Diffusion weighted imaging in breast cancer – Can it be a noninvasive predictor of nuclear grade?

R Rupa, R Thushara, S Swathigha, R Athira, N Meena, Mathew P Cherian

Division of Breast Imaging, Department of Diagnostic and Interventional Radiology, Kovai Medical Center and Hospital, Coimbatore, Tamil Nadu, India

Correspondence: Dr. Mathew P Cherian, Department of Radiology Services, Kovai Medical Center and Hospital, 99, Avinashi Road, Coimbatore - 641 014, Tamil Nadu, India. E-mail: dr.mathewcherian@gmail.com

Abstract

Background: DWI and ADC values are noninvasive MRI techniques, which provide quantitative information about tumor heterogeneity. **Aim:** To determine the minimum and mean ADC values in breast carcinoma and to correlate ADC values with various prognostic factors. **Settings and Design:** Prospective observational study. **Materials and Methods:** Fifty-five patients with biopsy-proven breast carcinoma were included in this study. MRI with DWI was performed with Siemens 3T Skyra scanner. ADC values were measured by placing regions of interest (ROIs) within the targeted lesions on ADC maps manually. The histopathological and immunohistochemical analysis of surgical specimen was done to determine the prognostic factors. **Statistical Analysis:** Students T test and ANOVA were used to study the difference in ADC between two groups. Pearson correlation coefficient was used to quantify the correlation between ADC values and prognostic factors. **Results:** Lower grade (grade I) breast carcinoma had a significantly high ADC value as compared to higher grade carcinoma (grade II and III). For differentiating Grade I tumors from grade II and III, a minimum ADC cut-off value was 0.79×10^{-3} mm^2/sec (83% sensitivity and 84% specificity) and a mean ADC cut-off value was 0.82×10^{-3} mm^2/sec (83% sensitivity and 71% specificity) was derived. There was no significant correlation between ADC and other prognostic factors. **Conclusion:** ADC values can be used to differentiate lower grade breast carcinoma (grade I) from higher grades (grade II and III). Minimum ADC values are more accurate in predicting the grade of the breast tumor than mean ADC value.

Key words: Breast cancer; diffusion; imaging; predictor; prognosis

Introduction

Breast cancer is the commonest cancer among women in the world.[1] In India the incidence rate of breast cancer is less. However, the mortality rate is at par with western countries. Further Indian women tend to have tumors (use - tend to have) 10 years earlier than western population with occurrence of more aggressive tumors.[2,3]

Purpose and rationale of the study

Breast cancer is a multispectrum disease.[4] The most important factors which determine its prognostication are histological grade (Elston-Ellis modification of Bloom-Richardson histologic grading system or Nottingham

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combined histologic grading system), histopathological type of cancer, Estrogen Receptor/Progesterone Receptor (ER/PR) status, Human Epidermal Growth Receptor (HER2) Neu status, lymph node status, and tumor size.[5-7] Prognosis also depends on other factors like lymphovascular and perineural invasion.[8,9]

MRI acts as a complementary diagnostic tool to Mammogram and ultrasound in evaluation of breast cancer, especially in young women with dense breast.[2,10,11] The sensitivity and specificity of Dynamic Contrast Enhancement (DCE)-MRI in detecting breast cancer is approximately 85-99% and 72% respectively.[12-14] With the addition of Diffusion Weighted Imaging (DWI), the sensitivity increases to 85-100% and specificity to 37-88%[15,16]

DWI assesses the physiological and functional environment of the lesion by studying the random motion of water molecules, tissue cellularity, fluid viscosity, membrane permeability, and blood flow which is measured quantitatively by Apparent Diffusion Coefficient (ADC) values.[17] Previous studies have shown lower apparent diffusion coefficient values for malignant breast lesions than for benign lesions and normal breast tissue.[16,18,19] In addition to differentiation of benign and malignant lesions, DWI is thought to have a wider role in assessing prognosis of breast carcinoma.[20] In the current study we have attempted to get cut-off values for minimum and mean ADC for breast cancer and correlated the ADC values with the histopathological prognostic factors, which helps to predict the tumor aggressiveness preoperatively and thus helps in treatment planning.

