plot and box plot graphics. Datas were reported as median, min., max., frequency and percentage. Two categorical variables did not show normal distribution so they were compared with Mann Whitney U test. Significance limit was considered as value of P <0.05 and bidirectional. All statistical analyses were performed using NCSS 10 and GPower 3.1.9.2 softwares.

RESULTS

Total 27 patients who had preoperative breast MRI and diagnosed as NOS-IDC after histopathological evaluation were included in study. Breast cancer was multicentric in 3 patients and histopathologic evaluations were made in 2 different areas in these 3 patients and ADC values were also calculated in these areas. Breast cancer was unilateral in all patients and bilateral diseases were not detected.

Tumor size (longitudinal axle) was mean 22±13.3 mm and tumor sizes ranged from 9 to 51 mm.

Mean ADC values of lesions were 0.911x10^{-3}mm^2/s (0.456-1.30x10^{-3}mm^2/s) and mean ADC values of normal breast parenchyma were 1.613x10^{-3}/s (1.116-2.453x10^{-3}mm^2/s).

30 lesions were classified according to SBR system after pathologic evaluation. 1 lesion reported as grade 1, 19 lesions as grade 2 and 10 lesions as grade 3. ADC value of grade 1 lesion was 1.026x10^{-3}mm^2/s. Mean ADC value of grade 2 lesions was 0.911x10^{-3}mm^2/s (0.70-1.30x10^{-3}mm^2/s) and mean ADC value of grade 3 lesions was 0.829x10^{-3}mm^2/s (0.456-1.069x10^{-3}mm^2/s). ADC values of grade 2 and grade 3 lesions were similar and it did not reach a statistical significance (p=0.074).

25 of 30 lesions were reported as ER positive. 4 of the remainder were ER negative and receptor condition of 1 lesion did not be known. Mean ADC value of ER (+) lesions was 0.910x10^{-3}mm^2/s(0.456-1.30x10^{-}

$^{3}mm^2/s$), mean ADC value of ER (-) lesions was $0.914x10^{-3}mm^2/s$ ($0.830-1.069x10^{-3}mm^2/s$). No statistically significant differences between ER (+) and ER (-) was detected (p=0.57).

21 of 30 lesions were PR (+), 8 of remainder were PR (-), and receptor condition of 1 lesion was unknown. Mean ADC value of PR (+) lesions was $0.910x10^{-3}mm^2/s$ ($0.456-1.30x10^{-3}mm^2/s$), mean ADC value of PR (-) lesions was $0.903x10^{-3}mm^2/s$ ($0.830-1.069x10^{-3}mm^2/s$). Statistically significant differences between PR (+) and PR (-) was not detected (p=0.66).

Ki-67 proliferative index over 14% is accepted as high, under 14% as low proliferative index. 20 of 30 lesions had high proliferative index and 5 of 30 lesions were low proliferative index. Ki-67 proliferative index of 5 cases did not be known. Mean ADC value of lesions of high proliferative index was $0.855x10^{-3}mm^2/s$ ($0.660-1.30x10^{-3}mm^2/s$), mean ADC value of lesions of low proliferative index was $1.040x10^{-3}mm^2/s$ ($0.985-1.70x10^{-3}mm^2/s$). Statistically significant difference between two groups was determined (p=0.007). However, post hoc power was found .046 (Figure 1).