Materials and Methods

This observational study was done to evaluate the role of ADC values in assessing the prognosis of breast carcinoma. This study has been approved (use- was or had been) by the institutional review board and written informed consent was obtained from all patients. Study population included women diagnosed to have breast carcinoma by histopathological study of the biopsy specimen and underwent breast MRI before any therapeutic interventions during a period of 2 years (from May 2015 to June 2017). Patients with motion artifacts on DWI, prior neoadjuvant chemotherapy, excision biopsy, those with *in situ* ductal cancer, and those with small invasive focus detected only in histopathology were excluded from the study. After exclusion, total of 55 patients with histopathologically proven breast carcinoma were included in the study (3 patients had bilateral malignancy).

Image analysis
MRI examinations were performed within 2 weeks before surgery. All patients were scanned in the prone position with Siemens (AG Healthcare, Erlanger, Germany) 3T Skyra

scanner with a dedicated 4-channel phased array breast coil. Before administration of contrast media, axial bilateral fat-suppressed T2-weighted fast spin-echo and DWI series were acquired. DWI was performed using spin-echo single shot echo-planar imaging with the following parameters: TR/TE 6230/65; FOV 340 × 340 mm; matrix 164 × 274; thickness 5.0 mm; gap 0.1 mm. Spectral presaturation with inversion recovery (SPAIR) was used for fat suppression. Motion-probing gradients in three orthogonal orientations were applied with b values of 50 and 800 s/mm². Isotropic diffusion-weighted images were reconstructed for each b value. For quantitative analysis of the data acquired from DWI, ADC maps were automatically created using software provided by the MRI system manufacturer using two b values (50 and 800 s/mm²).

Finally, dynamic axial bilateral breast images of fat-suppressed high-resolution T1-weighted 3D fast gradient-echo images (VIEWS) were sequentially acquired before and 60, 120, 180, 240 and 300 seconds after the administration of contrast medium. For the dynamic study, gadopentetate dimeglumine (Magnevist) was administered intravenously using a power injection at a dose of 0.1 mmol/kg of body weight at a flow rate of 2 mL/s, followed by flushing with 20 mL of saline.

ADC values of the lesions were measured by a senior radiologist with more than 10 years of experience in breast imaging by placing regions of interest (ROIs) of 5-10 mm² within the target lesions on ADC maps manually. The regions with high T2 within the lesion such as cystic part, necrosis, hematoma or fat, and the visual artifacts of DWI are avoided. The minimum and mean ADC values are automatically calculated from the ROI drawn. (please mention minimum size of tumor required for the ROI and put the rest of the cases i.e., smaller cancers in exclusion criteria).

Histopathological analysis
All the 55 participants who had done breast MRI underwent surgery (either breast conservation or modified radical mastectomy). The histopathological and immunohistochemical analysis of the surgical specimen was done to determine the prognostic factors like histopathological type of tumor, grade of the tumor, ER, PR status, Her 2Neu status, lymphovascular, and perineural invasion. The tumor size and axillary lymphnode status were also assessed.

Statistical analysis
Statistical analysis was performed using SPSS (Statistical package for social science version 16.0 for windows). Students T test and Analysis of Variance (ANOVA) were used to study the difference in ADC between two groups. Pearson correlation coefficient was used to quantify the correlation between ADC values and prognostic factors.

The efficiency of the ADC was evaluated using receiver operating characteristic (ROC) analysis. A *P* value <0.05 was taken to indicate statistical significance.

Results

The age of the patients ranged from 35 to 85 years. 28 had lesion on the right side, 24 had lesion on the left side and 3 had bilateral invasive breast carcinoma [Figure 1]. The maximum size was 7.2 cm and minimum size was 0.7 cm. All the 58 index lesions showed enhancement at DCE-MRI, out of which 45 (77.6%) had type III enhancement kinetics and 13 (22.4%) had type II enhancement kinetics. All the index lesions showed restricted diffusion on DWI. Both minimum and mean ADC values were calculated for all lesions in the study.

Out of all the total 58 breast lesions, 44 lesions were (75.9%) single, while 9 (15.5%) were multifocal carcinoma and 5 (8.6%) were multicentric multifocal breast carcinoma. Histological types included invasive ductal carcinoma no special type (53) invasive lobular carcinoma (1) mucinous carcinoma (2) papillary carcinoma (1) medullary carcinoma (1). The minimum and maximum size of the tumors in HPE were 0.5 cm and 7.5 cm respectively [Graph 1]. Majority of the patients (35 out of 57, about 60.3%) were included in T2 stage of TNM staging.

Tumors with lower grade showed significantly higher ADC value ($P < 0.001$) compared to tumors with higher grade [Table 1]. On *post hoc* analysis, there was significant difference in the ADC values (both minimum and mean ADC values) of tumors of grade I and II ($P < 0.001$) as well as grade I and III ($P < 0.001$) and insignificant difference between grade II and III (P value - 1.0). The ADC value was correlated with pathological grading of the tumor ($r = -0.497$, $P < 0.001$).

Further evaluation of the relationship between grade and minimum and mean ADC values was carried out using ROC analysis. The area under curve (AUC) was more for minimum ADC (0.922) than that for mean ADC (0.817) [Figure 2]. In ROC curve analysis in which grade I was compared with grade II and III, the minimum ADC cut-off value was calculated as 0.79×10^{-3} mm²/sec with 83% sensitivity and 84% specificity. For mean ADC cutoff was calculated as 0.82×10^{-3} mm²/sec with a sensitivity of 83% and specificity of 71%.

There was no statistically significant difference in minimum or mean ADC values in patients with positive and negative ER, PR status, Her 2 neu status, lymph node metastasis, lymphovascular, and perineural invasion. On Pearson correlation there was no significant correlation between ADC values and ER PR status and HER2 Neu status.
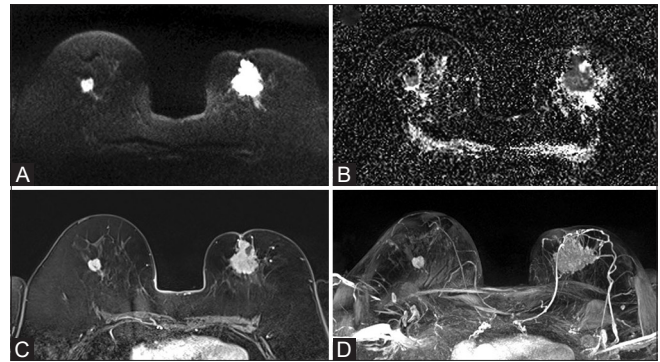

Figure 1 (A-D): Axial section of DWI (A), ADC map (B), post-contrast (C) and post-contrast MIP (D) images showing bilateral invasive carcinoma (no special type). Minimum and mean ADC values of the lesion were 0.57 and 0.79×10^{-3} mm²/sec respectively
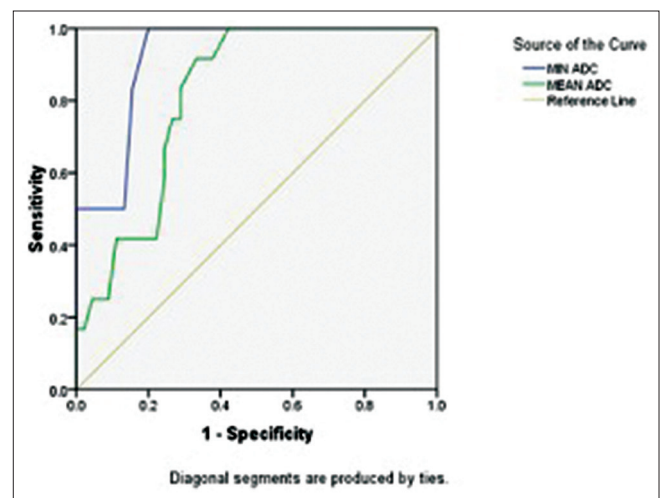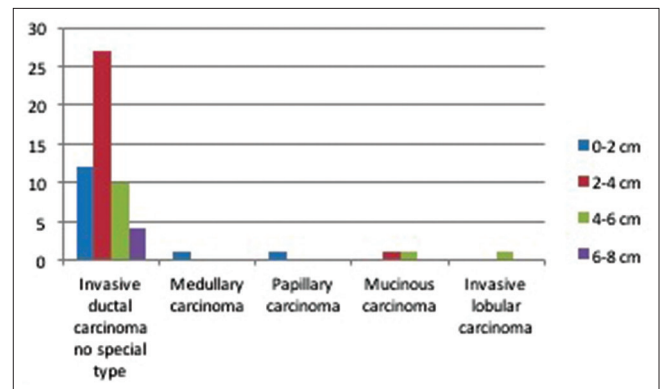

Figure 2: ROC curve for ADC values for grade of carcinoma

Graph 1: Graphical representation of distribution of tumour size and heterogenity

Discussion

Diffusion weighted imaging is a functional imaging technique that detects early changes at the molecular level, cellularity, and cell membrane permeability which correlate with tumor biology.[20] So there is a possibility that diffusion weighted imaging and ADC values would identify tumors

with high malignant potential and aid in preoperative prognostication and treatment planning.