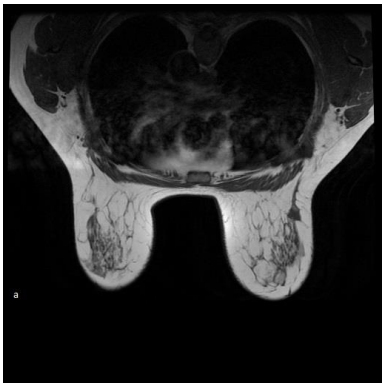

Figure 1a

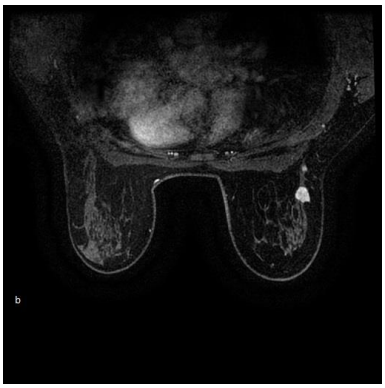

Figure 1b

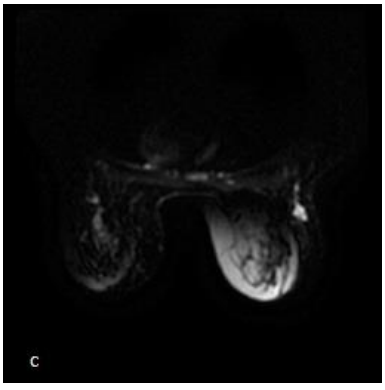

Figure 1c

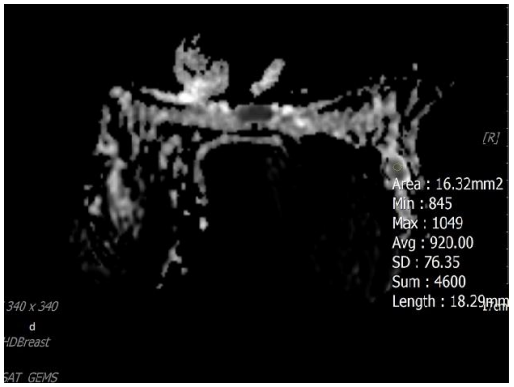

Figure 1d

Figure 1: 41 years-old female patients, 2x1.5x1x5 cm sized mass in axillar tail of right breast. Invasive ductal carcinoma was diagnosed pathologically. Lesion was hipointens on T1-weighted images (a), obviously contrast-enhanced on dynamic studies (b), hyperintens on diffusion-weighted images (c), hipointens on ADC map (d). The lowest ADC value calculated in lesion was $0.920x10^{-3}mm^2/s$. After operation, histologic grade 2, ER %30, PR %40 strong positive, HER2 (-), Ki-67 proliferative index 18% were reported.

Although 21 of 30 lesions were HER2 (-) and 8 of 30 lesions were HER2 (+), HER2 receptor of 1 case was not studied. Mean ADC value of HER2 (-) lesions was $0.910x10^{-3}mm^2/s$ ($0.660-1.070x10^{-3}mm^2/s$), mean ADC value of HER2 (+) lesions was $0.901x10^{-3}mm^2/s$ ($0.456-1.30x10^{-3}mm^2/s$). Statistically significant differences between HER2 (+) and HER2 (-) were not detected (p=0.58) (Table 1).

Table 1: Results of Analysis

Pathologic marker	Number	Mean ADC (interval)$x10^{-3}mm^2/s$	P value
Grade 2	19	0.911 (0.700-1.30)	0.074
Grade 3	10	0.829 (0.456-1.069)	
ER positive	25	0.910 (0.456-1.30)	0.57
ER negative	4	0.914 (0.830-1.069)	
PR positive	21	0.910 (0.456-1.051)	0.66
PR negative	8	0.903 (0.830-1.069)	
Ki-67 high proliferative index	20	0.855 (0.660-1.30)	0.007
Ki-67 low proliferative index	5	1.040 (0.985-1.70)	
HER2 pozitive	8	0.901 (0.456-1.30)	0.58
HER2 negative	21	0.910 (0.660-1.070)	

Note: -p values is calculated using Mann-Whitney U test

DISCUSSION

ADC values, which is negative logarithmic state of DWI signal ratio, are affected by molecular diffusion and perfusion of water. Diffusion of water is affected by cellularity, liquid concentration, and permeability of cell membrane. Number of microvessels determines perfusion and perfusion increases in malign tumor due to neoangiogenesis [9]. ADC value is lower in malign lesion than benign lesions in many previously reported studies. The lower ADC values were based on increased cellularity and decreased extracellular space rather than perfusion effect [10, 11, 12].

When value of diffusion gradient (b value) is lower, perfusion effect increases and high ADC values are calculated. NOS-IDC is characterized by increased size and number of vascular structures [9]. When b value is low, ADC value is affected by perfusion. b value in our study accepted as 1000 s/mm^2 and perfusion effect was intented to be minimum. Mean ADC value of lesions in our study was $0.911x10^{-3}mm^2/s$ and was coherent with literature [4, 13, 14, 15, 16].

Pathologic properties of tumor have prognostic importance. The most important ones of these are tumor type and grade. ADC value changes according to tumor type which has been seen in many previous studies. ADC values of medullar and mucinous tumor are higher than invasive ductal carcinoma. High ADC value has been reported in mucinous cancer due to mucin component and low cellularity, and in medullar cancer due to accompanying inflammatory reaction [15, 17]. For this reason, just only cases diagnosed as NOS-ICD were included in our study.