In this study, both minimum and mean ADC values were separately assessed for all lesions using a 3T MRI system. It can acquire high-resolution images while retaining high signal to noise ratio. Compared to 1.5T MRI, 3T MRI allows data acquisition with higher b values and high signal to noise ratio.[21,22]

Tumor grade of breast cancer is the most important prognostic factor which predicts the invasive behavior of tumor and its long-term prognosis. In this study the grade I carcinoma was found to have significantly higher ADC values than grade II and grade III [Figure 3]. But there was no significant difference in ADC values between grade II and grade III [Figures 4 and 5]. The mucinous tumors had the highest ADC values [Figure 6] and the lowest ADC obtained in the study in a grade 3 tumor was 0.3×10^{-3} mm^2/sec [Figure 7]. In the ROC analysis, minimum ADC was having an accuracy of 92.2% (AUC 0.922 graded as Excellent) and the mean ADC was having an accuracy of 81.7% (AUC 0.817 graded as Good). This suggests that minimum ADC is a more reliable measurement for predicting preoperatively, the grade of the tumor and can be used for future analysis. A cut-off value of 0.79×10^{-3} mm^2/sec was calculated by ROC analysis for minimum ADC for differentiation of grade I tumors from grade II and III with

a sensitivity of 83% and specificity of 84%. For mean ADC, cut off is calculated as 0.82×10^{-3} mm^2/sec with a sensitivity of 83% and specificity of 71%. Though both the cut offs are closer to each other minimum ADC is found to be more specific in differentiating grade I from other grades of tumor.

In a study done by Kizildag yirgin *et al*. a cut off of 1.05×10^{-3} mm^2/sec was proposed for differentiating grade I from higher grade tumors.[23] This value is higher as compared to the cut off derived in our study. A statistically significant inverse correlation between ADC values and tumor grading was seen in few other previous studies.[20,24] However Park *et al*. and Martincich *et al*. observed no statistically significant difference between ADC values and grade of tumor.[25,26] The difference in observations may be due to the heterogeneity of the lesion or due to observer variability or variability based on spatial focus of observation of slide for assessing grade.(this statement is vague and does not explain anything. Please explain properly and provide the references).

The Non-significant *P* values in axillary lymphnode metastasis in our study can be explained by the fact that these values also depend on the duration of the disease, size of index lesion and disease progression. A similar result was also observed by Choi *et al*.[27]

The immunohistochemical markers like ER and PR are intracellular steroid receptor proteins and are indicators of prognosis and guide to hormonal and endocrine therapy.[28] In this study there was no significant association between ER and PR with ADC values. This is consistent with various previous studies.[25,29-31]

It is known that, HER2-positive cells have a higher cell proliferation rate, more invasion and metastasis. So ADC values of HER2-positive Intra Ductal Carcinoma (IDC) are assumed to be lower because of its increased cellularity. In our study, on the contrast, the mean ADC values of lesions with Her-2-Neu positive were more than that of lesions with Her2-Neu negative cases, but they were statistically not significant. This can be explained by the increased angiogenesis suppressing diffusion restriction.[26] This result is consistent with other studies done by Martincich *et al*. and Park *et al*.[25,26]
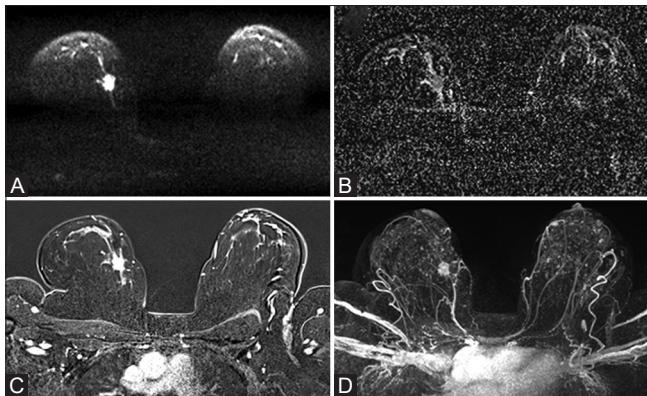

Figure 3 (A-D): Axial section of DWI (A), ADC map (B), post-contrast (C) and post-contrast MIP (D) images of invasive carcinoma (no special type) of right breast. Histopathologically proven grade I carcinoma. Minimum and mean ADC values of the lesion were 0.8 and 0.85×10^{-3} mm^2/sec respectively
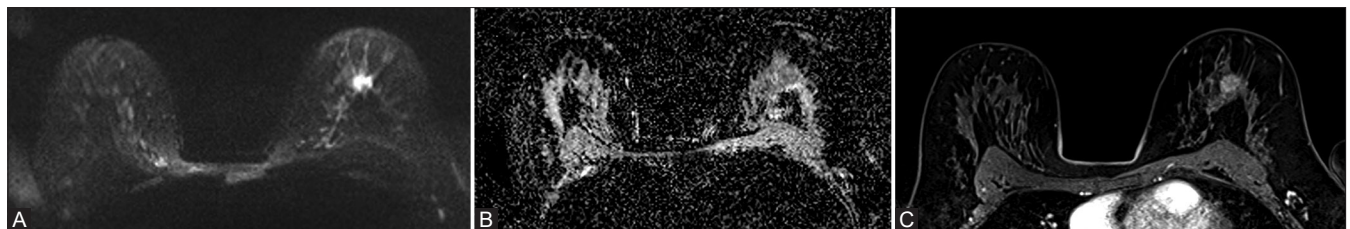

Figure 4 (A-C): Axial section of DWi (A), ADC map (B) and post-contrast (C) images of invasive carcinoma (no special type) of left breast. Histopathologically proven grade II carcinoma. Minimum and mean ADC values of the lesion were 0.63 and 0.76×10^{-3} mm^2/sec respectively

Table 1: Statistical analysis of ADC values with prognostic factors

| Factor	Number of lesions (*n*=58)	Mean ADC Value (×10⁻³ mm²/sec)		*P*	
		Minimum ADC	Mean ADC	Minimum ADC	Mean ADC
GRADE				<0.001	<0.001
Grade I	12 (20.6)	0.90±0.16	0.94±17		
Grade II	30 (51.7)	0.64±0.14	0.78±0.12		
Grade III	16 (27.6)	0.62±0.13	0.72±0.13		
ER				0.25	0.69
Positive	43 (74.1)	0.67±0.20	0.79±0.17		
Negative	15 (25.9)	0.74±0.07	0.81±0.09		
PR				0.23	0.65
Positive	40 (69)	0.67±0.20	0.79±0.18		
Negative	18 (31)	0.73±0.08	0.81±0.10		
HER 2 NEU				0.10	0.16
Positive	30 (51.7)	0.73±0.11	0.82±0.10		
Negative	28 (48.3)	0.65±0.22	0.77±0.20		
Lymphovascular invasion				0.26	0.27
Positive	32 (55.2)	0.67±0.13	0.77±0.12		
Negative	26 (44.8)	0.72±0.22	0.82±0.19		
Perineural invasion				0.70	0.41
Positive	13 (22.4)	0.71±0.12	0.83±0.09		
Negative	45 (77.6)	0.68±0.20	0.78±0.17		
Axillary lymph node status				0.22	0.20
Positive	29 (50)	0.66±0.15	0.77±0.13		
Negative	29 (50)	0.72±0.20	0.82±0.17		
Histopathological types				0.002	0.001
IDC NOS	53 (91.3)	0.67±0.14	0.77±0.12		
Other types	5 (8.7)	0.92±0.36	1.0±0.28		
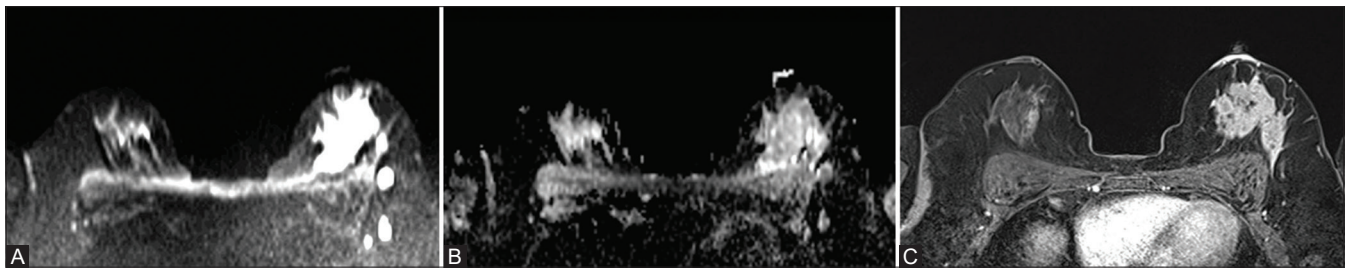
Figure 5 (A-C): Axial section of DWI (A), ADC map (B) and post-contrast (C) images of invasive carcinoma (no special type) of right breast. Histopathologically proven grade III carcinoma. Minimum and mean ADC values of the lesion were 0.69 and 0.75 × 10⁻³ mm²/sec respectively
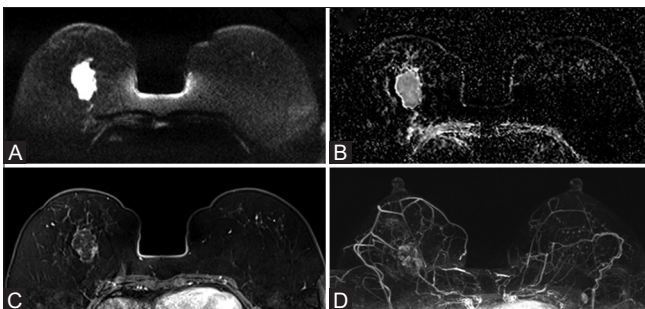