The most important determinant of tumor grade is cellularity. In DWI, water diffusion of higher-grade tumor is obviously more restricted than lower grade according to morphology of cancer cells and distribution of extracellular matrix. So, ADC value is inversely proportional to the cellularity [11, 12].

The lowest ADC value in grade 3 tumors according to histologic grade was reported in study that was performed by Kim *et al*. and total 67 invasive cancer cases were evaluated. Choi *et al*. evaluated total 335 breast cancers and Park *et al*. evaluated 110 breast cancers, and both of studies also reported lower ADC values in grade 3 tumors than the others. But differences in ADC values in between grades were not found statically significant in these three studies [13, 14, 16]. Also, Yoshikawa *et al*. did not find any correlation between cellularity and ADC values, and Buadu *et al*. did not find correlation between cellularity and grade [9, 18]. However, in contrast to these studies, Razek *et al*. determined correlation between low ADC value and high grade [19] and reported statistically significant results. Again, a study reported in 2010 by Constantini *et al*. showed inverse proportion between grade and ADC [20]. In our study lower ADC values was seen in grade 3 tumors than grade 2 tumors but statistically significant differences were not detected between grade 3 and 2 tumors.

Many studies in literature did not find correlation between ADC and prognostic factors such as tumos size and lymph node involvement [13, 14, 16, 18]. In our study, lymph node involvement and size of lymph nodes were not evaluated because we could not access all data.

ER and PR are proteins of intracellular steroid hormone receptors. These receptors are used to detect both utility of hormonal therapy (predictive factor) and prognostic factor [21]. Many studies showed that ER affected ADC and angiogenesis was suppressed in ER (+) cases and so perfusion decreased. It was found that ADC value in ER (+) cases was lower than ER (-) [13, 14, 22]. In our study, mean ADC value in ER (+) cases was lower than ER (-). But there was no statistical difference between positive and negative cases.

HER2 (+) cells have malign phenotype in terms of proliferation, invasion and metastasis. While Kim *et al*. reported that there was correlation between HER2 and ADC value, Choi *et al*. could not find correlation [13, 14]. Park *et al*. declared that ADC value in HER2 (+) was higher than HER2 (-) [16]. This condition was depended on increased tumor blood flow and so increased perfusion because of induced vascular endothelial growth factor in HER2 (+) cases [23, 24]. Martincih *et al*. emphasized the highest ADC value was calculated in HER2 (+) cases than the other markers [22]. However, in our study lower ADC values was detected in HER2 (+) than HER2 (-) differently from literature and statistically significant difference was not detected between these two groups.

Ki-67 is a nuclear antigen that appears during proliferative phase of cell cycle. High proliferative Ki-67 index is related with bad prognostic differentiation and lymph node metastasis. In many studies, relation between high proliferative index and low ADC value as mentioned and emphasized that Ki-67 could be indicator of increased cellularity [13, 14]. But, Martincih *et al*. did not state statistically significant correlation between Ki-67 index and ADC value [22]. In our study, we found meaningful difference between high Ki-67 proliferative index and low prolifrative index. However, post hoc power was found 0.46 and was lower than expected value (0.80).

The most important limitation of our study is low count case. For this reason, continue to the study and presentation of preliminary result of our study are intended.

In conclusion, correlation between ADC value and just only Ki-67 proliferative index among prognostic factors that we evaluated was detected and in other statistical meaningful difference was not established.