Figure 6 (A-D): Axial sections of DWI (A), ADC map (B), post-contrast (C) and post-contrast MIP (D) images of mucinous carcinoma of right breast. Minimum and mean ADC values of the lesion were 1.2 and 1.3 × 10⁻³ mm²/sec respectively

Lymphovascular invasion indicates increased risk of axillary lymph node involvement and distant metastasis in node negative cancer.[8] this high; lighted statement is unclear. please explain properly with references).No significant relation was noted between the lymphovascular invasion and ADC values in our study which is similar to that reported by Guvenc *et al.*[22]

Perineural invasion is reported in conjunction with lymphovascular invasion confounding its significance as an independent prognostic factor.[9] In this study no statistically significant relation is noted between the ADC values and perineural invasion.

DWI takes short acquisition time and post-processing time and does not need administration of contrast and provides a real quantitative functional parameter for assessing tumor aggressiveness. ADC values provide a powerful noninvasive predictive tool for the prognostication of the breast cancer preoperatively and thus helps in treatment planning and patient follow-up.
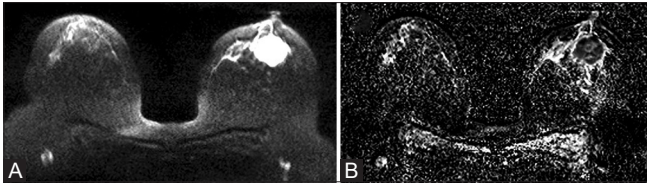
Figure 7 (A and B): Axial section of DWI (A), ADC map (B) images of invasive carcinoma (no special type) of right breast. Histopathologically proven grade III carcinoma. Minimum and mean ADC values of the lesion were 0.3 and 0.45 × 10^{-3} mm²/sec respectively

Conclusion

MRI studies using DWI can identify the biological heterogeneity of the tumor tissue and ADC values can vary significantly according to the biological features of the breast cancer. Lower grade (grade I) breast carcinoma has a significantly high ADC value as compared to higher grade carcinoma (grade II and III). According to this study, a minimum ADC of more than $0.79 × 10^{-3}$ mm²/sec and a mean ADC of more than $0.82 × 10^{-3}$ mm²/sec are good prognostic indicators of which minimum ADC has more specificity. Infiltrating ductal carcinomas have lower ADC values than other types of carcinoma reflecting its more aggressive nature. There was no significant correlation between ADC and other prognostic factors like ER PR status, Her 2 Neu status, axillary lymph node status, lymphovascular, and perineural invasion.

Limitations

1. As the study was conducted in patients with invasive cancers with a variety of histologies, it could not rule out bias due to histological variability. Invasive ductal carcinoma was dominant in the sub-group distribution of tumors. The number of special types of breast carcinoma and lobular carcinoma included in the study was too low for definitive assessment of a statistically significant mean ADC values for each histological type
2. Some of the tumors were small and ADCs of these tumors might be inaccurate due to partial volume effect
3. Patients undergoing neoadjuvant chemotherapy were excluded from the study. By doing so all the patients with aggressive breast cancers were excluded from the study resulting in selection bias
4. The ROI used for calculating the ADC values were small and need not represent the biological character of the whole tumor.

Conflicts of interest

There are no conflicts of interest.

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