REFERENCES

1. Landis SH, Murray T, Bolden S *et al*. Cancer statistics, 2001.CA Cancer J Clin 2001; 51:15-36.
2. Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998; 352:930-942.
3. Esteva FJ, Hortobagyi GN. Prognostic molecular markers in early breast cancer. Breast Cancer Res 2004; 6:109–118.
4. Park MJ, Cha ES, Kang BJ, Ihn YK, Baik JH. The role of diffusion-weighted imaging and the apparent diffusion coefficient (ADC) values for breast tumors. Korean J Radiol 2007; 8:390–396.
5. Yabuuchi H, Matsuo Y, Okafuji T, *et al*. Enhanced mass on contrast-enhanced breast MR imaging: lesion characterization using combination of dynamic contrast-enhanced and diffusion-weighted MR images. J Magn Reson Imaging 2008; 28:1157–1165.
6. Bloom HJ, Richardson WW. Histological grading and prognosis in breast cancer: a study of 1409 cases of which 359 have been followed for 15 years. Br J Cancer 1957; 11:359-377.
7. Le Doussal V, Tubiana-Hulin M, Friedman S *et al*. Prognostic value of histologic grade nuclear components of Scarff-Bloom- Richardson (SBR). An improved score modification based on a multivariate analysis of 1262 invasive ductal breast carcinomas. Cancer 1989; 64:1914-1921.
8. Viale G, Regan MM, Mastropasqua MG, *et al*. International Breast Cancer Study Group. Predictive value of tumor Ki-67 expression in two randomized trials of adjuvant chemoendocrine therapy for node-negative breast cancer. J Natl Cancer Inst 2008; 100:207–212.
9. Buadu LD, Murakami J, Murayama S, *et al*. Patterns of peripheral enhancement in breast masses: correlation of findings on contrast medium enhanced MRI with histologic features and tumor angiogenesis. J Comput Assist Tomogr 1997; 21:421-430.
10. Guo Y, Cai YQ, Cai ZL, *et al*. Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging. J Magn Reson Imaging 2002; 16:172-178.
11. Hatakenaka M, Soeda H, Yabuuchi H, *et al*. Apparent diffusion coefficients of breast tumors: clinical application. MagnReson Med Sci 2008; 7:23-29.
12. Woodhams R, Matsunaga K, Iwabuchi K, Kan S, Hata H, Kuranami M, *et al*. Diffusion-weighted imaging of malignant breast tumors: the usefulness of apparent diffusion coefficient (ADC) value and ADC map for the detection of malignant breast tumors and evaluation of cancer extension. J. Comput. Assist. Tomogr. 2005; 29:644–649.
13. Kim SH, Cha ES, Kim HS, *et al*. Diffusionweighted imaging of breast cancer: correlation of the apparent diffusion coefficient value with prognostic factors. J MagnReson Imaging. 2009; 30(3):615–620.
14. Choı SY, Chang YW, Park HJ, *et al*. Correlation of the apparent diffusion coefficiency values on diffusion-weighted imaging with prognostic factors for breast cancer. The British Journal of Radiology 2012; 85:474–479.
15. Marini C, Iacconi C, Giannelli M, Cilotti A, Moretti M, Bartolozzi C. Qualitative diffusion-weighted MR imaging in the differential diagnosis of breast lesions. Eur. Radiol. 2007; 17:2646–2655.
16. Park SH, Choi HY, Hahn SY Correlations Between Apparent Diffusion Coefficient Values of Invasive Ductal Carcinoma and Pathologic Factors on Diffusion-Weighted MRI at 3.0 Tesla Journal of Magnetic Resonance Imaging 2015; 41:175–182.
17. Woodhams R, Kakita S, Hata H, Iwabuchi K, Umeoka S, Mountford C, Hatabu H. Diffusion-weighted imaging of mucinous carcinoma of the breast: evaluation of apparent diffusion coefficient and signal intensity in correlation with histologic findings. AJR. 2009; 193:260-266.
18. Yoshikawa MI, Ohsumi S, Sugata S, *et al*. Relation between cancer cellularity and apparent diffusion coefficient values using diffusion-weighted magnetic resonance imaging in breast cancer. Radiat Med 2008; 26:222–226.

19. Razek AA, Gaballa G, Denewer A, Nada N. Invasive ductal carcinoma: correlation of apparent diffusion coefficient value with pathological prognostic factors. NMR Biomed 2010; 23:619–23.
20. Costantini M, Belli P, Rinaldi P, Bufi E, Giardina G, Franceschini G, *et al*. Diffusion-weighted imaging in breast cancer: relationship between apparent diffusion coefficient and tumor aggressiveness. ClinRadiol 2010; 65:1005-12.
21. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype. Cancer 2007; 109:1721–8.
22. Martincich L, Deantoni V, Bertotto I, *et al*. Correlations between diffusion-weighted imaging and breast cancer biomarkers. EurRadiol 2012; 22:1519-1528.
23. Makkat S, Luypaert R, Stadnik T, *et al*. Deconvolution-based dynamic contrast-enhanced MR imaging of breast tumors: correlation of tumor blood flow with human epidermal growth factor receptor 2 status and clinicopathologic findings–preliminary results. Radiology 2008; 249:471-482.
24. Petit AM, Rak J, Hung MC, *et al*. Neutralizing antibodies against epidermal growth factor and ErbB-2/neu receptor tyrosine kinases down-regulate vascular endothelial growth factor production by tumor cells in vitro and in vivo: angiogenic implications for signal transduction therapy of solid tumors. Am J Pathol 1997; 151:1523–1530.